Zodwa Dlamini *Editor*

Society 5.0 and Next Generation Healthcare

Patient-Focused and Technology-Assisted Precision Therapies

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Zodwa Dlamini
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP)
Pan African Cancer Research Institute (PACRI), University of Pretoria
Pretoria, South Africa

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Society 5.0: Realizing Next-Generation Healthcare

Zodwa Dlamini, Thabiso Victor Miya, Rodney Hull, Thulo Molefi, Richard Khanyile, and Jaira Ferreira de Vasconcellos

Abstract The concept of a new improved society known as Society 5.0 was first proposed in Japan in 2016 in the Japanese government's 5th basic plan for Science and Technology. This new improved smart society will rely on the use of new technologies such as artificial intelligence (AI), cloud computing, and the Internet of Things (IoT) to gather and analyze large amounts of data. This is then used to improve many aspects of society leading to sustainable development and the achievement of the United Nations (UN) sustainable development goals (SDGs). SDG-3 is to "Ensure healthy lives and promote well-being for all at all ages." This can be achieved in healthcare in society 5.0 through the use and integration of these new technologies. AI, machine learning (ML), and deep learning (DL) allow the creation of automated systems capable of learning, identifying features in patient data, and making a decision regarding diagnosis, prognosis, or treatment choices. AI can also be used to integrate large amounts of data to create digital twins of patients or populations to allow for more accurate modeling in many healthcare-related scenarios and implement precision medicine. Much of the data required to implement these technologies can be gathered through the IoT which allows personalized data regarding an individual's health, environment, and activity to be gathered by

Z. Dlamini (✉) · T. V. Miya · R. Hull
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: zodwa.dlamini@up.ac.za; thabiso.miya@up.ac.za; rodney.hull@up.ac.za

T. Molefi · R. Khanyile
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa

Department of Medical Oncology, Faculty of Health Sciences, Steve Biko Academic Hospital, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: thulo.molefi@up.ac.za; richard.khanyile@up.ac.za

J. F. de Vasconcellos
Department of Biology, James Madison University, Harrisonburg, VA, USA
e-mail: vasconjf@jmu.edu

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smart connected devices through the Internet. To be successful, this digital information must be used in such a way as to result in the merging of cyberspace and physical space through the integration of cyber-physical systems. All these new developments will require and drive a revolutionary change in the healthcare ecosystem. The use of these new healthcare technologies also presents governments and healthcare systems with new legal issues, ethical questions, and fears surrounding the restructuring of the healthcare ecosystem. Additionally, the implementation of these new technologies is complicated by the current worldwide energy crisis. The solutions to these problems are already being sought. Technologies such as AI, IoT, and digital twins are being used to design and manage newer smarter electricity grids and assist in the introduction of new energy sources, while Blockchain technology can possibly provide a solution to issues surrounding the responsible storage and management of data. The use of these technologies to implement healthcare based on the concept of Society 5.0 promises to give individuals a healthier, longer, and more productive life.

Keywords Society 5.0 · Healthcare · UN SDG3 · AI · IoT · Cloud computing · Digital twins · Blockchain technology · Safety · Privacy · Energy crisis · Rights · Security · Ethics

1 Introduction

1.1 Industrial Revolution

From the beginning of civilization, technology has been recognized by humankind as a tool for the advancement of society. This has been greatly accelerated since the First Industrial Revolution (Industry 1.0) (Mourtzis et al. 2022) (Fig. 1). The First Industrial Revolution began around the 1780s and comprised mechanical power production using fossil fuels, water, and steam. The Second Industrial Revolution (Industry 2.0) followed in the 1870s whereby manufacturers preferred electrical energy for mass production and assembly lines (Mourtzis et al. 2022). The Third Industrial Revolution (Industry 3.0) followed in the 1970s and was characterized by the integration of automation into the production industries using Information Technology (IT) and electronics (Fig. 1). The fourth industrial revolution (Industry 4.0) is defined by the use of artificial intelligence (AI), cloud computing, and the Internet of Things (IoT) to facilitate Cyber-Physical Systems (CPS) (Fig. 1). These systems serve as a real-time interface between physical and virtual worlds (Mourtzis 2016; Elmaraghy et al. 2021). Industry 4.0 signifies the rapid change in technology, social patterns, industries, and processes in the recent decade. Advancements of innovative technologies such as AI, big data analytics, and digital twins under Industry 4.0 framework have improved product and service quality as well as production efficiency (Rüßmann et al. 2015).

However, Industry 4.0 framework has limitations because engineers mainly focused on technological advancements in production and manufacturing systems

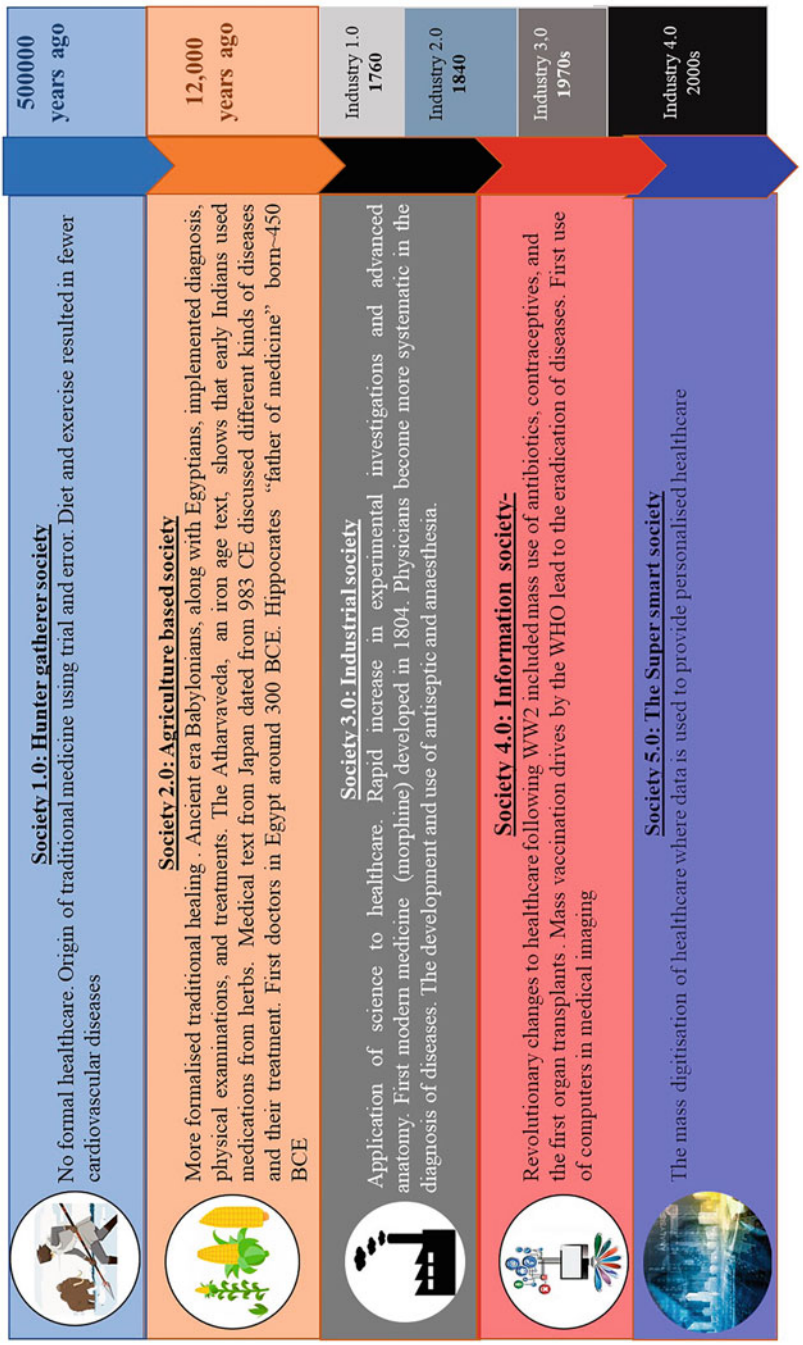

Fig. 1 Dateline of societies and industrial revolutions. The progression from society 1.0 to Society 5.0 is depicted alongside the changes in healthcare seen in each society

and networks (Xu et al. 2021). The engineers prioritized industrial efficiency and flexibility over worker welfare and industrial sustainability (Xu et al. 2021). Thus, the emergence of a new era of industrial transformation is soon. The new era will enable engineers to optimize current technologies for the benefit of humankind and social factories (Mourtzis et al. 2022). Countries such as Japan, the United States, and the European Union have already made a move toward the human-centric era of industrial transformation (Mourtzis et al. 2022). This new era is called Industry 5.0, and it also extends to Society 5.0. It is important to note that Industry 4.0 is still an ongoing technological transformation, and that Society 5.0 and Industry 5.0 are still under preparation (Mourtzis et al. 2022). This has created misconception that Industry 5.0 may not be recognized as an independent industrial revolution (Mourtzis et al. 2022).

1.2 What Is Society 5.0?

The Government of Japan launched the Society 5.0 (super-smart society) concept in April of 2016 (Fukuda 2020). Society 5.0 can be described as a novel society in the fifth stage which follows the hunting society, the agrarian society, the industrial society, and the information society as shown in Fig. 1 above (Fukuda 2020). This concept is aimed at creating a human-centered society whereby services and products will be easily accessible. Consequently, this will reduce social and economic gaps so that all people can lead prosperous lives (Fukuda 2020). Society 5.0 is the same as Industry 4.0; however, it takes a further step by portraying a data-driven society (super-smart society) and economy. Furthermore, it focuses on individual capabilities and needs (Mavrodieva and Shaw 2020). Society 5.0 conceptualizes a merge between the cyberspace and the physical space (real world) to effectively gather more personal and precise data, thereby improving value creation and problem solving (Fukuyama 2018). In addition, large quantities of data that have been collected over the years require time and human resources to analyze a job that could be performed rapidly using AI. This data could also be transformed into easy formats that can be understood and used by humans in various industries and social services (Mavrodieva and Shaw 2020). The Society 5.0 concept became an official policy in Japan when it was included in their 2016 Fifth Science and Technology Basic Plan for the first time (Mavrodieva and Shaw 2020). Parties involved pledged that this concept will significantly support the United Nations Sustainable Development Goals (UN-SDGs) and also create a sustainable, inclusive, and human-centered society (Mavrodieva and Shaw 2020). A sustainable society organizes itself to better the autonomy and the quality of life for its citizens. It also aspires to the common welfare economy, and it does not compromise its future opportunities. Sustainability is comprised of society, environment, and economy. Society is an important base among the three (Fig. 2).

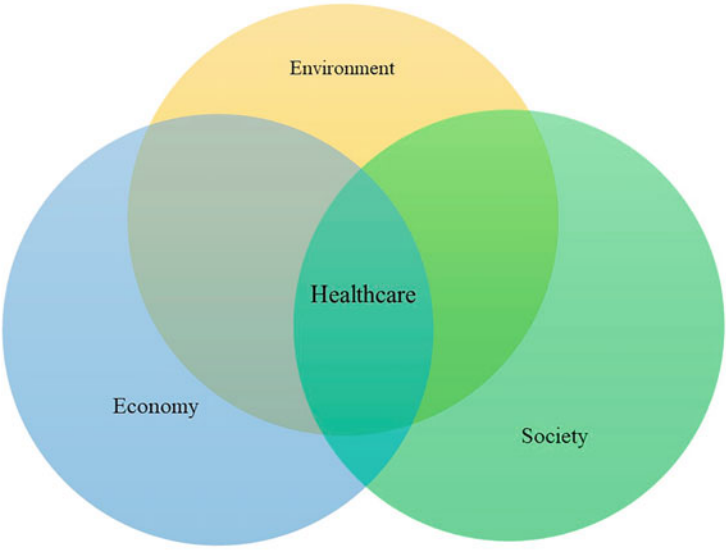

Fig. 2 Three bases that form sustainability. Adapted from Aquilani et al. (2020)

The UN-SDGs are aimed at achieving collective progress through co-operation between citizens and governments to eradicate social inequality (Gustiana et al. 2019). Since the establishment of these goals, many nations have directed their investments and research toward these sustainability goals (Fukuda 2020; Hayashi et al. 2017; Základsník and Putnová 2019). In this case, sustainable development is conceptualized from its planning, use of aspiring technology and infrastructure developments, to attain both an improved environment and efficient industrialization (Aquilani et al. 2020).

Japan plans to spread the Society 5.0 concept worldwide by working with other nations to achieve its implementation (Mavrodieva and Shaw 2020). The Society 5.0 concept could change the way society functions in all areas of life. This concept will positively impact the economy of Japan as well as other countries and also help in tackling numerous social challenges (Fukuyama 2018). Society 5.0 will impact all aspects of life, but it is mainly focused on nine social and economic sector, namely, healthcare, finance, energy, agriculture and food security, disaster prevention, cities and regions, logistics, manufacturing, and public services (Fig. 3) (Mavrodieva and Shaw 2020). When it comes to healthcare, Society 5.0 aims to focus on using AI-based medical services such as telemedicine, prevention and individualized healthcare services, as well as access to personalized life-stage data (Mavrodieva and Shaw 2020).

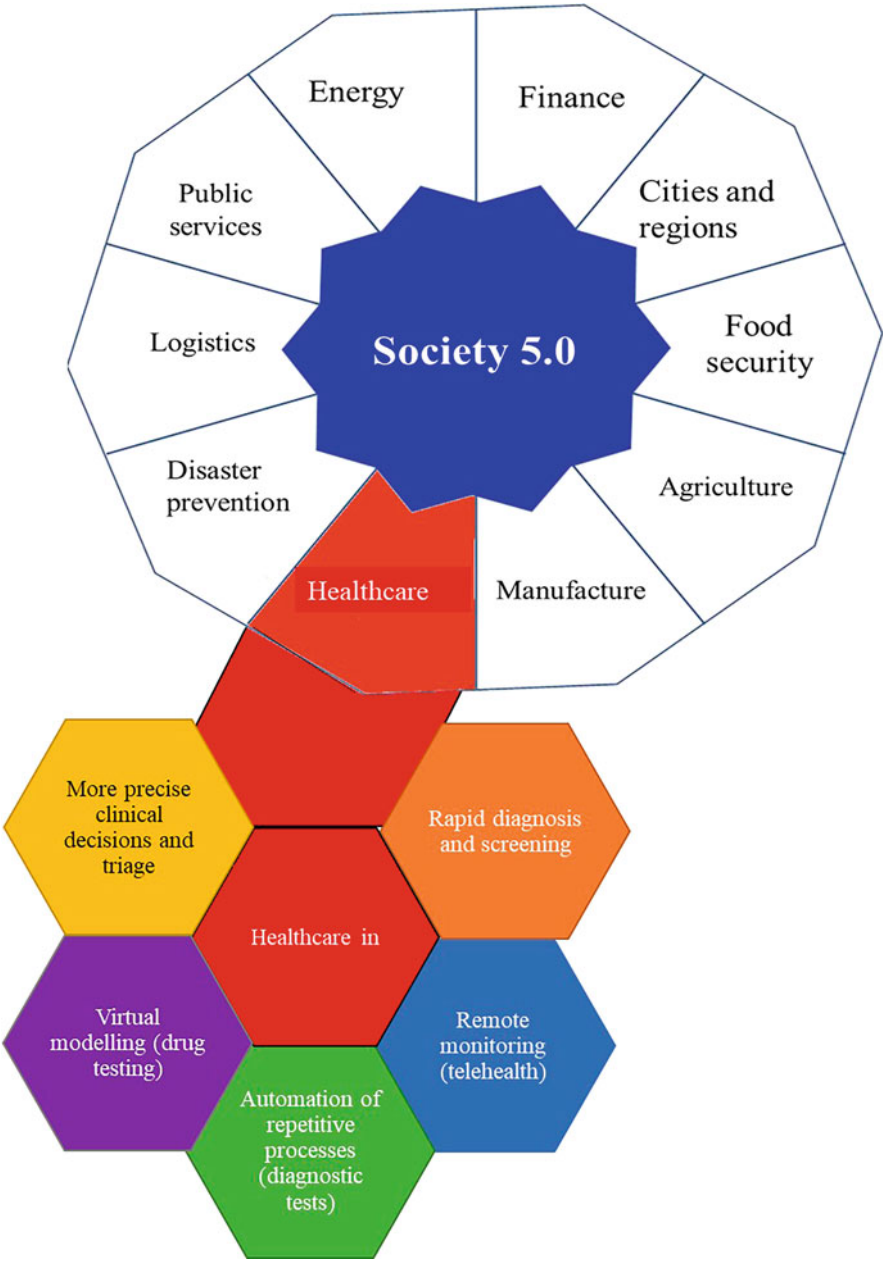

Fig. 3 Smart solutions facilitated by Society 5.0. Adapted from Narvaez Rojas et al. (2021)

2 Digital Transformation in Healthcare

Digital transformation has revolutionized many industries, especially the healthcare industry (Natakusumah et al. 2022). In the healthcare industry, technology enables individuals to live healthier, more productive, and longer lives. For instance, telemedicine was accessed by over one million people in 2015. In 2021, this number increased to 12 million people (Natakusumah et al. 2022). Thus, technology has allowed patients to access quality healthcare even in remote areas (Tortorella et al. 2022). According to Maiurova et al. (2022), Pappas et al. (2018), Ricciardi et al. (2019), and Natakusumah et al. (2022), several other health technologies such as Blockchain, IoT, robotics, and AI have been developed and applied in this industry. Different companies view technology as an asset and not just infrastructure. To this effect, data analysis can be used to improve access to quality healthcare and also lower healthcare costs (Natakusumah et al. 2022). Utilization of health technologies allows consumers (patients) to easily access information regarding diseases, treatment options, and also the ability to choose healthcare facilities that aligns with their needs (Maiurova et al. 2022; Natakusumah et al. 2022; Pappas et al. 2018; Ricciardi et al. 2019). Realization of the benefits of using health technologies has led to more healthcare providers adopting digital transformation into their management systems (Natakusumah et al. 2022). In turn, this has led to provision of improved quality healthcare (Natakusumah et al. 2022).

2.1 Health Technologies

Health technologies have constantly changed since the inception of medicine. Furthermore, increasing knowledge and diagnosis, treatments, rehabilitations, and prevention possibilities have changed healthcare systems (Ricciardi et al. 2019). Digitalization ranging from the use of computers to remotely monitor patients, electronic medical devices, as well as the computer-assisted visualization and decision support systems has affected many areas of healthcare systems (Ricciardi et al. 2019). Digital transformation involves the introduction of new digital information and communication technologies, as well as new corresponding processes into the healthcare industry. Digitalization can lead to changes and innovations in health technologies and delivery, thus impacting healthcare and health systems (Ricciardi et al. 2019).

2.2 Artificial Intelligence (AI)

AI and other related technologies are increasingly common in society and business and are now increasingly applied in the healthcare industry (Davenport and Kalakota

2019). In addition, these technologies can potentially transform multiple aspects of patient care as well as in the administration process within healthcare institutions and pharmaceutical companies (Davenport and Kalakota 2019). AI can be described as the intelligence of machines instead of the intelligence of humans or other living organisms (Minsky 1961; Weng et al. 2001). It also refers to occasions whereby machines can simulate human minds in learning and analysis. Thus, AI can be involved in problem solving, and this kind of intelligence is also called machine learning (ML) (Huang et al. 2015). AI technologies are relevant to the healthcare industry; however, their specific supported tasks and processes differ widely. For instance, ML is commonly applied in precision medicine whereby it is used to identify the correct treatment protocols to use and predict the potential successes of these treatments in a patient (Lee et al. 2018). Most ML and precision medicine applications need a training dataset with a known outcome (e.g., disease). This is also known as supervised learning (Davenport and Kalakota 2019). An even more complex form of ML exists, which is comprised of neural network. Neural networks are discreet organized units of algorithms that act together in a hierarchical manner to mimic the human brain. This technology has been available since the 1960s and is used for categorization applications (Sordo 2002). For example, it can be used to determine whether a patient will develop a certain disease over a certain period of time (Davenport and Kalakota 2019). Lastly, deep learning (DL) and neural network models (with many feature levels and variables) are the most complex ML technologies. There are potentially thousands of hidden features in these models. DL is commonly applied in healthcare to recognize potentially malignant lesions in radiological images (Fakoor et al. 2013). Furthermore, DL is also applied in radiomics, or the detection of features that are clinically relevant in medical images (Vial et al. 2018). Radiomics and DL are mostly found in oncology-related image analysis. Thus, integration can potentially be used to increase diagnostic accuracy compared to previous generations of image analysis. Image analysis can also be automated using computer-aided detection (CAD) tools (Davenport and Kalakota 2019).

AI applications in drug discovery can increase access to medicine and improve the experience of patients, their families together with healthcare workers, and everyone involved in the healthcare system. Access to affordable safe, effective, and affordable medicine is a fundamental human right. To try and attain universal human rights and improve the lives of all the earth's inhabitants, the UN-SDGs need to be achieved by the year 2030. Goal 3 talks about "Ensuring healthy lives and promoting well-being for all at all ages," and particularly, Goal 3.8 seeks to "Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all" (United Nations 2015). However, more than half of the people living in low- and middle-income countries (LMICs) do not have access to essential medicines for a variety of reasons including the high cost of medicines and poor healthcare infrastructure. New medicines are unaffordable for the majority of the population living in LMICs, while at the same time these countries have 75% of the world's poor, accounting for the majority of the global disease burden (Stevens and Huys 2017). Therefore, leveraging the

advantages of AI, its increased speed coupled with reduced cost of drug development, will be paramount if we are to attain Goal 3 of the UN-SDGs.

Although AI has a potential to transform the health industry, it has several technical challenges lying ahead (Yu et al. 2018). For instance, as ML-based algorithms rely on the presence of large amounts of high-quality training data, data that represent target patient population need to be cautiously compiled (Yu et al. 2018). Furthermore, proper data curation is needed for overseeing heterogeneous data. In addition, acquiring patients' gold standards requires health professionals to individually review clinical notes (Yu et al. 2018). This process is expensive on a population scale. Numerous high-performing ML models often create results that are hard to interpret by unassisted people. Additional AI challenges are economic, social, and legal (Yu et al. 2018). However, the greatest challenge to AI is ensuring its adoption into daily clinical practice (Davenport and Kalakota 2019).

2.3 Digital Twins

Digital twins are become an integral part of the digital transformation (Saracco 2019). This transformation is facilitated by the IoT and advanced data analytics (Fuller et al. 2020). A digital twin can be described as a virtual representation of a physical entity which can be utilized in the design phase to analyze, predict, and simulate behavior and store evolving descriptive data (Saracco 2019). A digital twin environment enables fast analysis and real-time decision-making using accurate analytics. Digital twin technology can be applied in various industries including healthcare, manufacturing, smart cities, etc. (Saracco 2019). In healthcare, digital twins can be used to simulate the effects of certain drugs on humans. It can also be used in planning and performing surgery (Gahlot et al. 2018). Furthermore, a digital twin enables doctors, researchers, and healthcare facilities to simulate environments that are specific to their needs in real-time or for future developments or utilizations. Integration of AI algorithms into digital twin technology enables smarter decisions and predictions (Saracco 2019). The use of digital twins for healthcare is still in its initial stages, but its potential is wide, for example, in hospital management where it can be used to improve the assignment of beds, management of large-scale wards, and hospital administration. This technology can also be used for predictive maintenance and repair of medical equipment (Saracco 2019). Lastly, digital twin technology together with AI can be used to make life saving choices that are based on real-time and historical information (El Saddik 2018; Ross 2016).

Digital twins can provide scientific data to address the current gaps in environmental policies and in the long term, reach the UN-SDG-3 goals with regards to maternal newborn and child deaths. Evidence shows that endocrine disruptor chemicals (EDCs) have a substantial impact on most if not all of the omics (Bornman et al. 2017; Singh et al. 2021). All this information is contained within the patient's digital twin (Voigt et al. 2021; Walsh et al. 2020).

Digital twins, new knowledge, the combining of data, and AI integration are set to transform the healthcare industry (Kamel Boulos and Zhang 2021). However, this technology faces several challenges. In particular, digital twins have common issues and challenges with big data analytics and modern AI (Guidance 2021). These challenges include issues with data quality, availability, sharing, interoperability, and integration (Kamel Boulos and Zhang 2021). Other issues include intellectual property concerns, data security and privacy, reproducibility and transparency, and AI biasness (Kamel Boulos and Zhang 2021).

2.4 Internet of Things (IoT)

The convergence of medicine and information technologies has changed the healthcare industry into a more advanced system with efficient and accurate services (Bhatt et al. 2017). Such convergence is achieved through the Internet of Things (IoT). This technology has great impact on healthcare and medicine applications (Bhatt et al. 2017). IoT technology comprises of a physical devices network together with embedded sensors, software, devices, and network connectivity for the exchange of data (Zanella et al. 2014). Thus, the IoT can be described as a method of connecting devices/objects like sensors and smart phones to the Internet to link the devices together (Kortuem et al. 2009). Linking of these devices/objects enables novel communication forms between the devices, system components, and humans (Kortuem et al. 2009). IoT technology integrates common domains such as embedded systems, control systems and automation, as well as wireless sensor networks for device-to-device communication through the Internet (Da Xu et al. 2014). The dependence of the healthcare industry on IoT technology is increasing healthcare access and quality, as well as reducing healthcare cost (Frederix 2009). Personalized healthcare is based on a patient's exclusive biological, behavioral, and social characteristics (Bhatt et al. 2017). In turn, this leads to a reduction in healthcare costs. Support services can target early disease detection and result in homecare instead of clinical care (Bhatt et al. 2017). IoT technology can provide health personalization serves while also preserving digital identification of all patients (Bhatt et al. 2017). Categorization of IoT regarding personalized healthcare systems is comprised of clinical care and remote monitoring (Simonov et al. 2008). Applications of IoT technology in the healthcare industry include:

- Heart rate monitoring, which involved independent monitoring of biometrics of each patient through specific threshold settings. Additionally, vital signs like blood pressure and weight are also remotely monitored through integrated supplementary devices (Bourge et al. 2008).
- Monitoring of aging individuals in hospitals using IoT ultrasound-based technologies as personalized home healthcare solutions tracking and locating patients' activities. In addition, emergency calls can be managed in a cost actual system for wide area communication interface. This system can be a wearable sensor which

is waterproof and can be programmed to send out reports including position signals to the ultrasound receiver (Bhatt et al. 2017).

IoT can make significant contributions to support the implementation of the SDGs with regards to social and environmental aspects. Pay-as-you-go and low-cost IoT can be potential solutions to achieve SDGs by 2030 (López-Vargas et al. 2020). IoT can help achieve sustainable and stronger development, and allows the opportunity for economical and human development while the impact in developing countries must not be overlooked (Rahim 2017). Developing countries are shown to be ideal for IoT innovation, since it can support economic growth, and contribute to cultural, environmental, and social development (Barro et al. 2018). IoT development has allowed for the management and monitoring of renewable energy systems that improve the electrical access (Biggs et al. 2016; Ramanathan et al. 2017). IoT has the potential to predict and minimize the destruction caused by natural disasters (Pelc and Koderman 2018) like tsunamis and earthquakes (Biggs et al. 2016), thereby avoiding serious injuries and also saving lives. The benefits of IoT fall into the UN SDGs. Specifically, IoT implements SDG goals 3 (Good Health and Well-Being), 6 (Clean Water and Sanitation), 14 (Life Below Water), 15 (Life on Land), and 17 (Partnership for the Goals). Goal 3 aims for good health and well-being. IoT allows the capturing of data on all devices and allows model predictions to improve health and well-being. Sensors of various devices will upload the data that can be analyzed. Goal 6 aims to ensure clean water and sanitation. IoT will allow the monitoring and management of water, sanitation, and electrical systems and technologies (Biggs et al. 2016; Ramanathan et al. 2017; United Nation ESCAP 2018). IoT will allow all the data captured by sensors to be analyzed and will provide reliable information about the water resources state, usage, wastewater generation, and treatment (Krishnamurthi et al. 2020). IoT can be used to improve life on land and in water (Goal 14–15) by allowing predictive modeling based on the capturing of data by various devices. Actions can be taken to avoid catastrophic events and improve the health of all living organisms on land or in the water. IoT will also facilitate the growth of partnerships worldwide to increase the collaboration between people, science, and technology (Goal 17). IoT allows all data to be captured and stored and will be accessible across the Internet. This will allow world contribution based on data analysis, and the partnerships will allow improved ideas for healthcare and healthcare management.

IoT services and devices will drive the healthcare industry toward novel generation of efficient services while also saving lives and time with greater accuracy in terms of the predictions and recommendations that can be made (Bhatt et al. 2017). However, IoT technology has several challenges that lie ahead. The standard web services are the most adopted Internet technology (Bhatt et al. 2017). Wireless healthcare systems need functionalities, and this is challenging in the future of the Internet. New technologies and standards need to address security and privacy features for the users, network, applications, and data in the future (Bhatt et al. 2017). In general, the most challenging issues facing IoT technology include settling

on security, device capabilities, merging the gaps between sensors, individuals, safety, and fabrication (Bhatt et al. 2017).

2.5 *Blockchain Technology*

The healthcare industry is constantly trying to keep up with modern technologies and apply them to improve healthcare services to patients (Dasaklis et al. 2018). In this regard, Blockchain technology has already been exploited in several areas of healthcare, including; healthcare data management, privacy, or interoperability (Esposito et al. 2018; Mettler 2016). Blockchain can be described as a secure digital ledger that records and stores transactions (Rathore et al. 2020). The ledger is kept in a decentralized network of nodes which are formed using cryptographic processes computed by all network users (Zhao et al. 2017). Blockchain ledger storage capacity is very dependable because it creates digital signatures and hash chains using consensus algorithms. To this extent, Blockchain technology offers numerous services such as security, traceability, integrity, and nonrepudiation. It does all this while also storing all the data in a public decentralized and privacy-protecting manner (Zhao et al. 2017).

Since Blockchain is decentralized and constantly updated, it presents many opportunities for the healthcare industry (Mettler 2016). For example, Blockchain can be applied in medical treatment processes like in chronic diseases or elderly care (Mettler 2016). The following are some of the key features of Blockchain that can benefit the healthcare industry (Yaqoob et al. 2022):

- **Health data accuracy**
  Since Blockchain maintains updated, traceable, secure records, it can be used to store the entire medical history of a patient (Wang et al. 2018). In turn, this allows healthcare workers to provide timely, efficient, and accurate treatments to the patient. Importantly, all data stored on the Blockchain network are transparent, immutable, traceable, and tamper-proof (Agbo et al. 2019).
- **Health data interoperability**
  Interoperability can be defined as the ability to exchange data between systems manufactured by different companies. A lot of e-health/medical records (EHR/EMR) are products created from different technical specifications, functional capabilities, and clinical technologies (Reisman 2017; Khan et al. 2014). These different systems prevent creation and sharing of data in single format. Thus, Blockchain can be used to store this data while also allowing it to be accessed and utilized by various healthcare institutions (Yaqoob et al. 2022).
- **Health data security**
  A significant number of healthcare institutions still use centralized infrastructures for storing and processing digital medical records (Redka 2019). However, these systems are outdated and vulnerable to cyberattacks and fraud (Redka 2019). Furthermore, these digital medical records can also be lost through events

such as natural disasters. Thus, Blockchain can be used to prevent data mishandling, fraud, or theft using its immutability feature (Yaqoob et al. 2022).

In terms of UN-SDG (Goal 3) "Good health and well-being," Blockchain technology could facilitate change in relation to sustainability that can impact health, medication, and humanitarian aid supply and distribution (Hughes et al. 2019). Developing countries still face challenges in relation to the integrity of basic food products and medical supplies. Furthermore, logistical management and enforcement across geographical diversity and linguistic barriers are also major challenges in developing counties (Hughes et al. 2019). Blockchain technology can help solve these challenges by enabling parties to ship and monitor the lifecycle of health products by using its transactional integrity and immutability features. This will in turn improve health and well-being of the citizens (Hughes et al. 2019).

Other Blockchain applications in the healthcare sector include global health data sharing, improved healthcare data audit, improved drug traceability, clinical trials and precision medicine, and health insurance coverage optimization (Yaqoob et al. 2022). Although Blockchain has numerous potential applications in the healthcare industry, it has challenges that still need to be addressed before it can be completely integrated into the healthcare system (Yaqoob et al. 2022). These challenges include scalability, interoperability, regulatory uncertainty, tokenization, irreversibility and quantum computing, and ensuring healthcare data accuracy (Yaqoob et al. 2022).

2.6 Health Informatics

Developing nations are facing serious challenges in delivering healthcare to their citizens (Norris 2002). These challenges are induced by factors such as the rising number of elderly citizens who need care, increasing costs of medical technologies, social, and economic changes that prevent governments from funding healthcare appropriately among others (Norris 2002). The aforementioned challenges increase costs and decrease equity of access to healthcare (Norris 2002). As such, governments and established healthcare organizations are increasingly interested in the ability of Health Informatics to save human lives, time, and money (Shukla et al. 2014). Health Informatics can be described as the science of how health information is collected, analyzed, and used to improve health and healthcare (Fridsma 2018). It involves devices, resources, and methods needed to improve processes for acquiring, recovering, storing, and usage of health and biomedicine information (Oyelade et al. 2015). Health Informatics can be applied in various areas of healthcare, including clinical care, health services administration, medical research and as well as training (Shukla et al. 2014). Health Informatics uses tools such as computers, information and communication systems, clinical procedures, as well as formal medical vocabularies (Oyelade et al. 2015). It also facilitates storage and retrieval of health information in an organized and more precise manner compared to the ability of patients to recall details such as allergies and medications details (Oyelade et al.

2015). This is a critical issue for the patients. Inaccurate or insufficient health information from patients can lead to severe drug side effects (Oyelade et al. 2015). Thus, provision of accurate health information is particularly important. Health Information permits joined-up care, whereby various health departments, e.g., surgery, radiology, laboratory, administration, or account sections, are interlinked (Oyelade et al. 2015). In turn, this facilitates reduction of efforts duplication and also allows processes to be much quicker (Oyelade et al. 2015). Lastly, computerized Health Informatics guidelines enable health professionals and patients to make better decisions. Thus, high-quality treatments and prescriptions can be sustained (Oyelade et al. 2015).

Advanced technology and AI-empowered tools are important in the efficient integration of informatics in Society 5.0. Furthermore, equitable health through Society 5.0 cannot be achieved without the integration of UN-SDGs. The UN-SDGs specific to this subsection are Goal 3 (good health and well-being of a society), Goal 8 (a healthy society with decent work driving economic growth), Goal 10 (reduced inequalities in healthcare systems will have a positive impact on overall reduced inequalities), Goal 11 (preventative medicine through health informatics and exposome data can aid built sustainable cities and communities), Goal 13 (considering climate changes can aid in building sustainable development), Goal 15 (investing in environmental health and education is key in a healthy and wealthy society), and Goal 17 (societies should build partnerships in achieving a smart and healthy society).

Health Informatics can potentially play a key role in the management and delivery of healthcare services in developed and less developed nations (Oak 2007). It can also facilitate the evaluation of healthcare needs of citizens and also the effectiveness and coverage assessment of healthcare programs (Oak 2007). Like other modern and innovative technologies, Health Informatics faces several challenges. These challenges include confidentiality and privacy breaching caused by inadequate security monitoring during data transmission or storage. Another problem is the substandard diagnostic quality of images generated by computers e.g., dermatological or X-ray images. Medical errors can also be induced by insufficiently constructed computerized care methods, insufficient protocols for novel computer-assisted practices, or unavailable or failed technology, among others. Finally, there are issues surrounding the privacy of electronic health records.

2.7 Merging Cyberspace with Physical Space to Improve Women's Health in Low- and Middle-Income Countries

Cyberspace can be described as a digital space where real-world data are collected and analyzed by computers to create various solutions (Deguchi et al. 2020). This is where virtual life or events are converted into applicable information. On the other hand, physical space refers to the real world. Thus, merging these two entities will

permit a smooth flow from the physical world to the cyberspace and vice versa (Deguchi et al. 2020). We envision a society where scientific and technological innovations culminate into the merging of cyberspace and physical space (Deguchi et al. 2020). In turn, this merge can be used to improve women's health and early detection of diseases where strategies and services are decentralized so that all women lead higher-quality lives (Deguchi et al. 2020). This would require a system where women's health information is collected and processed, with the results being applied in a real-world setting, be that rural or urban (Adel 2022). With the current advancement in technology, access to smartphones and other intelligent devices, such ideas should have long been implemented even in low- and middle-income countries (LMICs). Women, in this age of advanced healthcare services, should not be dying from preventable diseases such as cervical cancer. Besides advancements in primary cervical cancer prevention strategies such as HPV vaccines, the disease also has premalignant lesions, which when identified early can be destroyed and their development into invasive cancer can be prevented. These shortcomings are due to failure to merge cyberspace and physical space. Applying Society 5.0 to a subunit of society such as a village or a suburb in a Metropolitan city can provide solutions in an LMIC setting (Deguchi et al. 2020).

In Society 5.0, healthcare social issues surrounding screening programs can be addressed by connecting these programs and using technology to integrate big data, the IoT, and AI to develop digital and physical infrastructure for services such as cervical cancer screening (Narvaez Rojas et al. 2021). Implementation of programs to improve women's health in LMICs faces several challenges. For instance, the current red tape hinders progress in developing services such as building an intersector information integration architecture and striking a balance between the protection and access to personal information. Existing national and district regulations need to be eased so that innovation can be successful (Deguchi et al. 2020). Rural areas in these LMICs currently have little identifiable data management systems, and these should be established. On the other hand, the urbanized part of the LMICs has some regions with data management administered both privately and publicly, and these should be consolidated and coordinated, resulting in the building of intersector information integration architecture (Deguchi et al. 2020).

2.8 Integration of Cyber-Physical Systems in the Advancement of Society 5.0 Healthcare Management

The focal point of Industry 4.0 is efficient and optimal industrial production and data management. It is comprised of cyber-physical systems (CPS) in which the physical and digital worlds are intertwined by the industrial IoT. The aim is to create smart machines/factories that can be utilized in various sectors including health (Adebayo et al. 2019; Popov et al. 2022). Future technological advancements have sparked the

idea of smart or intelligent hospitals. Integration of AI technologies for the processing of high volumes of patient information through big data systems to allow prompt decision-making is essential for the new concepts adapted to Society 5.0 (Lindén and Björkman 2014). Most of the technologies used for monitoring patients' health status rely on embedded systems. The use of glucose/heart rate/blood pressure monitors, magnetic resonance imaging (MRI), computerized tomography (CT) scans, positron emission tomography (PET) scans, etc. has advanced medical diagnostics and monitoring (Lindén and Björkman 2014). These systems permit remote monitoring of patients and facilitate prompt diagnosis and treatment decisions. However, future technologies continue to advance toward nano and smart technologies, including microchips. Society 5.0 is expected to bridge the gap between cyberspace and physical space. To achieve this, Society 5.0 will facilitate the realization of modern smart technologies through the integration of AI algorithms which facilitates big data analytics, IoT, metaverse, robotics, digital twining, Blockchain, and networks-on-chip (NoC) for the optimization of personalized medicine.

The UN-SDG Goals 3, 9, and 10 aim to reduce premature mortality by ensuring good health and promoting well-being (Chotchoungchatchai et al. 2020). These can be achieved by the development of smart industrial innovation and infrastructure which will facilitate the implementation of virtual realities which will reduce the use of invasive health management protocols. The development and availability of infrastructure will reduce global inequalities and ensure global healthcare competitiveness.

The ability to tailor-make healthcare management systems according to specific disease/personalized treatment comes with its pros and cons. Medical CPSs are vulnerable to cyber-attacks making cyber security a big concern. These attacks could be due to terrorism or organized crime. The safety of these technologies must be assured by the development of high confidence, authenticated software that can guarantee security of medical CPS. Software systems handle big data and also guarantee confidentiality and safe keeping of these data while providing easy access to the user are critical. If this data falls into the wrong hands, it could compromise the patient' health, making them vulnerable to discrimination, possible bodily harm, and abuse. The performance of real time applications requires low fault latency to prevent delays that could disturb the operational cycle of medical CPS. This could lead to poor data sharing and consequently affect timeous patient diagnosis and treatment. Lastly, safety for the use of the medical CPS should be assured by issuing operational certificates. The process of approving and validating these devices should be cost-effective, thus ensuring that these devices are distributed to provide required services (Lee et al. 2011). Currently, the cost-effectiveness of medical CPS devices such as robotic systems is not certain as it is difficult to prove that the benefits of robotic surgery outweigh that of traditional open and laparoscopic surgery (Chiu et al. 2019).

2.9 *Society 5.0 and Quality Multidisciplinary Care of Malignant Solid Tumors in Low- and Middle-Income Settings*

Noncommunicable diseases have overtaken infections as the leading causes of mortality globally, including in LMICs. Noncommunicable diseases include trauma, cardiometabolic conditions, and cancer. The average life expectancy of adults in LMICs is less than 70 years, and cancer is the second most common cause of death in adults between the ages of 40 and 60 years. Around 70% of deaths due to cancer occur in LMICs. Breast, colon, prostate, gastric, cervix, uterine, ovarian, hepatocellular, skin, thyroid, and adenocarcinoma of the pancreas are among the most commonly diagnosed malignancies in both LMICs and high-income countries (HICs). The majority of LMICs are not able to provide quality curative or end of life care in oncological services. This is due to the advanced stage of the tumor at initial presentation, shortage of expertise, protracted diagnostic work-up, and limited access to advanced imaging and treatment (Akinyemiju et al. 2022; Hunter et al. 2022; Kenner et al. 2021; Raghupathi and Raghupathi 2020; Sharma et al. 2022). Among the goals contained in the Millennium Development Goals (MDG), UN-SDGs, and Vision 2030 include the provision of quality healthcare in all countries of the world (Araújo 2020; Van Tulder et al. 2021; Rahman and Qattan 2021). UN-SDGs and Vision 2030 specifically include prevention of cancer and improving access to early diagnosis and effective treatment. Technological and computational advances introduced from Society 1.0 to Society 4.0 have led to an even bigger gap in the quality of oncological care between LMICs and HICs. Society 5.0 intends to utilize modern technological development and digitalization to achieve borderless and classless personalized quality healthcare services.

All 17 UN-SDGs are interlinked and support promotion of well-being and healthy lifestyle (Budhathoki et al. 2017; Rahman and Qattan 2021). The pillars of UN-SDG 3 are prevention of diseases, timeous access to quality treatment, and reduction of out-of-pocket expenses (Kruk et al. 2018). Preventative strategies which are contained in UN-SDG 3 are access to clean water, sanitation, health education, immunization, and screening program (Budhathoki et al. 2017). The UN-SDG 3 envisaged that all governments in the world will provide leadership and encourage active participation by private companies including multinationals in programs to improve the health of every individual. Society 5.0, SDG, and Vision 2030 do not have programs which are offered based on the income level of a country. Little has been achieved due to lack of political will, competing needs, tough economic situation, and minimal involvement of the private sector. Collaboration between governments and the private sector would make the technological advances affordable and available in LMICs which would lead to an improvement in the quality of oncological services. Like smart cities, smart oncological services would be safe, convenient, and cheap. Quality multidisciplinary care of malignant solid tumors will allow UN-SDG 3 to be achieved by providing the needed care to improve the health and well-being of the patient.

Implementation of Society 5.0 faces several challenges. It requires investment in the infrastructure which may not be affordable in LMICs. Available health information system, computer network programs, and the Internet speed may not be adequate to support the rollout of the envisaged Society 5.0 programs. Most of the training, development, and testing of the program would happen in HICs which is different from the situation in LMICs. Society 5.0 also threatens confidentiality and autonomy. A fault in the settings of some of the devices may lead to complications. New technology, including robotic surgery or endoscopy may have a negative impact on the teaching and training of future generations of healthcare practitioners.

2.10 Technological Innovations and the Advancement of Preventive Healthcare for Society 5.0

The merits of preventive medicine in LMICs public health systems can never be overemphasized. Paradoxically, their health system capabilities are the most compromised and overstretched due to restricted financial and other resources in these regions. Technological advances that have capitalized on Industry 4.0 are mainly biased toward therapeutics and diagnostics where disease has already established itself. This approach is untenable in LMICs. Although these developments have revolutionized healthcare and dramatically improved the quality of life, these achievements have impacted a fraction of the population in wealthy countries. Therefore, there is a challenge for practical health technological solutions to prevent onset and progression of diseases that is inclusive of most of the poor and disadvantaged populations particularly in LMICs. This is in line with the core principle of the UN-SDGs which is premised on leaving no one behind, and the UN-SDG 3 calls for universal health coverage and health and well-being for all ages. As countries embrace this inclusive vision and collectively aspire for a better society by the year 2030 through the 2030 global agenda, there is a great demand to ensure that everyone succeeds in implementing the UN-SDGs—by using new approaches and tools that help identify and address health inequity in all its forms (World Health Organization 2016). One such approach is to optimize preventive medicine through technology for all vulnerable populations with the additional outcome of easing the burden to the healthcare systems for LMICs.

AI-based applications and sensor technologies for biomarker detection in biofluids face several challenges. High financial cost associated with the use of AI-based applications is a major challenge, which will have a negative impact on people from rural communities and low-income backgrounds who do not have medical aid insurance and do not have access to smart devices or the Internet. Furthermore, the majority of countries in Africa are exposed to poverty and do not have adequate healthcare facilities and infrastructures to support AI-based preventative medicine practices. As a result, there is an urgent need for more cost-effective solutions to tackle this issue. Furthermore, there is also a severe lack of research

funding in Africa, which requires immediate attention from first-world research and innovation funding stakeholders to assist African medical doctors, scientists, and computer and software engineers in developing simple and cost-effective AI-based healthcare software. A major issue with these advancements is the huge financial burden associated with purchasing wearable technologies and smart clothing, which will negatively impact individuals from low- and middle-income households. Furthermore, the majority of people from poor socioeconomic backgrounds, residing in rural areas do not have access to the Internet and wi-fi which is a challenge since wearable technology and smart clothing heavily rely on connectivity networks to communicate the monitored physiological parameters to the user (Ahsan et al. 2022; Chen et al. 2016; Ching and Singh 2016; Mokhtarian and Tang 2013).

2.11 Transformation of the Healthcare Ecosystem in the Era of Society 5.0

The term ecosystem is often used in healthcare to refer to a community consisting of patient and doctor, and all satellite figures involved in the patient care in and out of hospital. The COVID-19 pandemic has given us new lessons and changed the definition of the normal worldwide. Some lessons may be temporary; however, groundwork changes in our approach to healthcare ecosystem design will be necessary to assist in handling challenges of future catastrophes. The healthcare ecosystem is mainly comprised of value creation formula, customer value proposition, as well as partner network. These elements are driven by four business model pillars, namely, management, information, financing, and human resources. The use of AI in healthcare promises to revolutionize healthcare structural reforms in terms of robustness, agility, and accuracy. Digitization of healthcare systems is occurring on several fronts such as cloud-based technology, Blockchain technology, and medical IoT. Many of these health technologies offer a hope to improve access to healthcare to under-resourced communities as well as provide quick often real-time access to patient health data for quick real-time clinical decisions but are not without limitations. Whereas some of these limitations are purely technical, others are born from the risk of compromised patient privacy. These healthcare technologies further improve the wave of precision medicine in the long run. The health ecosystem digital era requires innovations that advance diagnosis and treatment, especially in hospital-based patient care usually by reducing error (Wadhwa 2020). Furthermore, numerous innovations are also required to ensure continuous care through the facilitation of off-site patient management. This can be achieved through telemedicine by reducing waste in the delivery system (Wadhwa 2020). By partnering with individuals to support self-management, digital innovation will positively impact on the social determinants of health (Serbanati et al. 2011).

The healthcare ecosystem transformation should be aligned to the UN-SDG "Good health and well-being" by working toward removing barriers of access to

healthcare using modern technology. An effective healthcare ecosystem will increase access to screening, early diagnosis, and improved accessibility of high-quality medicinal treatment. It can also assist to improve the community and patient's knowledge of cancer, lifestyle modifications, quality of life benefits, and diet. The improved healthcare ecosystem as previously mentioned, can be used to ensure that the patients focus on cure rather than the disease itself. At the same time, access without affordability will be meaningless, and thus, cost-effective funding strategies should also be pursued through collaborative partnerships especially targeting the low-income communities.

Digital technologies provide advantages that are associated with the possibility of remote access to many medical services, and in the last decade have led to the rapid spread of digital medicine. Furthermore, there are several negative factors that have emerged through the diverse use of digital technologies in medicine. These technologies may cause serious harm to the life and health of people and induce significant damage to the society (Mirskikh et al. 2021).

3 Barriers to the Implementation of Society 5.0-Based Healthcare the Energy Crisis

One of the greatest barriers to the implementation of the technologies required for the development of a new smart healthcare system is the lack of resources required to implement them. These include lack of storage capacity, cloud computing capacity, computational power, raw materials for the manufacture of the required hardware, expertise for the design and manufacture of both hardware and software, and perhaps most crucially energy. The implementation of Society 5.0 will require a reliable supply of energy (Kheirinejad et al. 2022). The current energy crisis was already a barrier back when the concept of Society 5.0 was proposed; however, recent events such as the COVID-19 pandemic and the Ukraine–Russia war have exacerbated the crisis. This crisis has important negative implication for healthcare as a whole, since clean, sustainable, and affordable energy plays a crucial role in advancing health (World Health Organization 2022). This clean energy is another SDG, SDG-7, and this goal is aimed at supporting sources of clean energy such as hydro solar, geothermal, sea waves, and wind. In this way, it hopes to decrease the generation of harmful by-products such as CO_2, thereby helping to achieve another SDG-SDG-13 Climate change action (Nam-Chol and Kim 2019; Zengin et al. 2021). The energy crisis is therefore a barrier to not only Society 5.0 but also to attaining the SDGs. This is in part due to an affordability crisis, where the generation of electricity is too expensive (Gabel 2022). This has resulted in some SDGs "going backwards" as families have been pushed into poverty (SDG-1) (International Energy Agency 2023). The affordability of energy will have a direct impact on industries required to support healthcare such as the pharmaceutical industry. The rising cost of energy may force companies to increase the cost of drugs, remove cheaper generic drugs,

and limit the availability of drugs (Hawkins 2022; Stewart 2023). The effect that the dwindling global energy supply on the implementation and use of digital healthcare technologies has is vast. These technologies require a constant supply of power with the IoT requiring power to collect, filter, and transmit data, with some studies indicating that IoT devices can waste up to 30% of the energy they consume (Shah et al. 2022). AI obviously requires energy to run the vast cloud computing networks required to provide the necessary computing power. These concerns in powering the use of Blockchain technology require large amounts of electricity for the validation of all Blockchain-based transactions or records (Schinckus 2022). These technologies have arisen despite most of these technologies using minimal energy. The energy crisis has impacted the entire world; however, these effects are even more damaging and far reaching in LMICs, resulting in these countries not being able to implement these new technologies which are so badly needed in these countries. Even without the energy crisis, it is common in many LMICs for there to be no power or an unreliable or limited supply in many villages and other establishments (Jamal 2015). LMCs would also suffer the most from effects such as increased electricity prices (Stewart 2023).

Many of these concerns can be partially negated by improved energy management, the use and integration of renewable energy systems, and the cautious implementation of these new technologies, so as to not overwhelm the energy supply (Schinckus 2022). An addition to this, it has been shown that many of these new digital technologies can also provide solutions to the energy crisis. AI, the IoT, and digital twinning have allowed for the management, monitoring, and consumption of energy resources (Sifat et al. 2022; Nandury and Begum 2015). Smart grids (SG) would improve the flow of data and electricity within the electricity system networks (ESN) and allow for the replacement of conventional fossil fuel-rich grid with distributed energy resources (DER) (Kumar et al. 2020). These SGs can be designed with the aid of AI and modeled using digital twin in order to assess them before they are implemented (Sifat et al. 2022). IoT can also assist in the implementation of SGs, through the more efficient transfer of power to smart devices and buildings, thus reducing consumption (Pan et al. 2015).

4 Ethical and Legal Challenges in Society 5.0 Next-Generation Healthcare

Many of these technologies that are the basis for the development of healthcare into a Society 5.0 are not without their own problems and issues. These issues include bias, ethical issues ranging from the violation of basic human rights, such as privacy and patient autonomy, to issues of cost and availability to issues around mistrust on the use of these new technologies to issues surrounding racial and cultural bias (Myers et al. 2008). Many of these issues stem from the basic requirement that personalized medicine in Society 5.0 requires vast amounts of information to be gathered about

everyone. This immediately brings the privacy of the individual into question. The rampant and unregulated information gathering through remote sensors, the IoT, and cloud computing means that information can be gathered without patient permission. It also means that an excess of information can be gathered, some of it with no bearing on patient health and well-being. This information can then be sold, known as data brokerage, to commercial companies. This data can also be used for purposes other than health, such as criminal investigations, in a process known as function creep (Xafis 2015). The intensive gathering and analysis of data can also lead to overdiagnosis. Overdiagnoses can lead to a population of hypochondriacs, unnecessary treatment, and unnecessary burden on a healthcare system (Kale and Korenstein 2018). The removal of patient autonomy is another real concern, where there is a fear that the use of AI will result in the patient becoming disempowered regarding the choices made about their own health. AI is by far the most controversial of these modern technologies, with many fears surrounding how untrustworthy or error prone an AI can be. To concerns regarding an AI not being able to adjust its analysis to suit diverse cultures or being prejudiced by learning from race specific data. The lack of transparency when it comes to AI, leading it to be dubbed a black box is an issue of concern for many clinicians. This leads to them not trusting the treatment decisions suggested by the AI because they do not know how it has reached these decisions (Guo et al. 2021). AI is also influenced by the adage garbage in garbage out, where the AI is only as good as the data it is given, or the training data used to teach it. This also highlights problems with the technologies used to gather information in that it is not clear how accurate many of these devices are (Clayson et al. 2021). This coupled with software upgrades and different operating systems or software on different devices leading to data corruption and the extent of mistrust in much of this information becomes clear. Mobile or remote devices also need to be calibrated using an external device. In LMICS, qualified technicians and calibration devices may be in short supply or only available in urban centers. There is also a valid fear that all this information, especially omics information, can be used by AI and digital twin technology for nefarious purposes. These include population control, segregation, and in the most extreme cases genocide (Poghosyan 2020). This all leads to the requirement of new laws and regulatory bodies to control and police these modern technologies, although this raises the question of responsibility. When these technologies fail and harm is caused to a patient, who will be held responsible. This is especially relevant when it comes to AI as the AI itself cannot be held responsible. However, should the manufacturers or designers be blamed or the endpoint users? Additionally, what if the error was caused by what the AI had learnt from other data or previous use. In this case, the manufacturer or designer may not be to blame, while the endpoint user may not possess the knowledge to understand or realize the failure of the system. The best solution may be a list of responsibility for every step of the usage of these new technologies (Dignum 2019). Companies involved in the development of these innovative technologies need to adopt ethical culture and indorse ethical leadership. Figure 4 below shows steps that companies need to take in order to develop an ethical structure (Tzafestas 2018). Despite all these problems, the promise these modern technologies offer cannot be ignored, and

Fig. 4 Steps that regulatory bodies need to take in order to develop new ethical standards in healthcare. Adapted from Tzafestas (2018)

as such, careful deliberation and planning must take place to ensure their ethical design and application for all stakeholders.

5 Conclusion

The implementation of healthcare in Society 5.0 aims to improve the longevity of individuals and allow them to exist with longer periods of good health. It will accomplish this by minimizing the incidence and severity of disease and optimizing medical expenses. Finally, this future healthcare system will provide care over the course of the life of all individuals without prejudice or bias. In order to accomplish this, it will use current and future technologies which are a defining feature of Society 5.0 (Fig. 5). This book will discuss the use of these technologies in the implantation of healthcare in Society 5.0.

The first chapter will discuss the use of Intelligent Bioinformatics in healthcare and outline how it can be used to analyze data to contribute to personalized medicine and healthcare. The second chapter will discuss the care of patients with malignant

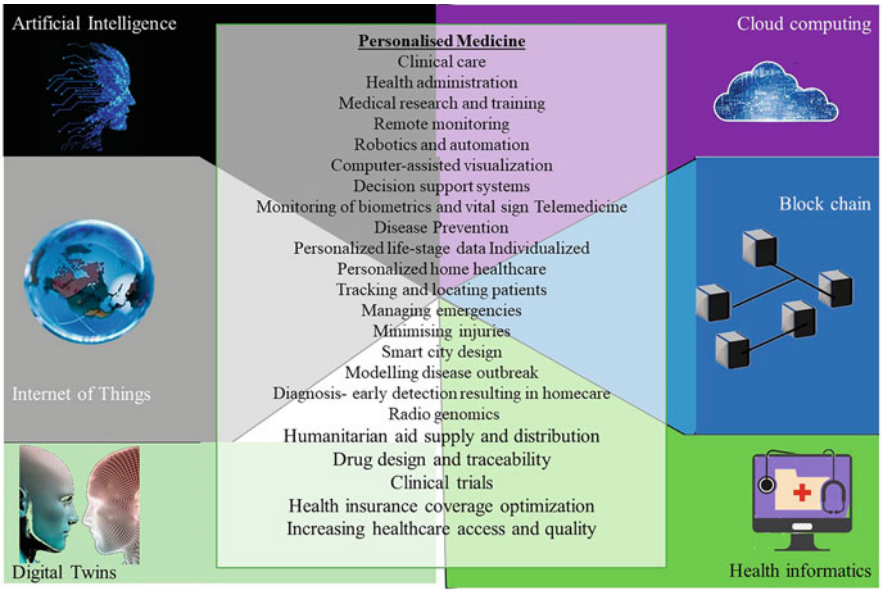

Fig. 5 A summary of healthcare in Society 5.0 detailing the different technologies that will transform healthcare and what they hope to achieve. Compiled by Rodney Hull

solid tumors in LMIC settings in Society 5.0. Specifically, it will discuss the implementation of multidisciplinary care in this setting and how the lives of these cancer patients in LMICs will be improved through the use of Society 5.0-based healthcare. The book will then move on to discuss the use of technology in a smart society to prevent diseases through the implementation of smarter knowledge-based screening and surveillance. It will then discuss the role played by the IoT in gathering the substantial amounts of personalized accurate and up-to-date data required for personalized healthcare. Moreover, it will discuss a specific example of the use of healthcare based on Society 5.0 in the screening, prevention, and management of cervical cancer in an LMIC healthcare setting followed by the use of AI in enhancing drug discovery for a human-centered health system. In addition, it will discuss the role played by digital twins in modeling patients, treatments, and public health in Society 5.0. The following chapter will discuss the implementation of integrated Cyber-Physical Systems in healthcare. This will be followed by a chapter on how the healthcare ecosystem will be revolutionized by the introduction of these technologies and how the interconnected roles and activities of patients, healthcare providers, policy makers, and administrators will be to make healthcare more affordable, robust, and efficient. Data security, privacy, and protection are major concerns for the implementation of this smart, data-driven healthcare system, and the next chapter will discuss the use of Blockchain technology in protecting this data and ensuring the continued safe development and use of large amounts of data to personalized medicine. Finally, this book will discuss the barriers and problems

facing the use of these new technologies. These include legal and ethical issues, issues surrounding the privacy and protection of information as well as issues concerning the safety and trust in these new technologies. These problems can and must be solved for the implementation of healthcare in Society 5.0 since the advantages of this smart information-based, personalized healthcare system would outweigh any drawbacks if it is implemented responsibly.

The digital transformation of healthcare allows for easier access to healthcare as well as giving patients the ability to be more in control of their own healthcare leading to a system that is driven by healthcare professionals and patients working together. It is hoped that this book will provide a comprehensive introduction to the various aspects of healthcare in Society 5.0 and will demonstrate the importance of the future implementation of Society 5.0.

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Health Informatics Applications in Healthcare and Society 5.0

Rahaba Marima, Nompumelelo Mtshali, Pumza Phillips, Thulo Molefi, Richard Khanyile, Zukile Mbita, Mandisa Mbeje, Aristotelis Chatziioannou, Kim R. M. Blenman, and Zodwa Dlamini

Abstract Social determinants are fundamental factors in healthcare and are key in a sustainable society. Society 5.0 concept is based on a future intelligent sustainable society that can enable and drive economic development of its own citizens, while ensuring health equities, social upliftment, and equalities using modern-day technology solutions. The ability of Society 5.0 in data management and analysis renders

R. Marima (✉) · Z. Dlamini
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: rahaba.marima@up.ac.za; zodwa.dlamini@up.ac.za

N. Mtshali
Department of Anatomical Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

AMPATH Laboratory, Lynwood, Pretoria, South Africa
e-mail: nompumelelo.mtshali@wits.ac.za

P. Phillips
Department of Anatomical Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
e-mail: pumza.magangane@wits.ac.za

T. Molefi · R. Khanyile · M. Mbeje
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa

Department of Medical Oncology, Faculty of Health Sciences, Steve Biko Academic Hospital, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: thulo.molefi@up.ac.za; richard.khanyile@up.ac.za; 20785102@tuks.co.za

Z. Mbita
Department of Biochemistry, Microbiology and Biochemistry, University of Limpopo, Sovenga, Mankweng, South Africa
e-mail: zukile.mbita@ul.ac.za

A. Chatziioannou
Department of Anatomical Pathology, School of Medicine, Faculty of Health Sciences, University of Pretoria, Hatfield, Pretoria, South Africa

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health informatics a potent tool in advancing Society 5.0 and healthcare. Health informatics is the intersection of various "informatics" fields, including clinical bioinformatics, biological bioinformatics, image informatics, translational bioinformatics, and public health informatics. Health informatics is key in the implementation and success of Society 5.0, thus enhancing the "health is wealth" concept. Society 5.0 aims at bridging inequality gaps in society through the construction of reliable, equitable, and optimized healthcare system that will benefit all people of its society. However, ethical concerns regarding patient data sharing, management, analysis, and security have been major obstacles in efficient applications of health informatics in healthcare, posing as threats of human rights and privacy invasion and loss of what it means to be human. This chapter will discuss the health informatics applications and their limitations in healthcare and Society 5.0 toward building an equitable super-smart healthcare system and ensuring sustainable development.

Keywords Health informatics · Bioinformatics · Clinical bioinformatics · Translational bioinformatics · Ethics in Health Informatics (EHI) · Omics · Exposome · Society 5.0

1 Introduction

Society 5.0 concept is based on a future intelligent sustainable society that can ensure health equities and drive social upliftment and equalities using modern-day technology solutions (Fig. 1). The ability of Society 5.0 in data management and analysis renders health informatics a powerful tool in advancing Society 5.0 and healthcare. Health informatics is the intersection of various "informatics" fields, including clinical bioinformatics, bioinformatics, image informatics, translational bioinformatics, and public health informatics (Oyelade et al. 2015; Fukuyama 2018). According to the US DoH, healthcare informatics can be defined as the collection, classification, storage, retrieval, and dissemination of recorded knowledge to promote good health and support healthcare delivery. Furthermore, health informatics has been reported to provide predictive, preventative, personalized, and participatory systems of healthcare (Saheb and Saheb 2019; United Kingdom, National Health Services 2002). Bioinformatics combines biology and data science, whereas health informatics combines healthcare and data science. Although genomics was the first

Center of Systems Biology, Biomedical Research Foundation of the Academy of Athens, Athens, Greece
e-mail: achatzi@bioacademy.gr

K. R. M. Blenman
Department of Internal Medicine, Section of Medical Oncology, School of Medicine, Yale Cancer Center, Yale University, New Haven, CT, USA

Department of Computer Science, School of Engineering and Applied Science, Yale University, New Haven, CT, USA
e-mail: kim.blenman@yale.edu

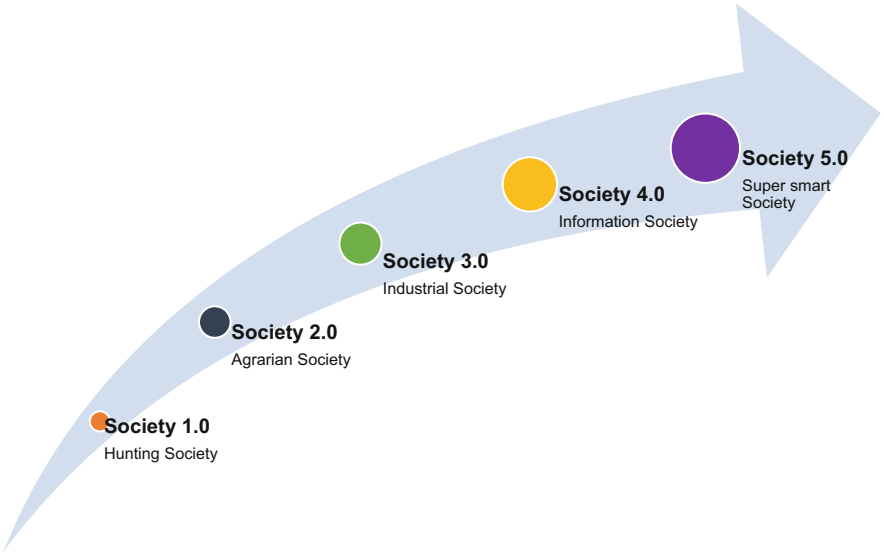

Fig. 1 The next generation of society concept, Society 1.0–5.0. The execution of society concepts dates back to BC years. Information technology continues to play a significant role in the recent society generations

area of biology in which bioinformatics was created/used, bioinformatics is now used for all omics. Different studies conducted on health informatics utilize data-specific levels of human existence. For example, public health informatics makes use of population data, image informatics employs tissue level data, bioinformatics uses molecular data, clinical informatics utilizes patient level data, while translational bioinformatics applies data from various informatics levels, i.e., molecular to population.

Healthcare sector is a fundamental aspect of the economy. For a society to maximally reach its sustainable growth, it is imperative that its members be in mental and physical equilibrium. The state of health of a society's wellbeing is key in its development and success; hence, health is wealth. Healthcare informatics emphasizes on patients' information, patients' knowledge about their clinical information and health data (Oyelade et al. 2015). On the other hand, translational and clinical bioinformatics relate genomics data and healthcare data and are used in all OMICS, aiming to unearth crucial, associative links between the molecular determinants and the phenotypic diversity of diseases. Healthcare data analytics' main objective is to offer cutting-edge information for academic researchers, policy-makers, and clinicians in tackling problems in healthcare organizations. Healthcare data analytics may be divided into predictive analytics, which mainly uses modeling to predict future events in healthcare, while descriptive analytics use historical patient data to gain insights into current trends. Prescriptive and discovery analytics both use Artificial Intelligence (AI) in healthcare. Prescriptive analytics depends on AI to recommend a strategy. Discovery learning examines clinical data using AI to

determine hidden patterns that may inform decision making. Thus, advancing IT tools correlates with society 1.0–5.0 concepts, illustrated in Fig. 1.

Due to large amounts of genomic data generated by sequencing technologies, it is not surprising that bioinformatics is at the core of health informatics. The bioinformatics history can be traced back to 1981 when in situ hybridization was used to map approximately 600 human genes. This initiative was corroborated by when Carruthers and Hood invented an automated DNA sequencing method around the same period. The Human Genome Project (HGP) completion in 2003 also paved a way for bioinformatics where biologists, mathematicians, scientists, statisticians, computer scientists, engineers, etc. converged expertise.

The need to create the bioinformatics field was necessitated by the large amounts of data generated from the human genome sequencing, to decipher and decode genes and how these genes relate to normal physiology and in pathology. Bioinformatics was further enhanced by the demand to produce massive databases such as EMBL and GenBank. These enormous databases are key in storing information and sequences produced from the HGP, and these sequences are thus used as a reference in health and medical research fields. Bioinformatics is not only constrained to "OMICS," but also is inclusive of patients' data from metabolic pathways, preclinical, and clinical trials (Müller and Nicolau 2005). Modern-day main challenges with the available bioinformatics data are minimum to lack of inclusivity of underrepresented groups such as African populations in global genomic studies, the temporal resolution and size of the data collections to as, assure reliable statistical representation of the real problem, as well as mitigation strategies for the inherent bias infiltrating in these collections, due to methodological causes. Overall, bioinformatics alone is insufficient in addressing health-related problems. This chapter will discuss various subfields of health informatics, and how these can be applied in healthcare and Society 5.0. Ethical concerns in health informatics will also be discussed. Health informatics is a convergent concept whose applications have a potential to advance healthcare and Society 5.0.

2 Informatics and Big Data in Healthcare

2.1 Patients' and OMICS Data in Healthcare

Patients' data generate large amounts of data which can be referred to as "big" data. Big data can be described as large amounts of data that is unmanageable by the use traditional software or Internet-based platforms is a concept used to describe complex large volume data sets that may not be optimally processed by traditional data processing methods. The most common way of describing big data is with the 5Vs, with the recent addition of the 6th V, as described in Table 1. These are Volume, Value, Variety, Velocity, Veracity, and Variability. Volume refers to the amounts of large data used. Data amount generated is enormous compared to the conventional sources of data. Velocity denotes the speed of generating new data. This speed is

Table 1 The description of big data in health informatics through the lenses of 6Vs

The 6Vs	Description
1. Volume	Enormous data sets generated and used in health informatics.
2. Value	Good quality of health informatics data.
3. Variety	Complex health informatics data generated from different sources such as machines and humans.
4. Velocity	The high speed at which health informatics data is generated.
5. Veracity	Health informatics data authentication.
6. Variability	The consistency of health informatics data.

exceedingly fast. Variety refers to the data complexity generated by various sources such as people and machines. Veracity refers to the big data authentication, as it is produced from different sources. Value refers to the good quality of the data. Variability deals with data consistency over time (Ristevski and Chen 2018).

In healthcare, distinct sources of big data may include patients' medical records, hospital records, findings from medical examinations, and medical devices that form part of the Internet of medical things (IoMT) (Dash et al. 2019; Laney 2001). Handwritten notes and typed reports have been common practice to store patient medical records. This includes medical examination reports. For example, some of the oldest case reports on papyrus text are from Egypt, dating back to 1600 BC (Doyle-Lindrud 2015; Gillum 2013). However, the electronic/digital storing of patient clinical and medical records using computer systems has become standard practice. Electronic Health Records (EHRs) is a concept that was birthed by the Institute of Medicine in 2003. This Institute is a division of the National Academies of Sciences, Engineering, and Medicine. Murphy et al. define EHRs as the computerized patients' medical records which include patients' past, present, and future. These records consist of physical or mental health information, stored within an electronic system. This information, which forms part of the big data, is used for data storage, transmission, and retrieval with the main purpose of improving healthcare, particularly through population-based or personalized healthcare (Reisman 2017).

On the other hand, big data generated from "OMICS" studies pose a challenge to bioinformaticians. Vigorous algorithms are thus required to analyze such complex "OMICS" data, with the overall aim of converting these big data sets into informative and usable knowledge to improve patient care and outcome. Translational bioinformatics is applying bioinformatics approaches in the transformation of genomics data to preventative and predictive health. Translational bioinformatics is key in data driven healthcare. Likewise, it is reported that the Human Genome Project-based Encyclopedia of DNA Elements project intended to determine all of the functional elements in the human genome employing bioinformatics approaches (Dash et al. 2019). Nonetheless, translational bioinformatics and other single-field bioinformatics approaches are inadequate to address healthcare problems. They primarily emphasize in increasing the value of the collected data, by scrutinizing and restructuring them in ways that unearth fundamental, causative links with the

investigated mechanisms, enabling robust correlation with other layers of digitized information. The integration of various data sets which include healthcare, wellness biomedical, and population-scale data would aid in the stratification of patients toward active health management. Convergence of these data sets will also help differentiate clinically asymptomatic patients from healthy individuals (Shameer et al. 2017).

2.2 *Bioinformatics in Healthcare: Integrating Biology and Bedside*

Efforts in integrating biology and bedside have been growing. Bioinformatics and healthcare informatics are at the forefront of this transformation. Genome- and phenome-wide studies use clinical data from patients' electronic medical records (EMR). Such data may be available from biobanks or clinical repositories (Shameer et al. 2017; Gottesman et al. 2013; Kullo et al. 2010; Kohane 2011; Jensen et al. 2012; Jouni et al. 2013; Bowton et al. 2014; Chute 2014; Jung et al. 2014; Li et al. 2014). Ongoing developments including exposome data (discussed later) in healthcare are also emerging. This type of data evaluates the patient–environment interactions and how these interfaces may impact on patient's health (Shameer et al. 2017; Ashley et al. 2010; Gottesman et al. 2013; Kullo et al. 2010; Kohane 2011; Jensen et al. 2012; Jouni et al. 2013; Bowton et al. 2014; Chute 2014; Jung et al. 2014; Li et al. 2014; Vrijheid et al. 2014; Rappaport et al. 2014; Wild et al. 2013; Martin Sanchez et al. 2014; Lewis et al. 2013; Vrijheid 2014). Clinical bioinformatics (CBI) is a new term in the bioinformatics arena. CBI combines bioinformatics, clinical informatics (including clinical notes, physical data, clinical chemistries complete blood counts, etc.), information technology, medical informatics, omics, and mathematics, thus combining OMICS and clinical data. CBI plays important roles in various clinical applications such as medical omics, metabolic and signaling pathways, high-throughput image analysis, human tissue bank, biomarker development and discovery, mathematical biology, and medicine. CBI aims to address challenges of the integration of clinical and genomic data toward precision medicine and targeted therapies (Xue et al. 2016). Translational bioinformatics is also narrowing limitations between standard clinical research studies and experimental biology, thus bridging the gap between basic science and clinical bioinformatics. Comprehending the complexity of genomic, physiological, and environmental factors in driving healthy physiological states to disease still poses as a challenge to basic and clinical researchers. Clinical studies usually collect data routinely after patients have been diagnosed with a clinically significant disease/pathological phenotype, leading to missed information on healthy and subclinical states, thus limiting chances of early diagnosis and prophylaxis (Wu et al. 2012). On the other hand, health informatics bridges gaps observed in single bioinformatics approaches, employing molecules to populations' approaches, as illustrated in Fig. 2.

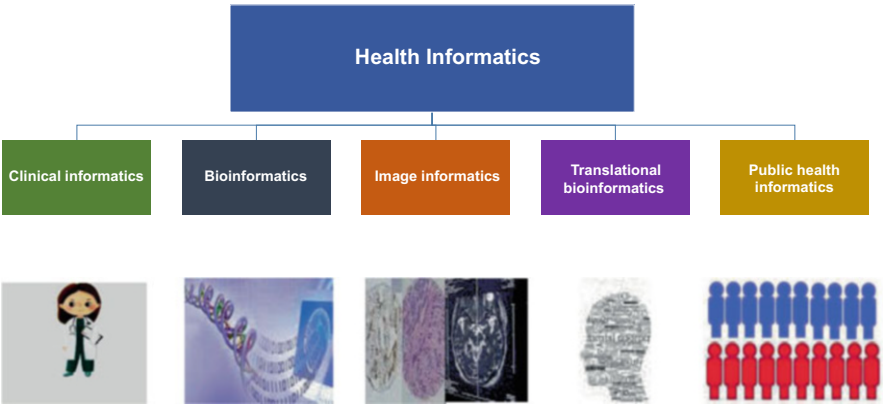

Fig. 2 Subdivisions of health informatics in healthcare. Health informatics is a convergent all-around bioinformatics concept that includes basic bioinformatics to populations-based informatics approaches and is key in advancing Society 5.0

3 Role of Informatics in Equitable Health and Society 5.0

Translational bioinformatics employs data from various informatics levels, molecular to population, and it is at the forefront of health informatics applications. Health and wellness monitoring data can be used to complement EMRs and to inform clinical decisions in various situations. Integration and correlation of health monitoring data with multiomics data can aid interpreting intrapatient variations and between different disease phenotypes. This type of integration holds great potential to studying patients' disease evolution during wellness, disease onset, and disease management (Jameson and Longo 2015). Furthermore, translational bioinformatics applications can also be useful in predictive modeling, diagnostic alerts, and data-driven clinical trials.

The integration of genomic medicine into clinical practice to improve healthcare systems is becoming common in diseases such as cancer, cardiovascular, etc. (Dlamini et al. 2020; Marx 2013). One of the pioneering clinical elucidation of whole genome demonstrated that the index patient was at a greater risk of cardiovascular disease, and this was not indicative with the existing risk prediction models (Katz et al. 2022; Dewey et al. 2014). Bioinformatics has the ability to exploit multiscale biological data to reveal biological pathway dynamics prior and during illness (Chen et al. 2012b; Stanberry et al. 2013), aiding the efficient disease stratification/personalization and contributing to clinically useful diagnostic or therapeutic approaches. Wearable medical devices have been implemented in health monitoring studies targeted at populations of patients with various illnesses which may include osteoarthritis, myocardial infarction, heart failure, and gait imbalance. Bioinformatics also aids in the integration of genomics, multiscale biological experiments, and medical/ health wearable devices in monitoring health and wellness of

Fig. 3 Interplay between health informatics, Society 5.0, and SDGs. Realizing Society 5.0 is dependent on the integration of UN SDGs, in pursuit of equitable health and social upliftment. Health informatics is at the core of this tripartite relationship

patients (Clifton et al. 2014). However, this may be more common in developed countries than in developing countries. Advanced technology and AI-empowered tools are important in the efficient integration of informatics in Society 5.0. Furthermore, equitable health through Society 5.0 cannot be achieved without the integration of UN Sustainable Development Goals (SDGs). UN SDG goals specific to this chapter are 3 (good health and wellbeing of a society), 8 (a healthy society with decent work driving economic growth), 10 (reduced inequalities in healthcare systems will have a positive impact on overall reduced inequalities), 11 (preventative medicine through health informatics and exposome data can aid built sustainable cities and communities), 13 (considering climate changes can aid in building sustainable development), 15 (investing in environmental health and education is key in a healthy and wealthy society), and 17 (societies should build partnerships in achieving a smart and healthy society) (Fig. 3).

For affordable and clean energy, an SDG 7 is crucial in the successful implementation of Society 5.0. This goal is aimed at supporting energy production from nonharmful resources such as hydro solar, geothermal, sea waves, and wind, aiming at CO_2 emission reduction (Zengin et al. 2021; Nam-Chol and Hun 2019). However,

sustainable development and ongoing global energy crisis particularly in low-and-middle income countries (LMICs) is concerning. This propels health systems in LMICs to improve health outcomes and social value for societies toward sustainable development (Kruk et al. 2018). Furthermore, human right to healthcare should be accompanied by good quality and sustainable care. Sustainable energy supply is a crucial determinant of high-quality healthcare and urgent interventions are thus warranted to ensure sustainable development in healthcare systems.

4 IoMT and ML in Healthcare and Society 5.0

The Internet of Medical Things (IoMT) also known as the Internet of Things (IoT) industry has advanced significantly over recent years. IoT is a collective network of devices that connect and exchange data over the Internet (Wilson et al. 2017). Similar to other data management and sharing platforms, privacy and security are the primary concerns of the IoMT. Both AI and Blockchain (BC) technologies have tremendously improved healthcare facilities and spawning a new era of Society 5.0 in healthcare, referred to as Smart Healthcare. This AI/BC concept is quite different from the traditional approach, with the key objective being the identification of concerns early and helping circumvent long-term damage (Rehman et al. 2022). While Society 5.0 aims to improve the quality of life of patients, this will also be accompanied by significant healthcare costs reduction. Similar to robust leaner-centered approach which fosters deep-learning in field of education, Society 5.0 in healthcare aims to engage patients as active participants in their healthcare journey by the integration of information technology and smart-interactive healthcare.

IoMT permits the joining of various objects in collecting data that may be used to enhance human health, which in turn will improve productivity and effectiveness (Risteska Stojkoska and Trivodaliev 2017; Folianto et al. 2015; Park et al. 2019). By connecting to this platform of IoMT, people can attain information on their physical and mental health, their lifestyles, and their surroundings/environment. In this manner, healthcare providers can remotely and in real-time monitor people's health. Simultaneously, the collected data may be used to support evidence-based interventions for early detection, rehabilitation, disease modeling, etc. Climate change and environmental pollution are also key concerns toward sustainable healthcare. Thus, home-based healthcare services are proposed that patients will be allowed medical examinations from the comfort of their homes, unless strictly requiring exclusive hospital services. Smart health monitoring system is proposed to remotely monitor patients' vital signs such as blood pressure, heart rate, etc., through data collection via a wireless connection, thus IoMT playing a fundamental role in smart health.

However, one of the challenges in combining medical data into a solitary location in training a machine learning (ML) has concerns associated with ownership, privacy, and compliance. Contrary to ML, federated learning (FL) overcomes the ML challenges by using a federal aggregate server, disseminating a global learning model. This model allows the local participant to keep control over patient

information, thus ensuring data security and confidentiality. FL is a decentralized ML for IoMT and allows devices to collectively learn ML models without the actual exchange of their authentic data, thus enhancing the smart healthcare system without leaking patient information. AI-enhanced bioinformatics applications are ideal in ML and FL settings. BC on the other hand has been reported to have achieved great success as cyber-security architecture backbone, thus addressing key concerns of security, ethics, and privacy in a smart healthcare system (Nasonov et al. 2018).

Using the IoMT devices, physicians can monitor and measure different parameters from their patients' respective locations. This may create room for early intervention and treatment when necessary and may therefore reduce the burden on the public health system, thereby reducing the costs. These IoMT devices may include fitness/ health tracking removable devices, vital signs monitoring devices, biosensors, etc. However, the reality of the limitation of these devices includes their inaccuracies and the fact they cannot replace real medical devices in a clinical context. Large amounts of patients/ client's health-related data may be generated from such devices. This sort of data has the potential predict and link patients' subclinical and pathological states, when integrated with patients' clinical data such as EMRs and personal health record (PHR) (Shameer et al. 2017). IoMT plays an essential role in the Society 5.0 concept and accessible and equitable health.

5 Social Health in Society 5.0

Connecting healthcare providers and patients beyond the hospital is one of the key aims of social health. This was evident during COVID-19 global outbreak. This sort of communication was expanded, involving social networks and fostering social interaction. This social interaction healthcare feature is reported to open new endeavors of patient-to-patient, patient-to-clinical team communication, as seen in support groups. This social integrated healthcare communication aims to break traditional boundaries of doctor-to-patient prototype (Andermann 2016; Ha and Longnecker 2010). It is also reported that about a quarter of chronic disease patients, including heart conditions, cancer, diabetes, mental health, and other noncommunicable diseases, make use of social networks to share their experiences. Such knowledge, information, and data-sharing platforms may be considered a potential source of big data. Furthermore, social apps and patients' geolocations, in conjunction with their biological information, may aid in understanding patients' social demographics and behaviors. However, invasion of patients' data privacy and human rights may pose as limitations. While these features in the smart healthcare society may promote health equity and sustainability, resource-intensive studies which also require enormous statistical sampling may be avoided. This integrated healthcare model has been tried by various epidemiological studies such as antibiotic misuse, infectious diseases outbreaks, smoking dynamics, etc.

In mental health management, for example, posts and text messages on social networks are an important source of information, utilizing social health to improve

healthcare. Furthermore, Larsen et al. (2015) demonstrated an association between emotional tweets, suicide, and anxiety rates. This illustration reportedly has the potential to offer analysis of expressed mood in real-time, compared to conventional methods such as surveys. Social health forms an integral part of the exposome and overall health informatics. Understanding the association between social, psychological, environmental, lifestyle, exposomal health, and genomics medicine is key in the success of Society 5.0.

6 Exposomics: Molecules, Lifestyle, Environment, and Populations Intersecting

The exposome may be defined as the entire lifestyle and environmental exposures to humans, which affect our internal, genetic processes and may thus serve as disease susceptibility indicator (Fig. 4). Wearable fitness and health monitoring devices and biosensors may aid in understanding and data collection of patient–environment

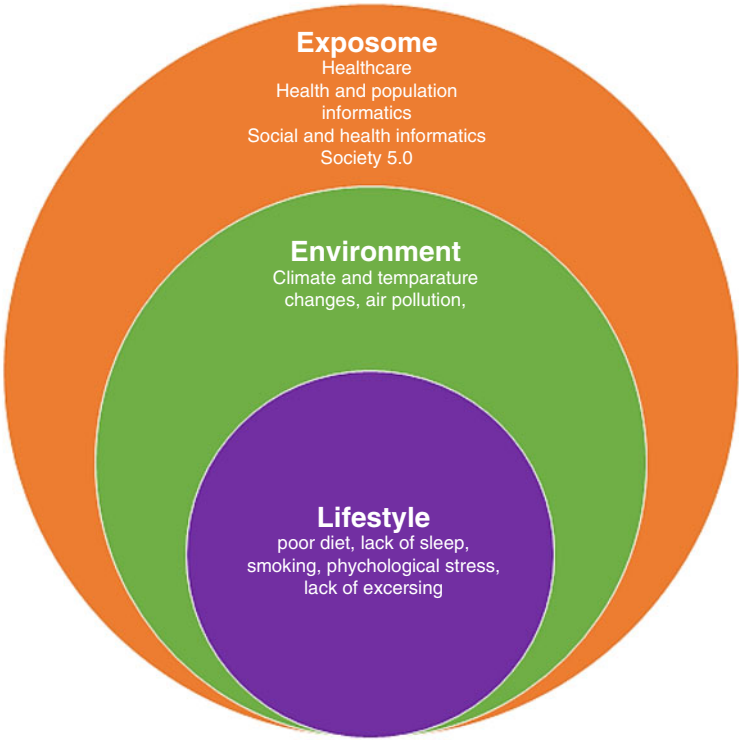

Fig. 4 An overview of the exposome, including environmental and lifestyle factors. Genetic and external factors are now considered active role players in persons' health. Both intrinsic and extrinsic factors are important in patients', populations', and societies' overall health

setting. These devices can help assess patients' environmental conditions such as quality of air, light, ozone, climate changes, and volatile organic compounds. Even though these devices can provide exposomic data, they cannot replace medical devices in the clinical context. (Shameer et al. 2017; Alvarez and Wildsoet 2013; Britigan et al. 2006; Negi et al. 2011; Chen et al. 2012a; Tsow et al. 2009). Integrating the exposome data with EMR and PHR data sets may aid in deciphering how environmental factors affect the healthy and disease states of communities and individuals.

Current human exposome studies focus mainly on the total environment exposures throughout the entire lifespan (Fang et al. 2021). Challenges about real-life exposome applications are constant and accurate interaction of environmental factors together with the entire individual's life. Although autonomy, human data privacy, and security should be considered, such challenges can be overcome by active collaboration between various experts which include clinicians, scientists, epidemiologists, economists, chemists, mathematicians, statistician, and sociologists. The global disease burden has estimated that 50% of mortality can be attributed to environmental factors and lifestyle (Vrijheid 2014; Lim et al. 2012). Simultaneously, a gap still exists in understanding the etiology of complex pathologies. For example, asthma has been reported to have underlying complex interactions between lifestyle, social, and environmental factors (Vrijheid et al. 2014; Martinez 2007). Data collection from physical exposures, chemical exposures, and molecular omics generates massive, big data amounts that require storing, management, analysis, and interpretation.

However, unfortunately, the measurements of environmental factors have not been able to match accuracy in the measurement of genomic factors. This may be attributed to uncertainties in assessing environmental exposures, usually requiring data from different exposure variables. These parameters are usually measured through geographical mapping, questionnaires, lacking a comprehensive approach. Exposomics offers new innovative approaches toward understanding the complexity of multiple exposure factors and associated health outcomes. These new approaches defile one-dimensional methodologies, one risk factor, and one health outcome.

7 Human Rights and Privacy Protection: Rising Ethical Concerns in Health Informatics

The transformation of human societies is inevitable. The opportunities presented by smart societies are coupled with challenges presented by technological revolutions and growth (Aldabbas et al. 2020). These challenges are primarily centered around ethics in health informatics (EHI). Ethics can be defined as the moral principles governing people's behaviors or activity conducting. EHI governs moral practices in healthcare. EHI may be derived from medical ethics, embedded within the Hippocratic Oath, which relies on four pillars, autonomy, justice, beneficence, and

nonmaleficence. Data privacy, security, and confidentiality have raised concerns since the introduction of electronic health records (EHRs) (Séroussi et al. 2020). Ethics is a type of lens used to identify issues and therefore used to enforce best practices that will have good outcomes in the societies. Advances in science and technology have been reported to outpace ethics in healthcare. This simultaneously poses threats in protecting and advocating patient agency and consent in the healthcare system. While attempts to contemporary measures toward mitigating these challenges exist, these efforts still seem inadequate (Goodman 2020). The possibility of data misuse by third parties is a growing concern. Public–private partnerships in AI implementation have been reported to result in poor privacy protection. These concerns include patient data access, use, and control in private hands (Murdoch 2021). Giant tech corporations such as Google, Apple, Microsoft, and others are reportedly in their own ways preparing bids on the health future on different facets of the healthcare industry (Powles and Hodson 2017). These tech giants have in their hands a bulk part of AI-related technology, which is crucial in implementing and sustaining health informatics. Information sharing agreements between public–private institutions may be used to grant these private technology institutions access to patient data (Cuttler 2019). This implies that various applied ethics fields will have to converge with medical ethics and ethics in health informatics to uphold best ethical practices in accessing, sharing, and handling of confidential patient health information. This reality also increases privacy protection risks, leveraging private AI companies to control patient data, despite proposed anonymity.

Healthcare data breaches have been reported in various developed countries such as the United States, European countries, and Canada (Murdoch 2021). While AI-algorithms may be used in advancing health informatics, their inability to protect patient data is also growing. For example, a study by Ji et al. (2019) demonstrated that anonymous health data can be reidentified and linked to real-world people, illustrating the susceptibility of online patient health information (Ji et al. 2020). It has been proposed that AI companies can make use of generative data with the potential to generate realistic though synthetic patient data that will minimize connection to real world people (Yoon et al. 2020; Baowaly et al. 2019). Additionally, there is a need for technologically-enhanced intermittent informed consent for subsequent or new data uses. This will aid in controlling access and use of patient data, advocating for patient agency and privacy. Human rights, privacy, safety, security, and oversight are serious concerns in the successful applications of health informatics in healthcare and Society 5.0. These ethical concerns need to be addressed by collaborating with various stakeholders such as health informaticians, patient advocacy groups, and ethics activists.

8 Limitations and Challenges of Health Informatics in Healthcare and Society 5.0

Major concerns for the implementation of health informatics and Society 5.0 in healthcare include human rights, autonomy, privacy, safety, security, control, oversight, loss of what it means to be human, etc. The misuse of the power of knowledge generated and acquired also poses as a major threat. Even though some of these health informatics' applications may be in use in developed countries, low-and-middle income countries (LMICs) are still lagging, and this may be further exacerbated by the rising energy and resource crisis facing LMICs and threatening sustainable development. Furthermore, even though the intended technological platforms can be efficiently implemented, their use by society members may have unintended undesired side effects (Gladden 2019). For instance, the pervasive Society 5.0 systems may construct new risks of technology-related addiction similar to the addiction of smart phones, Internet, and video game addiction. This is a dangerous critical problem that currently has detrimental impacts on the lives on adults and children. For example, upward of 90% of US population engaging in these activities are obese, have attention deficit/hyperactive disorder, and/or have mental health issues (suicides, depression, etc.). We cannot gloss over these very important outcomes. Compared to the previous society 4.0, where for example employees of a company had to spend limited time with AI robots within a confined workspace, it may be overwhelming for various society members ranging from children, youth, adults, and the elderly people to ubiquitously incorporate such super-smart technologies into their every private space, especially if such devices will be remotely and globally controlled.

On the other hand, the issues of integrating artificially augmented human beings with natural human beings in the society need to be addressed, as the extent to which a natural human being can be artificially augmented is unclear. Even though advanced technologies such as FL and BC are proposed to address data privacy-related issues in health informatics, concerns around data accessibility and security are still alarming. Healthcare patients' data is one of the most valuable information for both the patient and the society. Health informatics inclusive of exposomics may also not be accurately measured, considering all variable parameters involved. Health informatics and exposomics are an ideal concept in advancing the Society 5.0 concept. However, this concept still needs great amount of work to meet feasibility and sustainability.

9 Conclusions

Health informatics holds promising potential to realizing the success of Society 5.0. Good health status of society members is key to sustainable economic development; thus, social health and social determinants should be considered as active

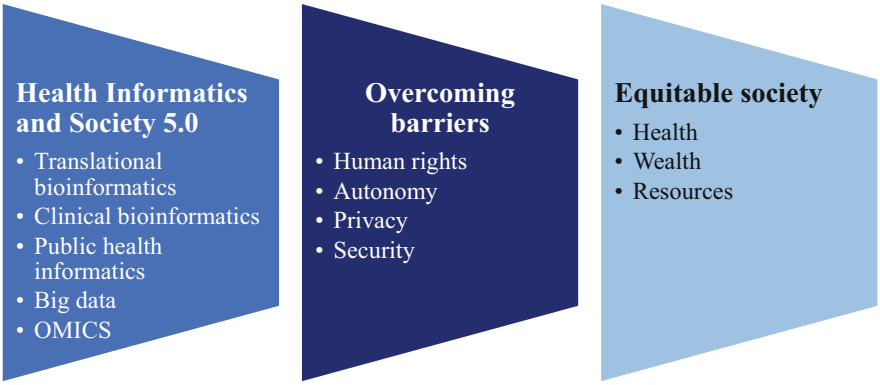

Fig. 5 Applications of health informatics in healthcare and Society 5.0. Barriers such as human rights, privacy, autonomy, safety, and security still pose as a major challenge toward effective applications of health informatics in Society 5.0 and healthcare. Overcoming these barriers may lead to efficient health informatics use and an equitable and sustainable society

participants of this transformation. A healthy society is key to a wealthy and equitable society. Additionally, society concept particularly in healthcare is significantly reliant on the integration of the UN Sustainable Development Goals (SDGs), in pursuit of equitable health and social upliftment. Health informatics is at the core of this tripartite relationship. It is to no surprise that basic bioinformatics approaches are no longer adequate to addressing the preeminent healthcare issues; hence, super-smart bioinformatics approaches are needed to be integrated to an effective and smart healthcare system. Furthermore, clinical and translational bioinformatics approaches are also disintegrated from population informatics and exposomics. Thus, health informatics is a promising approach toward improved informatics applications in healthcare and Society 5.0. Most patients present in the clinics/hospitals with advanced diseases, determining that the preclinical/subclinical states have been challenging to the healthcare professionals. While environmental and lifestyle factors influence health status of society members, integrating the exposome into clinical practice has been challenging. Despite emerging numerous challenges, decentralized ML approaches such as FL also form an important part of the Society 5.0 concept. Nonetheless, major challenges such as human rights, autonomy, privacy, safety, security, control, and oversight still exist in the successful implementation of health informatics and Society 5.0 in healthcare. Thus, counteractive innovative strategies are required to mitigate these challenges (Fig. 5). This chapter sought to discuss opportunities in various subfields of health informatics applications in healthcare and Society 5.0. It has also highlighted how the one-centered traditional approach in healthcare is derisive to Society 5.0. Both intrinsic (genome) and extrinsic (environment, lifestyle) factors play a fundamental role in the society's health. A healthy society is a wealthy society. Disease development, progression, and management are now considered all-round phenomena which warrant active participation from all stakeholders, including leveraging appropriate resources such

as health informatics, and develop approaches that will alleviate opposing barriers toward the effective use of health informatics.

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Society 5.0 and Quality Multidisciplinary Care of Malignant Solid Tumors in Low- and Middle-Income Settings

Thifhelimbilu Emmanuel Luvhengo, Mmamoletla Kgoebane-Maseko, Boitumelo Precious Phakathi, Pumza Magangane, Nompumelelo Mtshali, Demetra Demetriou, Henry A. Adeola, Jyotsna Batra, and Zodwa Dlamini

Abstract The average life expectancy of adults in low- and middle-income countries (LMICs) is less than 70 years. Noncommunicable diseases which include trauma, cardiometabolic conditions and cancer are the leading causes of death

T. E. Luvhengo (✉)
Department of Surgery, University of the Witwatersrand, Parktown, Johannesburg, South Africa
e-mail: Thifhelimbilu.luvhengo@wits.ac.za

M. Kgoebane-Maseko
Department of Anatomical Pathology, Faculty of Health Sciences, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: mw.kgoebane-maseko@up.ac.za

B. P. Phakathi
Department of Surgery, College of Health Sciences, University of KwaZulu Natal, Durban, South Africa
e-mail: PhakathiB@ukzn.ac.za

P. Magangane
Department of Anatomical Pathology, University of the Witwatersrand, Parktown, Johannesburg, South Africa
e-mail: pumza.magangane@wits.ac.za

N. Mtshali
Department of Anatomical Pathology, University of the Witwatersrand, Parktown, Johannesburg, South Africa

AMPATH Laboratory, Lynwood, Pretoria, South Africa
e-mail: nompumelelo.mtshali@wits.ac.za

D. Demetriou · Z. Dlamini
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: dd.demetriou@up.ac.za; zodwa.dlamini@up.ac.za

H. A. Adeola
Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, University of the Western Cape and Tygerberg Hospital, Cape Town, South Africa

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globally. Cancer is one of the two most common causes of deaths in adults between the age of 40 and 60 years. Around 70% of deaths due to cancer occur in LMICs. Cancers of the breast, colon, prostate, gastric, cervix, uterine, ovarian, hepatocellular, skin, thyroid and pancreas are among the more commonly diagnosed cancers worldwide. Majority of LMICs are not able to provide quality curative or end of life oncological care of the individuals who have cancer as they commonly present when the cancer is at an advanced stage, shortage of expertise and protracted diagnostic work-up due to limited resources including access to modern imaging and treatment. Millennium Development Goals (MDG) and Vision 2030 include provisioning of quality healthcare across all countries of the world regardless of the income status and include prevention of cancer and the promotion of personalized oncological care to all citizens of the world. The MDG emphasizes the importance of participation by all the countries and every capable individual in the world, and prevention of environmental degradation. Recent technological developments and advances in computing have increased the gap in the quality of oncological care between LMICs and high-income countries (HICs). The ability to communicate and share information widely is also a potential threat to independence and sovereignty of countries and autonomy of individuals. Advances in computing Society 5.0 is human-centric and promotes physical and cyber space integration in its economic development and innovation framework. Society 5.0 intends to promote human centeredness to make life better for all individuals across the world. Over 70% of mortalities due to cancer occur in LMICs. Quality personalized oncological care requires a multidisciplinary team. The chapter presents a theoretical framework of how the implementation of Society 5.0 would improve access to personalized quality oncological services in LMICs. It concludes with suggestions on how potential threats to the environment, sustainable energy supply, human rights including safety, privacy and security, autonomy of countries, communities and individuals and management of e-waste can be ensured.

Keywords Cancer · Human rights · Low- and Middle-Income Countries · Multidisciplinary Team · Personalized Care · Society 5.0 · SDG · Energy

Division of Dermatology, Department of Medicine, Faculty of Health Sciences and Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa
e-mail: henry.adeola@uct.ac.za

J. Batra
Centre for Genomics and Personalised Health, Queensland University of Technology, Brisbane, Australia

Translational Research Institute, Queensland University of Technology, Brisbane, Australia

School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, Australia
e-mail: jyotsna.batra@qut.edu.au

1 Introduction

The rate of occurrence of cancer has increased exponentially globally and the outcome following treatment is influenced by the income status of a country (Akinyemiju et al. 2022; Bray et al. 2021; Conderino et al. 2022; Maresso et al. 2015; Mathers and Loncar 2006; Miller et al. 2020; Sharma et al. 2022). The life expectancy of individuals diagnosed with cancer in low- and middle-income countries (LMICs) is lower than for those in higher income countries (HICs). The outcome following treatment of cancer in LMICs is worse, regardless of the stage (Petrova et al. 2022; Sharma et al. 2022; Fitzmaurice et al. 2018; Global Burden of Disease Cancer 2019). Among the factors that contribute to poorer outcomes of cancer in LMICs include delayed presentation, poor health infrastructure, limited availability of resources and traditional or religious beliefs (Akinyemiju et al. 2022; Hunter et al. 2022; Kenner et al. 2021; Raghupathi and Raghupathi 2020; Sharma et al. 2022).

Around 50% of cancers occurring in adults are preventable. The most cost-effective strategy in the management of cancer is primary prevention. Primary prevention of cancer entails measures to prevent, detect or treat the cancer early, when it is still localized (Akinyemiju et al. 2022; Conderino et al. 2022; Ekwueme et al. 2022; Maresso et al. 2015; Raghupathi and Raghupathi 2020). Majority of cancers would be curable if the diagnosis is made early and appropriate treatment is instituted timeously (Hunter et al. 2022; Kenner et al. 2021). Some of the challenges that militate against early diagnosis and timeous initiation of therapy in LMICs are high patient-to-staff ratio, inability to provide one-stop services, delayed access to imaging and shortage of expertise for interpretation of imaging or histopathology results (Hricak et al. 2021).

Breast, colorectal, cervical, prostate, skin, stomach, esophageal, hepatocellular, ovarian, uterine, thyroid and pancreas cancer are among the more commonly diagnosed malignant tumors in adults (Maresso et al. 2015; Matulonis et al. 2016; Rompianesi et al. 2022; Ugare et al. 2022; Fitzmaurice et al. 2018; Global Burden of Disease Cancer 2019). The risk factors of the commonly diagnosed cancers in adults include genetics, environmental and lifestyle factors (Ekwueme et al. 2022). Majority of cancers in adult are however sporadic and due to modifiable factors, such smoking, obesity, infections, alcohol misuse, sedentary lifestyle and exposure to harmful agents (Conderino et al. 2022; Ekwueme et al. 2022). Some of the harmful environmental factors that are risk factors for the development of cancer are excessive exposure to ultraviolet light and chemicals. Obesity is prevalent in LMICs and is among the factors that explain the disproportionate increase in the rate of occurrence of cancers in LMICs when compared to the situation in HICs (Franchini et al. 2022; Morrione and Belfiore 2022; Park et al. 2014). Most cancers in adults would therefore be preventable through programs to reduce the levels of obesity and other modifiable risk factors. The cancer prevention strategies would also include a rollout of public awareness campaigns, vaccination, chemoprophylaxis and regular screening program for individuals at risk.

The use of gastrointestinal endoscopy is among the effective tools in some countries for primary prevention of esophageal, stomach and colorectal malignancies (Maresso et al. 2015). Other measures that are utilized for primary prevention of cancer include chemoprophylaxis such as the use of aspirin against colorectal cancer and estrogen receptor modulators or aromatase inhibitors for breast cancer (Conderino et al. 2022; Maresso et al. 2015). Individuals who are confirmed to be genetically predisposed to an aggressive cancer can be offered prophylactic removal of the organ organs that is/are most at risk (Haverkamp et al. 2015). Most of the screening programs including genotyping and prophylactic measures are however not available or affordable to the majority of the citizens in LMICs. Furthermore, some of the citizens of the LMICs may not even be aware of the existence of, as well as risk factors and preventative measures against cancers.

The package for curative or palliative care of patients who have cancer include surgery, radiotherapy, chemotherapy and targeted molecular or radionuclide therapy (Keek et al. 2022; Liberini et al. 2022; Rompianesi et al. 2022; Russo et al. 2022). Clinicopathological staging, genotyping and molecular analysis should precede management of any cancer because cancer is a heterogeneous disease (Vietti Violi et al. 2022; Zhou et al. 2022). The availability of options for curative or palliative management of cancer in LMICs is limited mainly due to shortage of expertise and radiotherapy machines, as well as the currently exorbitant cost of targeted therapy (Hricak et al. 2021). Even where the services are available the timing, delivery and sequencing of neoadjuvant chemotherapy, surgery and radiotherapy is often disrupted leading to poorer outcome.

Over 70% of adult patients who have premalignant and malignant solid tumors require surgical intervention for preventive, curative or palliative intent. Regardless of the intent, the phases along the continuum surgical care of an individual who has cancer include diagnostic evaluation, scheduling of intervention, preoperative preparation, intraoperative management and immediate postoperative follow-up. Each phase, during the management of cancer requires good record keeping which is nonexistent in the majority of LMICs. Additionally, most patients in LMICS present when the cancer is locally advanced or metastatic requiring neoadjuvant chemotherapy, radiotherapy, radionuclide or targeted molecular therapy or complex surgical resection and intensive postintervention care (Sharma et al. 2022). Often the shortage of equipment or consumables, lack of intensive care unit (ICU) beds leads to postponement of cancer operations (Chang and Cameron 2012).

Management of an individual who has cancer is intimate and life-long regardless of whether it is curative or for palliation. The ability to do regular or on-demand follow-up is absolutely necessary as patients on treatment for cancer are prone to complications, tumor progression or recurrence, and opportunistic infections, and thus require close monitoring (Matulonis et al. 2016; Russo et al. 2022). Psychosocial support by the primary physicians, nurses, psychologists and peer groups needs to be readily available to patients who are on treatment for cancer (Hugar et al. 2021). The ability to offer close follow-up in LMICs is limited and recurrence and/or cancer progression is often discovered late. Management of individuals who have

Table 1 Factors contributing to low quality of oncological care in LMICs

Quality dimension	Challenges
Safe	Infrastructure challenges. Workforce shortage. Lack of equipment. Lower level of expertise.
Timeliness	Delayed presentation. Protracted diagnostic work-up. Delayed staging investigation. Delay in surgical treatment. Radiotherapy delay.
Effectiveness	Understaging. No access to bioinformatics. Reliance on TNM staging. Transcriptomics.
Efficiency	Poor record keeping. Precision medicine.
Equitability	Imaging. Genomics. Proteomics. ICU care.
Patient centeredness	Out of pocket expenses. Personalized medicine.
Staff centeredness	Low staff to patient ratio. Low opportunities for training. Poor psychosocial support.

cancer should be by a multidisciplinary team (MDT) as it would be difficult to offer quality personalized oncological care outside an MDT.

The MDT must include patients, families, nurses, dieticians, radiologists, pathologists, pharmacists, anesthetists, surgeons, medical oncologists, radiation oncologists, nuclear physicians, geneticists, physiotherapists, occupational therapists, psychologists, social workers, data specialists, palliative care specialists and peer support groups (Jain et al. 2021; Shao et al. 2019). Most of LMICs are not able to establish MDTs for cancer mainly because of limited human resource (Bukhman et al. 2020; Chang and Cameron 2012; Iragorri et al. 2021; Ng-Kamstra et al. 2016; Sharma et al. 2022). Where MDT is available, the time and attention paid to each patient and family is insufficient because of the high volume of patients. Table 1 summarizes challenges that militate against the provision of quality oncological care in LMICs.

The disparity in the management of cancer between LMICs and HICs is even greater regarding the ability to characterize the cancer and the possibility of micrometastasis (Visaggi et al. 2021; Zhou et al. 2022). Ideally, the volume of tumor must be quantified, and molecular subtype established before the initiation of treatment, even when the tumor is metastatic as it is likely to be heterogeneous in nature and prognosis. Management of cancer in LMICs solely guided by the result of TNM staging which incorrectly considers malignant tumors to be a homogenous disease amenable to standardizable treatment. Unfortunately, cancer is

heterogeneous within itself, at various stages including metastatic sites and in different individuals (Kann et al. 2021). Cancer treatment that is prescribed without knowledge of the full extent of the disease is likely to be ineffective, inefficient or futile (Canzoneri et al. 2019; Rompianesi et al. 2022). Palliative and hospice care in LMICs is usually deficient (Jain et al. 2021). Cancer-related pain, regardless of the stage, is managed poorly in majority of LMICs (Charumbira et al. 2022; Hugar et al. 2021; Mushosho et al. 2021).

2 Technological Development and Advanced Digitalization and Computing Platforms for Society 5.0

The first to fourth Industrial Revolutions (Societies), which include mechanization, enhanced communication and digitalization, were necessitated by the need to improve life and living, to sustain human life (Adel 2022; Fukuyama 2018). The drive behind industrial revolution is to improve productivity for sustenance and enhanced quality of life of humans (Adel 2022; Grabowska et al. 2022; Fukuyama 2018; Kwon et al. 2022; Sarfraz et al. 2021). Societies 1.0 and 2.0 were hunting and agricultural societies, while Societies 3.0 and 4.0 were industrial and information societies, respectively. The technological advances and digitalization in the more recent societies have led to an increase in the ability to generate, store and disseminate data in various industries including healthcare (Conderino et al. 2022; Ioppolo et al. 2020).

Some of the advances in the healthcare industry resulting from Society 4.0 include electronic health information system (Conderino et al. 2022; Nikiforova 2021). Biomarker technology for analysis of malignant tumors and portable or wearable technologies for continuous monitoring have also been introduced (Hernández-Neuta et al. 2019; Hunt et al. 2021; Kwon et al. 2022; Lu et al. 2016; Majumder and Deen 2019). The other innovations include Internet of Things (Al-Kahtani et al. 2022; Sætra and Fosch-Villaronga 2021; Sahu et al. 2021; Dadkhah et al. 2021), telemedicine (Hassan et al. 2022; Johnson et al. 2021; Sætra and Fosch-Villaronga 2021; Shaverdian et al. 2021) and robotics (Marlicz et al. 2020). Developed communities are using the drone technology to improve the delivery of timeous healthcare services (Eichleay et al. 2019; Rosser et al. 2018). The block chain technology is useful for secure storage and transmission of confidential medical records. Block chain technology can also improve efficiency during the performance of surgical procedures (Alsamhi et al. 2021; Carrano et al. 2022; Zhang et al. 2021; Hölbl et al. 2018).

Other advances resulting from modern computing include virtual reality and augmented reality and 3D printing (Lam et al. 2022; Chen et al. 2021a). The application of personal digital twin program enables early diagnosis of cancer and is helpful for prediction of the response of the tumor to treatment (Gumbs et al. 2022; Sahal et al. 2022). The other advances the ability to mine big data (Canzoneri et al.

2019; Rompianesi et al. 2022). Stereotactic-guided adaptive radiotherapy (Keek et al. 2022; Kim et al. 2022), multiomics and artificial intelligence (AI)-guided decision-making (Barragán-Montero et al. 2021; Chen et al. 2021b; Chua et al. 2021) and AI-assisted nanomedicine for personalized oncological care (Adir et al. 2020; Chua et al. 2021; Chen et al. 2021b) are currently possible due to modern technology and computing.

A combination of new technologies and digitalization advancements have led to the development of the so-called "smart cities." Similarly, there is an increasing move toward smart healthcare delivery services (Kwon et al. 2022). Quality healthcare is among the SDGs which were agreed by over 120 countries in 2015 at the United Nation Assembly and is also included in Vision 2030 (Van Tulder et al. 2021). Unlike the Millennium Development Goals (MDGs) which prioritized reduction of maternal and infant mortality, and management of common infections, SDGs and Vision 2030 emphasize on prevention and early treatment of noncommunicable diseases (Bhutta 2006; Vicente et al. 2020). Among the targets contained in Vision 2030 is the reduction of the occurrence of cancers by at least 30% globally and equitable access to personalized care to increase the average quality of life expectancy across all nations to over 100 years.

No country among the LMICs has achieved any of the healthcare-related goals set in Vision 2030. Additionally, the LMICs are not able to benefit from the technological advances and digitalization of Society 4.0 because of lack of infrastructure, prohibitive costs of newer technologies, competing needs, lack of political will and visionary leadership, and minimal involvement by academic institutions and private industries (Ng-Kamstra et al. 2016; Van Tulder et al. 2021). The implementation of Society 5.0 with greater emphasis on collaborative effort among governments, the private sector and academic institutions is however likely to enhance the effort to address the current challenges and inability to provide quality personalized oncological services in LMICs (Mondejar et al. 2021; Rahman and Qattan 2021).

Society 5.0 will most likely expedite the implementation of quality personalized oncological care for all citizens of the world regardless of their gender, age, religion, income status and the country of residence. The subsections below outline how the implementation of technological advancement and digitalization through Society 5.0 would lead to an improvement in the quality of care for cancer in LMICs. Society 5.0 will be effective if it is able to improve the quality of oncological care services across the entire continuum from prevention to the follow-up of every individual who is at risk or diagnosed with cancer.

3 Society 5.0 and Prevention of Malignant Solid Tumors in Adults

More than 80% of malignancies in adults are sporadic and are therefore preventable. The common predisposing factors of sporadic cancer are environmental factors that include smoking, infections, environmental factors, diet and obesity (Quail and

Dannenberg 2019; Wang et al. 2009). The most effective weapon against cancer is prevention and key preventative strategies include immunization, life-style modification, screening and elimination of premalignant lesions (Maresso et al. 2015; Iyengar et al. 2016). Although much of the insight on cancer prevention relies on studies conducted in HICs, key strategies for the prevention of the development of cancer globally include awareness campaigns.

Among the campaigns, include programs to encourage immunization, for example against HIV or HPV. Other activities are encouraging regular exercise, regular screening of common tumors in individuals who are at high risk, chemical prophylaxis and ablation of premalignant lesions or early cancers (Conderino et al. 2022; Fernández et al. 2014; Maresso et al. 2015; Raghupathi and Raghupathi 2020; Sharma et al. 2022; Leatherdale and Rynard 2013). Smart phones, Blockchain technology and Internet of Medical Things (IoMT) would be useful for awareness campaigns. Smart phones can assist in the detection and monitoring of precancerous lesions (Mungo et al. 2021; Phillips et al. 2019). Digital personal twinning and AI can also assist in the timeous detection of pathological changes and autonomous recommendation of subsequent investigation (Chua et al. 2021; Sahal et al. 2022). Other technological advances which are potentially helpful for early detection of cancer is the use of tumor markers (Kenner et al. 2021). The drone technology can also be used for delivery of vaccines and medicines for cancer prophylaxis to remote areas in LMICs (Rosser et al. 2018).

The package of available technologies can help to stratify the level of risk and guide prescription of the most feasible and effective strategies to prevent the development of cancer. The use of telemedicine, Internet of Things, robots and drones can improve access to effective methods for use to prevent cancer even in LMICs (Hassan et al. 2022; Johnson et al. 2021; Rosser et al. 2018; Sætra and Fosch-Villaronga 2021). Other technologies introduced recently for use to screen, diagnose and treat cancer timeously include liquid biopsy (Stewart and Tsui 2018), virtual endoscopy and chromo-endoscopy (Clarke and Feuerstein 2019). Knowledge of the risk factors is essential for the implementation of programs to reduce the incidence of cancer (Leatherdale and Rynard 2013).

4 Society 5.0 During Diagnosis and Staging of Cancers in Adults

Staging provides a format for the uniform exchange of information among clinicians regarding extent of the disease and is used to guide selection of appropriate treatment options (Hudgins and Beitler 2013). The most widely used staging system for cancer is the tumor node metastasis (TNM) system. The TNM system describes the anatomic extent of the cancer and is used before surgical resection of a tumor, i.e., clinical staging (cTNM) or after the removal of the cancer (pTNM). The clinical stage is done at presentation before treatment whereas pathologic stage is assigned

following surgery and posttherapy stage is after the first course of nonoperative treatment. The T part of TNM staging is divided into at least four subcategories (T1 to T4) based on the maximum diameter of a tumor and involvement of adjacent structures. Similarly, nodal and metastatic disease have subcategories. The stage of a cancer before treatment remains the most significant factor to determine prognosis and additional therapy and is used during the reporting of the overall outcome (Hudgins and Beitler 2013). Imaging investigations such as plain x-ray, ultrasound, endoscopic ultrasound, CT scan, MRI and radionuclide scan for staging of cancer are only useful when the size of the tumor or its metastasis is detectable (Kothari et al. 2020; Sah et al. 2019). The TNM staging system is therefore not able to quantify the volume of the disease and is silent regarding the possibility of microscopic metastases.

Radiomics based on findings on CT scan, MRI or positron emission tomogram can assist in accurately diagnose, grade and accurately predict the existence of distant metastases (Kothari et al. 2020). Digital pathology and pathomics also allow for segmentation of the cancer tumor and precise characterization that include tumor grading. The presence of metastases may be predicted following AI-assisted pathological assessment. Recent advances in biomarker technology have led to the use of liquid biopsy for the detection of tumor markers such as tumor associated DNA and cell free DNA (Stewart and Tsui 2018; Wu et al. 2021). Atri (2006), Ehman et al. (2007) and Hillman (2006) reported on the usefulness of biomedical imaging in the staging of cancer, which continues to play an ever more important role during the management of patients following the diagnosis of cancer (Atri 2006; Ehman et al. 2007; Hillman 2006). Among the techniques which are used for biomedical imaging in the staging of cancer is the so called lipidomic-based mass spectrometry imaging (Holzlechner et al. 2019). The benefits of biomedical imaging and pathomics include prediction (Pinsky 2015), screening (Pinsky 2015), biopsy guidance for early detection (Abati et al. 2020), staging (Hudgins and Beitler 2013; Chang et al. 2014), prognosis (Chang et al. 2014), therapy planning (Hongo et al. 2021; Kocher 2020), therapy guidance (Wang and Mao 2020), therapy response (Wang and Mao 2020), recurrence (Cairncross et al. 2020; Xu et al. 2019) and palliation of cancers or their metastases (Chan et al. 2021). Ample opportunities abound in LIMCs to explore application of AI to various imaging data for improvement of oncological care and development of integrated smart health technology (Fig. 1).

5 Society 5.0 and Risk Stratification for Prognostication of Cancer

Cotemporary treatment of cancer emphasizes a personalized approach (precision oncology) regardless of whether the aim is curative or palliative. Precision oncology implies prescribing the most cost-effective treatment for the right patient and

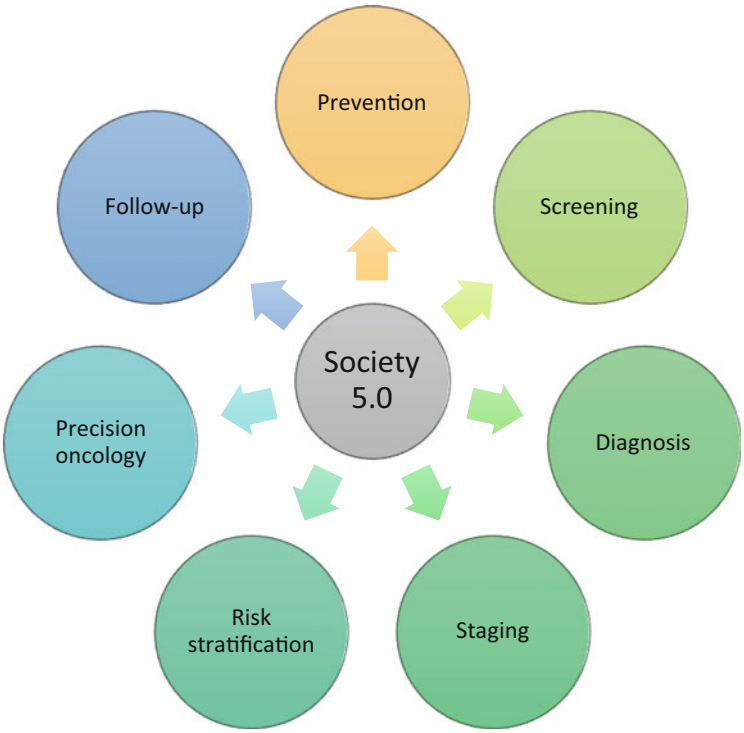

Fig. 1 Areas of potential benefits of Society 5.0 in the management of cancers in LMICs

considering the full extent of the disease while minimizing side effects and the risk of recurrence or progression. The assessment of the extent of disease in the TNM system includes measurement of the diameter of macroscopic disease and whether there are lymph nodes or distant metastases are present. Traditionally curative treatment was reserved for patients who had early or resectable locally advanced cancers. The TNM focuses on the local extent of the cancer and qualitative spread of the tumor and does not quantify the volume of microscopic and macroscopic disease. Notwithstanding, decisions regarding the need of surgical intervention, chemotherapy, radiotherapy, targeted therapy or end of life care in majority of LMICs are based on the TNM which is often not helpful as it tends to under-estimate the extent of the cancer consequently leading to the prescription of treatment that is potentially adequate and ineffective. A select group of patients who have objectively quantified limited metastatic cancer (oligometastatic disease) can be cured (Bong et al. 2021).

Tumor differentiation, ploidy, mitotic count, Ki67 index, evidence and extent of tumor necrosis and immunohistochemical stains are used to risk stratify some of the cancer. Genomics, epigenomics, proteomics and metabolomics are also used for characterization of some of the cancers. Almost all cancers require a biopsy or fine needle aspiration cytology (FNAC) for their confirmation. Both biopsy and FNAC are invasive and may lead to complications such as bleeding or injury to adjacent

structures (Tselikas et al. 2019). Sampling of a cancer either during biopsy or FNAC is limited to a minute area in the tumor and metastatic deposits are almost never biopsied, excluding metastatic lymph nodes following sentinel lymph node biopsy or therapeutic lymphadenectomy (Falk Delgado et al. 2019). Additionally, pathologists tend to sample tiny areas of the biopsy specimen despite knowing that cancer is heterogeneous disease (Tselikas et al. 2019). The heterogeneity of a cancer extends to the tumor microenvironment (TME) in the cancer, which include the different types of cells and the extracellular matrix (Kothari et al. 2020; Lin et al. 2020; Li et al. 2020). Among the cells in the TME of most cancers are the adipocytes, dendritic cells, endothelial cells, fibroblasts, lymphocytes, macrophages and neutrophils (Kothari et al. 2020; Iyengar et al. 2016). The nonmalignant cells and the stroma influence both the initiation, growth and spread of a cancer (Lee and Cheah 2019; Kothari et al. 2020). The other constituents of the TME that can influence the behavior and outcome of a cancer include the level of expression of noncoding RNA such as micro-RNA (miRNA) and long noncoding RNA (lnRNA) (Lee and Cheah 2019).

Cancer and its TME are genetically unstable from the moments it develops and therefore require frequent repeat sampling or biopsy to keep pace with metamorphosis of the primary tumor and its metastasis (Tselikas et al. 2019). Although liquid biopsy and quantitative or digital PCR and next generation sequencing are useful for characterization of cancers, they require invasive sampling and currently are relatively expensive and not freely available for patients in LMICs (Tselikas et al. 2019; Chen and Zhao 2019). Advances in imaging and computing have led to the use of AI for virtual biopsy (Sah et al. 2019). Collation of information obtained following imaging with ultrasound, CT scan, MRI and PET can accurately diagnose a cancer, its grade, genomic landscape, molecular subtype. Radiomics is also able to predict the likelihood of metastases and metastatic sites, how the cancer is going to respond to treatment, the likely side effects, tumor recurrence and the prognosis (Sah et al. 2019; Yu et al. 2021). Furthermore, radiomics can characterize the entire cancer, TME and all its metastatic deposits without the need for biopsy or histopathological analysis. Another benefit of radiomics and virtual biopsy is the possibility of regular repeat imaging to track the genetic changes.

6 Society 5.0 Facilitation of Multidisciplinary Decision-Making in the Management of Cancer

Cancer is a heterogeneous and complex disease which requires a collaborative and MDT approach to its management. Since its introduction in the early 1990s, the MDT approach in cancer care is recognized as a critical aspect in cancer care and is now regarded a "gold standard" in the management of cancer across the world including in LMICs (Hoinville et al. 2019; Selby et al. 2019). Quality personalized oncological care would not be possible outside and MDT. The MDT for

personalized oncological care should comprise of various specialists involved in the treatment of cancer. Depending on the site of the cancer, the team-members may vary, but must include at least surgeons, medical & radiation oncologists, radiologists, pathologists, geneticists, palliative care, specialists, social workers and psychologists. To ensure effective and continuity of care, effective communication is essential among all team members and this can be achieved through regular, coordinated MDT meeting, which serves as a platform for collaborative, not competitive, discussion and treatment decision-making by all team members involved in the care of the cancer patient (Pillay et al. 2016). Moreover, the meeting also serves as a teaching and learning platforms for all members, including trainee specialists. The MDT may in turn help improve the knowledge and work satisfaction of all team members and identify key research questions for translation research which will further enhance the quality of care offered to patients.

Several studies have confirmed the positive impact the MDT meetings have in the treatment decision-making for patients with cancer (Hoinville et al. 2019). Around 4% to 45% more patients discussed at MDT meetings receive accurate preoperative staging and comprehensive cancer care than those who were not (Pillay et al. 2016). However, there is still conflicting evidence as to whether MDT meetings improve the overall and disease-free survival of patients with cancer (Hoinville et al. 2019; Pillay et al. 2016; Selby et al. 2019).

The following principles are essential for the success of MDT meetings:

- The chair of the meeting should be decided on by the team and the terms of reference should be agreed upon by all members.
- Multidisciplinary team meetings should be held regularly, preferably on a weekly basis.
- All patients diagnosed with cancer must be discussed at the MDT meeting before any treatments can be offered. This will ensure that comprehensive diagnostic and staging work up, treatment plan and the follow-up thereof is discussed and decided on upfront.
- They should be "patient-centered" as opposed to being "disease-centered." After the discussion and the treatment plan has been made, it is important that the patients be made aware of the stage of the cancer, the decision taken, available treatment options, and the predicted outcome to allow the patients to make informed decisions. Moreover, patients' preferences should also be taken into consideration provided they are well-informed preferences.
- Prior to the meeting, all cases to be presented should be thoroughly prepared and shared with all team members.
- All decisions taken at the meeting should be documented.
- All team members should take responsibility for all decisions made and commit to implementing them.
- A follow-up meeting with team members and the patient should also be considered to monitor the response of cancer to treatment, patient's adherence to treatment and tolerability to systemic therapy given (Hoinville et al. 2019; Pillay et al. 2016; Selby et al. 2019).

Among the technological advances that would introduce "smart" running of MDT meetings and processes is the Blockchain technology for secured record keeping and communication between patients and healthcare practitioners or among staff members, teleconference and IoT. The use of digital technology would either reduce or eliminate the need for travelling, waiting times and poor record keeping. Facilitation and enabling access to MDT and adoption of artificial intelligence-guided decision-making would lead to an improvement in the quality of oncological services by every individual throughout the world.

7 Society 5.0 and Precision Oncology in the Management of Cancer Including Surgical Treatment, Radiation Therapy, Chemotherapy, and Targeted Molecular and Radionuclide Therapy

Vision 2030 for health emphasizes elimination or reduction of the known risk factors of cancer, early detection and waiting time for treatment (Van Tulder et al. 2021). The roll-out of digital surgery as part of Society 5.0 will lead to timeous, effective and efficient personalized oncology services. Among the technologies which would assist in early detection of cancer include the use of smart phones (Hernández-Neuta et al. 2019; Kwon et al. 2022; Majumder and Deen 2019; Hunt et al. 2021), wearable monitoring devices (Lu et al. 2016), Internet of Things (Al-Kahtani et al. 2022), telemedicine and teleconsultation (Johnson et al. 2021) and Blockchain-enabled (Zhang et al. 2021), augmented or 3D-guided, video-assisted or robotic surgery including endoscopy (Carrano et al. 2022; Chen et al. 2021a; Kwon et al. 2022; Lam et al. 2022). Other technological advances in the healthcare industry include computer aided autonomous action surgery (Gumbs et al. 2022), intelligent knife for determination of adequacy of the excision margin to reduce the rate of tumor recurrence (Hänel et al. 2019), computer aided virtual surgery or endoscopy (Chen et al. 2021a; Gumbs et al. 2022), virtual biopsy (Balana et al. 2022) and AI-guided decision-making including surgical treatment (Hashimoto et al. 2018). The use of AI may also reduce waiting by facilitating preconsultation automatic ordering and performance of some of the diagnostic investigations (Li et al. 2021). The Blockchain technology and IoT also enable safe storage and/or sharing of information related to cancer awareness, treatment or follow-up by practitioners and patients (Carrano et al. 2022; Hölbl et al. 2018). Smart oncology services allow for shared intraspecialty services to timeously and collectively manage the load of patients needing imaging, evaluation of pathology slides, chemotherapy, radiotherapy, radionuclide therapy or nanotechnology-based treatment (Adir et al. 2020).

The mainstay for treatment of premalignant or early malignant tumors in adults is surgery. Adjuvant radiotherapy, chemotherapy or targeted therapy is added if the probability of local or systemic recurrence is high based on the results from multiomics and digital twinning. Smart technology is also helpful for scheduling

to improve for example theatre efficiency which lead to a reduction in waiting time and cancellation of surgical procedures (Kwon et al. 2022; Lam et al. 2022). The Blockchain technology platform is excellent for monitoring of equipment for malfunctioning and timeous replacement of equipment and consumables (Carrano et al. 2022). Technological advances and digitalization have led to an improvement in the safety, efficiency and effectiveness the intraoperative phase of surgery through computer aided training in for example minimal access surgery, adoption and the use of MAS (Humm et al. 2021). The other strategies to improve safety and efficiency of surgery in LMICs would be through teaching and training of video-assisted surgery, robotic endoscopy and surgery and block chain aided surgery (Caruso et al. 2016; Marlicz et al. 2020). Additional aids for efficient oncological care include fluorescence angiography-guided surgery, AI-assisted display virtual and/or augmented reality facilitated surgery and AI guided intraoperative assessment of the adequacy of the resection margin of a tumor (Hänel et al. 2019; Phelps et al. 2018; Santilli et al. 2020). Some of the additional benefits of smart-driven and digitalized surgery include realistic scheduling of operations, reduced blood loss and therefore the need for blood transfusion, quicker surgery, fewer postoperative complications, shorter hospital stay and improved record keeping (Lam et al. 2022). The same components of smart healthcare services such digital twinning and AI are used to guide AI-enabled personalized treatment of a cancer using radiotherapy, chemotherapy and targeted therapy (Adir et al. 2020; Keek et al. 2022).

8 Society 5.0 During Follow-Up After Treatment of Cancer

The commonly used unit to measure of outcome in the management of cancer is 5-year survival rate which is defined as: "The percentage of people in a study or treatment group who are alive five years after they were diagnosed with or started treatment for a disease, such as cancer." Follow-up during treatment of cancer at appropriate interval is mandatory but is often influenced by socioeconomic circumstance of individuals which may affect the application of protocols and negatively affecting outcomes (Strasser-Weippl et al. 2015). Follow-up guidelines for malignant solid tumors are curated by various international bodies, at the helm of which is the World Health Organization (WHO)'s cancer division. The guidelines are similar, influenced by geopolitical occurrences and the relevant bodies are constantly communicating through intercontinental periodic conferences ensuring regular updates and continued medical education of the treating healthcare professionals (Table 2).

The table above only focuses on medical oncology. These have their surgical and gynecological counterparts internationally. The main specialties involved in the management of cancer are medical oncology, surgical oncology and radiation oncology. Pillars of follow-up are surgical, medical, radiological and psychological all of which are supported by medical laboratory workup. Follow-up focuses on relapse and remission and is further guided by whether treatment was curative or palliative (Galjart et al. 2022). Terminology in this field of follow-up of cancer is

Table 2 Nonexhaustive list of institutions providing guidelines on cancer management

At the helm	Continent	Institute
WHO	USA	National Institute of Health: National Cancer Institute American Society of Clinical Oncologists
	Europe	European Society for Medical Oncology (ESMO)
	South America	Latin American and Caribbean Society of Medical Oncologists
	Africa	The South African Society of Clinical and Radiation Oncology
	Middle East	Arab Medical Association against Cancer
	Australasia	Clinical Oncology Society of Australia Pan Asian Guidelines Association (ESMO-PAGA)
	Canada	Canadian Association of Medical Oncologists

either broad or very specific with "active surveillance" being reserved lingo specific to the field of prostate and colorectal carcinoma follow-up. The general approach to the follow-up of cancer includes history taking which should cover symptoms, previous diagnosis, clinical stage, treatment received, physical examination, laboratory tests and imaging. Approaches are varied and may either be symptom based or follow strictly protocolled intervals (Fig. 2).

Follow-up is not only limited to the initially diagnosed cancer, but it also includes screening for secondary cancers and other adverse events resulting from cancer treatment. The level of surveillance is guided by the type and stage of a cancer, its treatment and predicted prognosis. Follow-up intervals for cancer are directly related to survival rates and are usually designed over a 5-year period or longer. Survival is measured over a 5-year period, thus 5-year survival. Factors influencing success of follow-up include the socioeconomic status, lifestyle, patient compliance, psychological factors and stage at presentation (Dührsen et al. 2019). At the heart of Society 5.0's value system is the use of modern technological development and digitalization to achieve borderless and classless personalized quality healthcare services. We have seen major roll out of 5G fiber-based Internet infrastructure in South Africa. This is however undermined by an unreliable national electrical grid. As the wealth gap grows wider, Society 5.0 ideals around societal equality will be hard to achieve, especially in poorly under-resourced African health sectors unless if there is an improvement in the collaboration between governments and private companies. This is further confounded by newfound reasons for war and climate change among others, which are already showing the extend of under-development in LMICs which was the onset of the severe acute respiratory coronavirus-2 (COVID-19) pandemic.

Alas! There is always a light. Life always finds a way. Using what we already have at our disposal, African countries may create a functional version of Society 5.0 in the context of cancer follow-up. The patient care system adapted by Lesotho, if well innovated, can serve African patients and elevate patient care and cancer follow-up on the continent as patients are taught to take full responsibility of their own clinical records. The average patient in Lesotho can produce such a booklet regardless of where they may find themselves on the continent, assisting healthcare

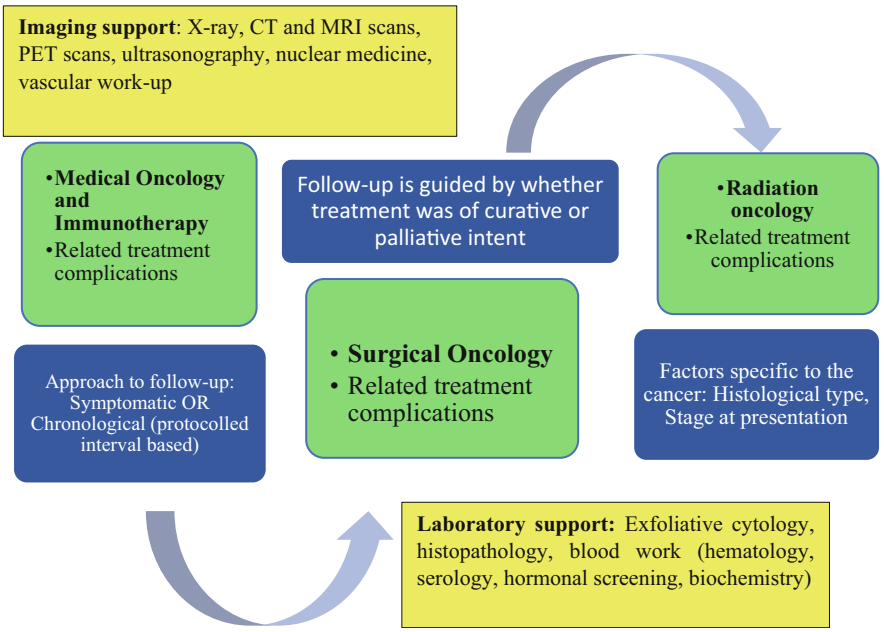

Fig. 2 Key areas: follow-up of a patient during management for cancer

professionals immensely. The Society 5.0 approach would translate this simple yet affective approach into a mobile app that will be able to accommodate laboratory and imaging results, as well as any procedures and medical treatment administered with each visit, this information would be available on secure clouds, accessible to both the patient and the treating team. Collaboration with the private may also make what appears daunting achievable even in LMICS (Hellowell 2019). The Granted this would be marred by all manner of hacking and other cyber-negativities, but the value of such an approach would add much value in the following ways:

- Reduction and eventual elimination of duplication of expensive investigations.
- Valuable information resulting in efficient cancer follow-up such as laboratory and imaging results from each visit.
- Ease of evaluation of trends and availability of statistics for research.
- Shared responsibility for individuals' health among healthcare professionals and patients themselves, a practice that is long overdue.
- Allowed sharing of such information would assist MDT efforts, making these time-consuming efforts more effective.
- Facilitation of remote consulting by well-educated healthcare professionals, at the patient's fingertips.

The one thing a patient will always have with them is their mobile phone. With these devices becoming more affordable, supported by strong Internet service provision, Society 5.0 could be just a few months away on the African continent.

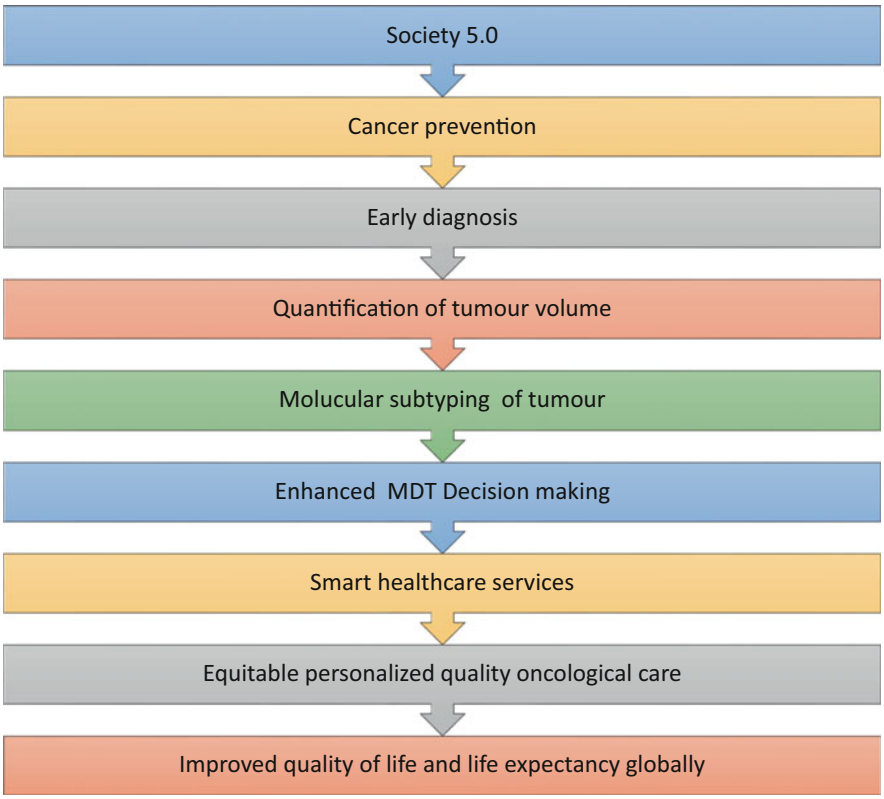

Fig. 3 Potential benefits of the application of Society 5.0 in oncological care in LMIC

Figure 3 is a summary of what would be achievable following the implementation of Society 5.0 during follow-up and other phases of management of individuals after a diagnosis of cancer.

9 Society 5.0 for Sustainable Development Goals and Vision 2030 in Low- and Middle-Income Countries

Quality healthcare delivery is influenced by the economic status of a country and access to quality healthcare has a positive influence on the economy (Rahman and Qattan 2021). The main aim of the agreed 17 SDGs was to encourage countries to collaborate among themselves and with multinational companies to implement programs to enable UHC. The 17 SDGs are:

(a) Measures to end poverty (SDG1).
(b) Food security and defeating hunger (SDG2).

(c) Good health for every individual regardless of the economic status (SDG3),
(d) Universal high-quality education (SDG4).
(e) Ending gender discrimination (SDG5).
(f) Increasing access to clean water and basic sanitation (SDG6).
(g) Affordable clean and reliable energy (SDG7).
(h) Facilitation of economic growth and employment opportunities (SDG8).
(i) Innovation and industrial development (SDG9).
(j) Lowering of within-country and global inequality (SDG10).
(k) Sustainability of communities and cities (SDG11).
(l) Responsible production and consumption of goods (SDG12).
(m) Reduction of the speed of climate change (SDG13).
(n) Protection of life in water (SDG14).
(o) Safeguarding life on land (SDG15).
(p) Strong governance, peace and justice.
(q) Promotion of intergovernmental partnership and collaboration between governments and multinationals (SDG17) (Mondejar et al. 2021).

All 17 SDGs are interlinked and support promotion of well-being and healthy lifestyle) (Rahman and Qattan 2021; Budhathoki et al. 2017). The pillars of SDG3 are prevention of diseases, timeous access to quality treatment and reduction of out-of-pocket expenses (Kruk et al. 2018). Preventative strategies which are contained in SDG3 are access to clean water, sanitation, health education, immunization and screening program (Budhathoki et al. 2017). The SDG3 envisaged that all governments in the world will provide leadership and encourage active participation by private companies including multinationals in programs to improve the health of every individual. Society 5.0, SDG and Vision 2030 do not have programs that are offered based on the income level of a country. Little has been achieved due to lack of political will, competing needs, the difficult economic situation and minimal involvement of the private sector. Collaboration between governments and the private would make the technological advances affordable and available in LMICs, which would lead to an improvement in the quality of oncological services. Like smart cities, smart oncological services would be safe, convenient and cheap. Quality multidisciplinary care of malignant solid tumors will allow SDG3 to be achieved by providing the needed infrastructure to improve the health and well-being of individuals who either are at risk or have cancer. Society 5.0 like SDGs and Vision 2030 emphasizes human centeredness and universal health coverage. There would not be anything that is a preserve of citizens of HICs or individuals who are able to access private healthcare. Society 5.0 will therefore increase cancer awareness, education on cancer prevention, early diagnosis, monitoring, timeous and cheaper access of patients to healthcare practitioners and multidisciplinary oncological services through platforms such telehealth, Blockchain technology, IoT and AI.

10 Limitations

Society 5.0 is reliant on solidarity and willingness to collaborate by countries and private companies. Implementation of Society 5.0 will require investment in the infrastructure the cost of which may appear prohibitive and not be affordable for LMICs. The available health information systems, modern computer network programs and speed of the Internet may not be adequate to support the rollout of the envisaged Society 5.0 programs. Most of the training, development and testing of the program would have happened in HICs and thus different from the situation in LMICs. The ethics and governance of the use of the new technologies and digitalization is still being debated. Society 5.0 also threatens confidentiality and autonomy. Some of the decisions that are guided by AI and other technologies may be difficult to defend ("black-box"). A fault in the setting of some of the devices may lead to complications. The nature or sample size used for modeling might have been inappropriate or inadequate, leading to faulty decisions. New technology including robotic surgery or endoscopy may have a negative impact on hands-on teaching and training of future generations of healthcare practitioners, and provision of healthcare in resource-scarce LMIC settings. Reliance on imported technologies associated with Society 5.0 developed or funded by HICs or multinational companies may make LMICs vulnerable to exploitation.

The rollout of Society 5.0 may threaten the autonomy and independence of countries, communities and individuals. Society 5.0 relies on the ability to share information, which may violate confidentiality and practitioner-patient relationship. Implementation of Society 5.0 will require a reliable supply of energy, clean water and network for communication (Kheirinejad et al. 2022). The technologies which would facilitate the implementation of Society 5.0 were developed in HICs may not necessarily be compatible and effective in the LMICs. New technologies may produce substances which are hazardous and can lead to the degradation of the environment. There are not yet effective strategies developed to dispense with electronic waste (e-waste) (Bajpai and Srivastava 2022).

11 Recommendation

Governments, academics institutions and multinational companies across LMICs must work together to prepare the infrastructure for Society 5.0 as it is likely to assist in improving access to quality and patient-centered for all citizens of the world regardless of the economic status.

12 Future Prospects

Automatic referral for screening following early detection of features suggestive of cancer uses technology like facial recognition system, smart phones and wearable technology. Such features would include nonintentional reduced physical activities or weight loss, altered dietary habits abnormal per vaginal bleeding, skin lesions, anemia and jaundice. The other possibilities from technological, digital and computing include smart phone-enabled virtual liquid biopsy for early detection of circulating tumor cells and hand-held mass spectrometry for liver or lung metastases in exhaled air.

13 Conclusion

The majority of cancers are occurring in LMICs where resources are limited. Cancers in LMICs are diagnosed late, and results of curative treatment are poorer in LMICs when compared with HICs. The most effective weapon against cancer is primary prevention. Primary prevention of cancer includes risk reduction, screening and early diagnosis followed by timeous treatment. There is minimal progress in the fight against cancer in LMICs despite the ambitious goals contained in the SDGs and Vision 2030. The chapter has covered some of the Society 5.0 strategies, which may be used to lower the incidence of cancer, expedite diagnosis and improve access to personalized quality oncological services to individuals who are diagnosed with cancer globally, including in LMICs. Despite the limitations of Society 5.0 such as the violation of human rights including security, safety and privacy, energy waste, etc., the benefits can outweigh the limits with proper oversights and management.

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Technological Innovations and the Advancement of Preventive Healthcare for Society 5.0

Zilungile Mkhize-Kwitshana, Pragalathan Naidoo, Leony Fourie, Rupert C. Ecker, and Zodwa Dlamini

Abstract There have been significant developments in the digitization of diagnostic and therapeutic regimes of the healthcare sector. However, the preventative medicine practice is lagging in taking full advantage of the rapidly advancing world of technology. This chapter summarizes the latest developments in both therapeutics and diagnostics in the healthcare settings, including surgical robotics, telemedicine and artificial intelligence. Then, we explore traditional methods of disease prevention and their challenges, consider the technological developments such as advancement of data analytics methods including geospatial surveillance for disease prevention such as heart disease, stroke and other chronic diseases, and, in

Z. Mkhize-Kwitshana (✉) · P. Naidoo
Department of Medical Microbiology, School of Laboratory Medicine & Medical Sciences, Medical School Campus, College of Health Sciences, University of KwaZulu-Natal-Natal, Durban, South Africa

SAMRC Research Capacity Development Division, South African Medical Research Council, Cape Town, South Africa
e-mail: mkhizekwitshanaz@ukzn.ac.za; naidoop5@ukzn.ac.za

L. Fourie
Department of Surgery, University of the Witwatersrand, Parktown, Johannesburg, South Africa
e-mail: info@fouriesurgery.co.za

R. C. Ecker
Translational Research Institute, Woolloongabba, QLD, Australia

School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia

R&D Department, TissueGnostics GmbH, Vienna, Austria
e-mail: rupert.ecker@tissuegnostics.com

Z. Dlamini
Translational Research Institute, Woolloongabba, QLD, Australia

SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: zodwa.dlamini@up.ac.za

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preventive healthcare, practice and identify gaps in the latter. Challenges of big data related to safety, resource limitation, energy crisis, data ownership and ethics are highlighted. Lastly, we propose adoption of health technology advances for individual health data integration into predictive, precision, participatory and preventive health medicine.

Keywords Preventive medicine · Healthcare · Therapeutic healthcare · Diagnostic healthcare · Low- and middle-income countries · SDGs · Energy crisis · Human rights · Data ownership

1 Introduction

The definition of health by the World Health Organization (WHO) refers to holistic wellness as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO 1946). In this context, the concept of prevention of disease is part of this latter description of health. The merits of preventive medicine in low- and middle-income countries (LMICs) public health systems can never be overemphasized. These countries inadvertently bear the heaviest burden of disease since they have highest numbers of poorer populations most at the risk for both communicable and noncommunicable diseases (Lopez and Murray 1998). Paradoxically, the health system capacities and capabilities are the most compromised and overstretched due to restricted financial and other resources in these regions (Ritchie et al. 2016). The technological advances that have capitalized on the fourth industrial revolution are mainly biased toward therapeutics and diagnostics where disease has already established. This approach is untenable in LMICs. In addition, although these developments have revolutionized healthcare and dramatically improved the quality of life (Thimbleby 2013), these achievements have impacted mainly a fraction of the population in wealthy countries. There is therefore a challenge for practical health technological solutions to prevent onset and progression of disease that is inclusive of the majority of the poor and disadvantaged populations particularly in LMICs. This is in line with the core principle of the Sustainable Development Goals (SDGs) which is premised on leaving no one behind, and the SDG 3 calls for universal health coverage and health and well-being for all at all ages.

As countries embrace this inclusive vision and collectively aspire for a better society by year 2030 through the 2030 global agenda, there is a great demand to ensure that everyone makes it on to the bus of the SDGs—by using new approaches and tools that help identify and address health inequity in all its forms (Bustreo and Stone 2016). One such approach is to optimize preventive medicine through technology for all vulnerable populations with the additional outcome of easing the burden to the healthcare systems for LMICs. The present chapter begins by summarizing the sharp contrast in advances made in diagnostic and therapeutic medicine where diseases have already established, describes traditional approaches to disease prevention and then highlights technological developments in preventive medicine.

The last section explores the opportunities to exploit the exponential information and technological capabilities of the fourth industrial revolution (4IR) advantages for disease prevention in the future Society 5.0.

1.1 The Traditional Methods of Disease Prevention

The natural course of disease follows five phases, namely underlying, susceptible, subclinical, clinical and recovery/disability/death. Likewise, the approaches for disease prevention are structured around these stages: primordial prevention, primary prevention, secondary prevention and tertiary prevention (Kisling and Das 2022) with the ultimate goal of preventing disease onset as well as delaying the development of complications when the disease has already occurred.

1.1.1 Primordial Prevention

This mode of prevention assumes an epidemiological approach of preventive activities targeting whole populations who are healthy and is mostly regulated by laws and policies. The aim is to prevent underlying risk exposures (Kisling and Das 2022). An example would be a policy on mandatory inclusion of sports and related facilities at schools to prevent childhood obesity and subsequent diabetes and cardiovascular disease development.

1.1.2 Primary Prevention

Primary prevention uses data collected from a large pool of patients, such as adolescents, children under 5 years, women of childbearing age, all men or all adults. The data is compiled for implementing interventions to prevent disease onset or the development of chronic disease or injury by mitigating predisposing risk factors (Charkawi 2019). Examples of this strategy include regular prophylactic vaccination throughout life; use of condoms among sexually active individuals; provision of health promotion and behavioral counseling for drinking or smoking cessation and promotion of healthy lifestyle behaviors such as good nutrition and activity. The Covid-19 pandemic presented a good example of the importance of vaccination, use of masks and border control to eliminate and curb the spread of the SARS-Cov-2 virus.

1.1.3 Secondary Prevention

This strategy encompasses screening for early detection of subclinical disease among symptomless individuals who exhibit pathological changes that would

otherwise be not detected without screening (Charkawi 2019). Examples include the Papanicolaou (Pap) smear and mammography for early detection of cervical and breast cancers, respectively.

1.1.4 Tertiary Prevention

The tertiary prevention delays the development of complications when the disease has manifested, essentially to slow down disease progression and restores the patient's functioning after diagnosis as exemplified by rehabilitative therapy (Charkawi 2019).

1.1.5 Quaternary Prevention

This mode of prevention refers to the prevention of iatrogenic diseases after treatment of an existing condition, to protect patients from treatment/interventions likely to cause them more harm than good (Martins et al. 2018).

1.2 Preventive Medicine Approaches

Preventive medicine efforts targeting prevention and early detection of disease (primordial, primary and secondary) or mitigating complications of established disease can foster improved quality of life, longevity and reduce the cost of healthcare in countries that are economically disadvantaged and overburdened with disease challenges.

1.2.1 Lifestyle, Food and Nutrition

This preventive approach targets healthy individuals to forestall the development of disease (primary); symptomless individuals for early detection and forestalling disease manifestation (secondary) and also ameliorates patients' disease progression (tertiary).

1.2.2 Immune System Boost

Vaccination is the most common and widely applied method of disease prevention through immune system boost. Recurrent monitoring of biomarkers such a prostate specific antigen are also part of primary disease prevention strategies.

1.2.3 Policy Regulations

Policies regulate the environment to minimize risk exposure, for example restricted smoking zones and increased taxes for cigarettes. This prevents disease at larger scale to protect populations (primordial and primary prevention).

1.3 Challenges of the Traditional Methods of Preventive Medicine in LMICs

Many aspects of this model of disease prevention rely on the individual's and population's adherence with less interaction and guidance from the healthcare professionals. Examples include the fact that a parent may decide not to take their infant for vaccination; resistance to smoking cessation and the low uptake of Pap smear screening services that are available. These key two phases (primary and secondary) of prevention occur at stages where overt disease has not occurred and therefore requires intentional effort from the individuals to participate. Lack of knowledge about risk exposure, the benefits of preventive strategies and socioeconomic and poverty-related impediments and illiteracy are some of the main barriers to effective traditional preventive medicine practices that are predominantly dependent on an individual's circumstances for uptake.

The second challenge is the time-constraints on healthcare providers who are overstretched and therefore less able to provide preventive health promotion messages to apparently healthy individuals. In some countries, the responsibility for health promotion activities is outside the ambit of the healthcare providers. In LMICs, who have limited resources, health promotion for the healthy population competes for interventions prioritized for the sick patients. In addition, there is difficulty in getting buy-in for engagement in health matters from individuals who perceive themselves as healthy and have other pressing needs such as food security, access to energy and water.

Thirdly, although large amounts of electronic health records (EHR) data are generated daily, transforming this data into useful information for disease prevention strategies is still lagging behind particularly in LMICs. The demand for skilled personnel in data mining, data analytics and big data exceeds the supply. Such data requires multisectoral collaboration across the health, IT and engineering domains for development of interoperable applications, data access and exchange.

The major challenge for LMIC is access to technology and more importantly the cost of continuous maintenance and availability of experts for these technologies in a sustainable manner in rural and poor areas. This was illustrated by successful implementation of telemedicine in the rural province of Eastern Cape, (South Africa) which established effective network communication between outlying clinics and a central regional hospital. However, this ideal development in medical technology later faced major challenges of connectivity, IT maintenance

and availability of IT personnel in these rural settings (Kachienga 2008). This highlights the plight of many rural populations in emerging economies, despite the major advances in information technology and state of the art medical devices.

2 Overview of Technological Advances in Artificial Intelligence-Based Therapeutics and Diagnostics for Preventive Medicine Practice

Technological advancements during the (4IR such as the Internet of Things, virtual reality, robotics, machine learning and artificial intelligence (AI) have revolutionized modern medicine and healthcare practices by promoting the development of sophisticated and innovative artificial intelligence (AI) systems, such as systems for computational pathology, surgical robots and telemedicine software applications.

The spread of telemedicine started in the 1980s and referred to systems where medical data, in particular microscopic images, were shared in real-time with experts at a different geographical location to obtain a second opinion. An advanced version of telemedicine started in the early twenty-first century, where images were stored and could be reviewed any time later and also long-term archived in digital form. This technology became known under the term "digital pathology." While digital pathology has become very popular and an important aspect of current health economy, it is still limited in that pathological examination and diagnostics are still based on visual analysis by a human expert (looking at a computer monitor rather than through the oculars of a microscope). Consequentially, the next step was to expand the digital workflow from scanning (digitizing samples) to analysis and diagnostics—the actual act of "pathology," which is the art of recognizing diagnostically relevant information in any given tissue sample. This has been referred to as "next-generation digital pathology" (Mungenast et al. 2021) or computational pathology. Automated slide scanners, tissue cytometers and image cytometry software including machine learning and in particular deep learning algorithms for computer-guided recognition of individual cells in tissue context and automated classification of histological structures support human experts with recognition and understanding of complex cellular interdependencies (Shakya et al. 2020) and help to elucidate the multilayered nature of immune responses against cancer as well as pathogens (Kaneko et al. 2022). Understanding those molecular mechanisms is a prerequisite for the development of targeted therapies, effective drugs but also methods of early detection and prevention. That the new era of AI-based diagnostics has already started is indicated by the fact that the US Food and Drug Administration (FDA) has officially approved the first AI-based software-only diagnostic system, in this case for prostate cancer, in September 2021 (FDA 2021).

Surgical robots have proven useful for minimally invasive surgeries, including transoral, knee replacement, dental and benign and brain tumor removal surgeries. Apart from being advantageous in offering surgeons greater visualization, precision

Table 1 Summary of innovative artificial intelligence-based surgical robots used for tertiary prevention medicine

Surgical robot	Use	Advantages	Limitations	References
da Vinci Surgical	Minimally invasive surgeries.	(i) Ability to perform surgery through tiny incisions, leading to smaller scars and less trauma. (ii) Greater visualization, precision and accuracy. (iii) Less pain and discomfort during patient recovery. (iv) Patients have reduced risk of blood loss and infection. (v) Patients staying at hospital are reduced. (vi) Reduced surgeon fatigue.	(i) Expensive (ii) Requires medical facilities with advanced technologies and highly trained surgeons. (iii) Nerve damage and compression can occur in patients (iv) Robotic malfunction and maintenance	DiMaio et al. (2011)
Flex Robotic System	Minimally invasive transoral surgery.			Mattheis et al. (2017)
DLR MiroSurge	Minimally invasive robotic telesurgery.			Hagn et al. (2010)
Mazor X	Spinal surgery.			Mao et al. (2020)
Mako SmartRobotics	Knee replacement surgery.			Grutter (2022)
THINK Surgical	Knee replacement surgery.			Liow et al. (2017)
Yomi Robotic System	Dental implants surgery.			Dimri and Nautiyal (2020)
CyberKnife System	Radiosurgery to treat benign tumors.			Kilby et al. (2020)
Neurosurgical Intracranial Robot	Minimally invasive surgery for removal of brain tumors.			Liu et al. (2021)

and accuracy during surgical procedures, surgical robots also have limitations including the high costs associated with purchasing them and maintenance, and there has been evidence of nerve damage and compression occurring in patients (Table 1).

Several AI software applications are currently available that have revolutionized diagnostics, drug discovery and patients' experience in healthcare. A summary of the latest AI-based diagnostic software, including the Viz LVO AI, Path AI, Buoy AI, Enlitic AI, Freenome AI, Iterative Scopes AI, ViruSense AI/VSTAlert AI/VSTBalance AI, Beth Israel Deaconess Medical Center AI and Caption AI software, and their use in diagnosing diseases can be found in Table 2. These AI-based diagnostic software have been shown to be useful in treating stroke patients, radiological diagnostics, detecting earliest stages of cancer and tumors, lowering cancer diagnostic error, treating for gastrointestinal tract infections and screening for bacterial infections.

Table 2 Summary of innovative artificial intelligence-based software applications used for primary, secondary and tertiary prevention medicine

Artificial intelligence software companies	Use	Limitations	References
(i) Diagnostics		***(i) Data challenges:*** – Data availability is the first barrier. Health data is expensive, there is ingrained reluctance toward sharing of data between hospitals, and the availability of data following introduction of the algorithm analyzing it is uncertain. – Data privacy and security are a major issue since patient data are prone to be hacked by cybercriminals, leading to a breach in users' personal data and information. – Quality of data that is used to train systems is difficult to ascertain. – Health data can be messy, inconsistent, inaccurate and may lack standardization in how it is formatted and stored. ***(ii) Developer challenges:*** – Biases may occur in collection of data used to train models which can lead to biased outcomes. – Overfitting may occur when the system studies the relationship between patient variables and outcomes that are irrelevant. This happens when there are too many viable parameters and less outcome parameters, leading to inaccurate results. – Data leakage may occur, where the	
COLUBRIS *Tissue Cytometer with AI* & StrataQuest image cytometry software from TissueGnostics GmbH Austria (Tertiary prevention medicine)	– Tissue cytometry platform with deep learning algorithms for precise recognition of individual cells in tissue context and machine learning-based histological classifiers for detection of tumor areas and other pathologies. – Allows to automatically determine molecular expression profiles and spatial distribution patterns of cellular subpopulations. – Automated detection of biomarker correlations in high-plex assays for tissue analysis.		Meshcheryakova (2021) Mungenast et al. (2021) Aung et al. (2021)
Viz LVO AI software app (Tertiary prevention medicine)	– Uses cutting-edge deep learning to send urgent information about stroke patients directly to a medical professional who can act and treat them. – Can immediately identify problems and alert care teams, allowing medical professionals to evaluate options and make treatment decisions that could save lives.		Petrone (2018) Built In (2022) Aung et al. (2021)
Path AI software (Secondary prevention medicine)	– Using machine learning technologies, pathologists can make diagnoses that are more precise. – Goals include lowering cancer diagnostic error and creating techniques for personalized medical care.		Built In (2022) Aung et al. (2021)

(continued)

Table 2 (continued)

Artificial intelligence software companies	Use	Limitations	References
Paige AI software (Secondary prevention medicine)	– FDA approved software application. – To aid pathologists in the detection of suspicious foci, grading and quantification of tissue and indication of perineural invasion (PNI) in needle core biopsy samples from the prostate tissue.	algorithm has extremely high predictive accuracy. It is possible that a covariate in the dataset has inadvertently alluded to the outcome, negating the algorithm's significance in predicting outcomes outside of the training dataset. – "Black-box" problems can occur, where algorithms are unable to give a comprehensive explanation for their predictions. ***(iii) Challenges in clinical implementation:*** – Lack of empirical evidence in validating the efficacy of AI-based healthcare software interventions in clinical trials. – Challenges with implementing and integrating into physician workflow, including high amounts of time and money needed to train physicians and healthcare workers to use the devices. – Lack of involvement of multiple stakeholders in development of AI healthcare software to ensure that the product can be easily integrated into the physician workflow with high throughput. ***(iv) Ethical challenges:*** – Data privacy and safety:—Concerns over ownership and oversight—who owns the data and has the overall oversight	Paige (2022) Aung et al. (2021)
Buoy Health AI (Secondary prevention medicine)	– Computer program that utilizes algorithms to detect symptoms and find treatments for illnesses. – A chatbot considers a patient's symptoms and health concerns before recommending the best course of action based on its diagnosis.		Built In (2022) Aung et al. (2021)
Enlitic AI (Secondary prevention medicine)	– Creates medical deep learning techniques to speed up radiological diagnostics. – Provides doctors with greater understanding of a patient's current needs by analyzing unstructured medical data, such as radiological images, electrocardiograms, blood tests, patient medical history and genomics.		Built In (2022) Aung et al. (2021)
Freenome AI (Secondary prevention medicine)	– Makes use of AI to discover the earliest stages and warning signs of cancer to develop novel treatment regimen.		Built In (2022) Aung et al. (2021)
Iterative Scopes AI (Tertiary prevention medicine)	– Automates the process of selecting patients who are qualified to be potential candidates for clinical trials for gastrointestinal tract infections, including		Built In (2022) Aung et al. (2021)

(continued)

Table 2 (continued)

Artificial intelligence software companies	Use	Limitations	References
	inflammatory bowel disease.	responsibility over data control. – Accountability: Should the physician or developer be held accountable if the AI application generates incorrect patient health results? ***(v) Social challenge:*** – Fear with regards to job loss, thus rendering healthcare workers obsolete. – Inequality and stigmatization. – Misunderstanding and mistrust of AI in its various forms. – Misunderstanding of AI may lead to unrealistically high expectations of its efficacy and results.	
VirtuSense AI/VSTAlert AI/VSTBalance AI (Quaternary prevention medicine)	– ViruSense AI tracks a patient's movements using AI sensors so that medical professionals and caregivers can be alerted to possible falls. – VSTAlert AI can foresee when a patient plans to stand up and warns the relevant medical staff. – VSTBalance AI uses machine vision to estimate a person's risk of falling within the next year.		Built In (2022) Aung et al. (2021)
Beth Israel Deaconess Medical Center AI devices (Secondary prevention medicine)	– For early detection of potentially fatal blood diseases. – AI-enhanced microscopes can screen blood samples for harmful pathogens like *E. coli* and staphylococcus faster compared to manual screening, with a 95% accuracy level.		Built In (2022) Aung et al. (2021)
Caption Health AI (Secondary prevention medicine)	– Uses both AI and ultrasound technology to detect diseases at early stages. – Produces high diagnostic-quality images which are then interpreted and assessed by the software.		Built In (2022) Aung et al. (2021)
(ii) Drug discovery			
BioXcel therapeutics AI (Secondary and tertiary prevention medicine)	– Uses AI for the identification and development of new medicines within the field of neuroscience and immuno-oncology.		Built In (2022) Aung et al. (2021)

(continued)

Table 2 (continued)

Artificial intelligence software companies	Use	Limitations	References
BERG AI (Primary prevention medicine)	– Creates disease maps to expedite the discovery and development of ground-breaking medications. – Employs an "interrogative biology" approach with conventional research and development to produce product candidates to combat rare diseases.		Built In (2022) Aung et al. (2021)
XtalPi AI (Primary and Secondary prevention medicine)	– Uses a crystal structure prediction technology to identify the chemical and pharmaceutical properties of candidate molecules for drug design and development		Built In (2022) Aung et al. (2021)
Atomwise AI (Tertiary prevention medicine)	– A convolutional neural network-based discovery engine powered by machine learning that searches through large chemical libraries to find novel small molecule drugs and to predict their bioactivity. – Used to combat serious diseases, including multiple sclerosis and Ebola. – Between 10 and 20 million genetic molecules can be screened daily and provides results 100 times faster than conventional pharmaceutical companies.		Built In (2022) Aung et al. (2021)
Deep Genomics AI (Secondary prevention medicine)	– Used to identify candidates for developmental drugs related to neurodegenerative and neuromuscular disorders.		Built In (2022) Aung et al. (2021)

AI-based software, including BioXcel therapeutics AI, BERG AI, XtalPi AI, Atomwise AI and Deep Genomics AI, have played a pivotal role in the discovery and development of drugs and medications, and in scrutinizing currently available drugs to enhance its therapeutic potency. These software have been proven to be useful in finding medications to treat neurodegenerative and neuromuscular disorders and cancer, and in employing an "Integrative Biology" approach to develop products to combat rare and serious diseases such as multiple sclerosis and Ebola (Table 2).

As part of tertiary preventive strategies, AI-based telemedicine software, including the Kaia Health AI, Spring Health AI, Twin Health AI, Baylon AI and One Drop AI, have also played a pivotal role in transforming patient experience in healthcare. For example, the Kaia Health AI software uses live physical therapists on a live digital platform to offer exercise routines, case reviews, learning resources and relaxation activities for patients with chronic back pain and chronic obstructive pulmonary disease. The Twin Health AI software uses a variety of AI, internet of things (IoT), data science and medical science to treat and possibly reverse chronic illnesses such as diabetes by offering patients with personalized physical activity and nutrition to suit their individual needs. Another software, the One Drop AI, also offers an innovative solution to control body weight and chronic illnesses such as high blood pressure and diabetes. This innovative software offers patients with predictive glucose readings that are generated by data science and AI by considering lifestyle and nutritional changes and daily glucose monitoring by using the One Drop's Bluetooth-enabled blood glucose reader (Table 3).

3 Application of Geospatial Technologies for Disease Control and Prevention

The birth of the Geographical Information System (GIS) in the 1960s laid the foundation for the use of technology to strengthen capabilities of visualizing, analyzing and detecting disease patterns. This was building on earlier versions of this geospatial tracking of disease such as during the London cholera outbreak and the 1918 influenza (Faruque and Finley 2016). This epidemiology method of using associations between disease location, the environment and human behavior has seen dramatic leaps during the Covid pandemic through the power of big data analytics coupled with advanced technology and molecular biology. Novel use of spatial big data from smartphones, social media and personal wearable devices to locate individuals' addresses and associate them with epidemiology, genetics, social and behavioral traits to map infectious diseases was aptly illustrated during the pandemic, to trace contacts, undertake variant genotyping and disease spreading patterns. Such an approach can be easily adapted for prediction and control of noncommunicable diseases.

Table 3 Summary of innovative artificial intelligence-based telemedicine software applications for secondary and tertiary prevention medicine

Artificial intelligence software companies	Use	Limitations	References
Kaia Health (Tertiary prevention medicine)	– Employs live physical therapists on a live digital therapeutics platform to offer therapy to patients around their schedules. – Includes personalized programs with exercise routines, case reviews, learning resources and relaxation activities for treating chronic obstructive pulmonary disease and severe back pain.	(i) Expensive. (ii) Requires mobile devices with advanced software technology and strong internet signals. (iii) Lack of infrastructure for telehealth sustenance, especially in undeveloped and developing countries. (iv) Data privacy and security is a major issue since patient data are prone to be hacked by cybercriminals, leading to a breach in users' personal data and information. (v) Patients and health worker's bias toward telehealth. (vi) Patients' unwillingness to pay for services. (vii) Challenges peculiar to each country such as gender inequality, insecurity, stigmatization and civil unrest.	Built In (2022) Babalola et al. (2021)
Spring Health (Secondary prevention medicine)	– A clinically-validated digital examination that provides participants with a clear picture of their current mental situation while screening for more than 10 mental health disorders. – Matches patients, by using a machine learning methodology, with the appropriate specialist for in-person care or telemedicine appointments.		Built In (2022) Babalola et al. (2021)
Twin Health (Tertiary prevention medicine)	– Uses a combination of AI, IoT technology, medical science, data science and healthcare to address and maybe reverse chronic illnesses like type 2 diabetes. – The whole-body digital twin software provides a digital overview of human metabolic function constructed around thousands of health data points, personal preference and daily activities. – Offers personalized nutrition, sleep, physical activity and breathing guidance to members.		Built In (2022) Babalola et al. (2021)
Baylon (Secondary prevention medicine)	– AI software developed by deep learning scientists and doctors that acts as an interactive symptom checker, by using known risk factors and symptoms to give a		Built In (2022) Babalola et al. (2021)

(continued)

Table 3 (continued)

Artificial intelligence software companies	Use	Limitations	References
	comprehensive and up-to-date medical report to patients.		
One Drop (Secondary prevention medicine)	– Provides a discrete solution for controlling body weight as well as chronic illnesses like high blood pressure and diabetes. – Provides interactive coaching from live health professionals, learning resources, predictive glucose readings generated by data science and AI, and daily tracking of glucose by using one Drop's Bluetooth-enabled blood glucose reader.		Built In (2022) Babalola et al. (2021)

To take full advantage of the 4IR in its entirety, including wearable technologies for lifestyle, environmental exposure risk and biomarker monitoring, machine learning and big data analytics for analyzing large amounts of unstructured, heterogeneous, nonstandardized and incomplete data can assist in risk and disease susceptibility, discovery of communicable and noncommunicable disease patterns, biomarker changes and convert this information into valuable predictive and preventive medicine practices. This requires concerted, transdisciplinary collaboration efforts between biology, computational technology and the healthcare system for scientific analysis, interpretation and collation of health, lifestyle and environmental exposure information using mathematical epidemiological and geo-statistical approaches to predict and prevent diseases.

While the disease mapping, GIS, remote sensing, epidemiological and mathematical modeling have had more predilection toward infectious diseases such as malaria remote sensing application (Roberts and Rodriguez 1994) and the recent SARS-Cov-2 epidemiological tracking, recent developments have also exploited the availability of large amounts of real time, real world geospatial health-related data, the computational power and big data analytics to direct efforts toward prevention of non communicable diseases (NCD) to mitigate the spiraling epidemic of NCD modifiable risks (Canfell et al. 2022a, b). The precision public health model is emerging, marrying data that is continuously updated with digital technology analytics. The main focus is to improve preventive decisions and care for future consumers, populations and the public to prevent NCDs at scale (Canfell et al. 2022a, b).

The use of geospatial technologies has always had the advantage of targeting large populations, as shown in Table 4, which gives examples of how both historic

Table 4 Traditional and modern geospatial technologies for large-scale preventive medicine

Geospatial technology:	Intervention	Prevention outcome	References
Malaria	Combined remotely sensed data and GIS application to identify villages with high vector-human contact risk.	Identify villages with high risk for malaria to target interventions for entire villages	Beck et al. (1994)
Earth observations	Real-time surveillance to track air pollutants.	Avert 2–4 million deaths associated with air pollutant exposure	Apte et al. (2015)
Covid-19	AI, cloud-based screening for Covid-19 infection using a smartphone app (AI4 covid) engine to distinguish covid-19 cough sounds.	Large-scale reduction of the misdiagnosis risk-population wide.	Imran et al. (2020)
Riskscape (USA, Massachusetts)	Collates monthly HER real time data on chronic conditions and infectious diseases for mapping and trend analysis.	Risk monitoring and plan interventions for chronic noncommunicable and communicable diseases in approximately 20% of the population	Cocoros et al. (2021)
PopHQ (Australia)	Pilot to test aggregating real time obesity data.	Monitoring and prevention of obesity among approximately 1 million population	Canfell et al. (2022b)

and modern applications of this preventive approach have a wide-scale reach, thus impacting larger populations (Table 4).

Some of the challenges with the use of these technologies include stigmatization of communities by linking diseases to specific locations, for example use of GIS for mapping HIV testing revealed that women moved to other subdistricts of India to avoid being tested in their neighborhoods (Kandwal et al. 2010). Other concerns include protection of individual privacy where possible negligent handling of health data may compromise this privacy, breach ethics and compromise human rights (Thomas and McNabb 2019).

4 Technological Advances in Preventative Medicine

4.1 Leveraging the Adoption and Use of Digital Technology for Dissemination of Preventive Medicine Information

At the very least, opportunities provided by the increase in use of digital communication platforms such as local radio and television, the internet, mobile devices and social media should be optimally used for health education and promotion for wide-scale reach, including low-income households. The communication platforms offer the opportunity to reach the unreachable in the language they understand. These

communication technologies, albeit being low hanging fruits, are currently underutilized with regards to health promotion and prevention messages. A survey of 11 emerging economies in four regions of the world showed that between 70% and 97% (median 89%) own a mobile device, and in seven of these countries, more than 50% own smartphones with access to Internet and mobile apps (Silver et al. 2019). This provides a great opportunity to take advantage of this growing access to information by populations in these emerging economies.

4.2 *Use of Technologies for Treatment Adherence (Secondary Prevention)*

As a form of secondary disease prevention, collection of vital information, such as blood pressure, cholesterol measurement, fasting plasma glucose is recorded electronically, collated and analyzed for automatic risk prediction. In this respect, the exponential growth of cellular networks provides opportunity for continuous contact with patients.

Risk reduction through reminder-based applications such as text messages for supporting diabetic patients to modify their self-management behaviors and better control of disease is another example of secondary disease prevention. Other modes used for disease risk-reduction include emails, calls, social media and wearable devices to effect reminder-based disease prevention or risk reduction (Razzak et al. 2019).

4.3 *Sensor Technologies for the Detection of Biomarkers in Body Fluids for Preventative Medicine*

Several sensor technologies have been developed for the detection of nonvolatile and volatile biomarkers in body fluids that are associated with a broad spectrum of bacterial and viral infections and diseases. Lately, the development of miniaturized sensor technologies, wearable technologies and big data analysis have opened new avenues for improving healthcare quality while lowering costs through early detection and prevention of fatal and chronic diseases (Tricoli et al. 2017). There are several types of technologies that have been developed or currently in developmental phases for the measurement of key biomarkers without the use of invasive procedures. These technologies can be used through contact (tear fluid, saliva, sweat and digestive system analysis) or contactless (breath and perspiration analysis, and optical sensors) approaches in the human body (Tricoli et al. 2017).

4.4 Sensor Technologies for Nonvolatile Biomarkers

4.4.1 Tear Sensors

Human tears contain over 1500 proteins which can be used as biomarkers for a broad spectrum of viral and bacterial infections and diseases (Tricoli et al. 2017). It can be used to detect glucose levels with a limit of detection (LOD) of 1.5×10^{-6} M in individuals displaying symptoms of diabetes using amperometric glucose biosensor/capillary tube configuration sensing technology (Yan et al. 2011). Theranostic contact lens have a dual-functional hybrid surface to modulate and detect a pathogenic attack, and studies have found them useful in detecting interleukin-1α levels, a biomarker for detecting pathogenic infections, with an LOD of 1.43 pg/ml (Mak et al. 2015). Lactoferrin, a biomarker for Sjögren's syndrome, can also be detected using an alkaline microfluidic homogeneous immunoassay, with an LOD of 3×10^{-9} M (Karns and Herr 2011).

4.4.2 Saliva Sensors

The CD59 glycoprotein, also known as MAC-inhibitory protein (MAC-IP), membrane inhibitor of reactive lysis (MIRL) or protectin is a useful biomarker for oral cancer diagnosis. CD59 can be detected in saliva using the CD 59 targeted ultrasensitive electrochemical immunosensor, with an LOD of 0.38 fg/ml (Choudhary et al. 2016). Cytokeratin 19 fragment (CYRFA 21–1) can also be used as a biomarker for oral cancer diagnosis and can be detected in saliva using a nanostructured zirconia decorated reduced graphene oxide-based efficient biosensing platform. The LOD for CYRFA 21–1 using this sensing technology is 0.122 ng/ml (Kumar et al. 2016). Diabetic kidney disease can also be detected by monitoring salivary chloride levels using the Sudoscan®, a device that uses electrochemical skin conductance to measure sweat gland dysfunction, and chronoamperometry. The LOD for chloride using this technology is 300 mg/g (Freedman et al. 2015). Salivary glucose levels can be detected as well using electrochemical biosensor based on bioenzyme and carbon nanotubes incorporated into an osmium-complex thin film with an LOD of 0.003 mM (Liu et al. 2016), electrochemical nanostructured biosensors (constructed by layering single-walled carbon nanotubes, gold, chitosan nanoparticles and glucose oxidase onto a screen-printed platinum electrode) with an LOD of 1.1 mg/dl (Du et al. 2016), and a novel disposable enzymatic electrochemiluminescent biosensor based on the sensitization from Au/TiO2 nanocomposite with an LOD of 0.22 μM (Yu et al. 2016).

4.4.3 Sweat Sensors

A study found human sweat samples can be used to detect l-3,4-dihydroxyphenylalanine (levodopa or L-dopa), a medication used for the treatment of Parkinson's disease. Using a monolithic silica disk-packed spin column and the high-performance liquid chromatography-electrochemical detection system, the authors were able to detect L-dopa levels as low as 5 nmol/l. This sensing technology has proven to be useful in understanding the metabolism of L-dopa (Tsunoda et al. 2015). Glucose can also be detected in sweat using an artificial neural network trained by the Levenberg–Marquardt algorithm (glucose LOD is 83 mg/dl) (Saraoğlu and Koçan 2010) and a dual-enzyme biosensor composed of glucose oxidase and pistol-like DNAzyme (glucose LOD is 720 μM) (Liu et al. 2015).

4.5 Sensor Technologies for Volatile Biomarkers

4.5.1 Breath Sensors

Acetone is a diabetes-specific breath marker that may aid in the monitoring of hyperglycemia-related metabolic disorders. Silicon-doped tungsten oxide nanoparticle films were shown to have the potential of being good portable acetone detectors, with LOD of 30 ppb (Righettoni and Tricoli 2011). Ammonia, a biomarker of liver failure, can be detected using chemoresistive nanometal oxide semiconductors (MO_x) (ammonia LOD is 50 ppb) (Gouma et al. 2009) and the p–n oxide semiconductor heterostructure (n-type In_2O_3 and p-type NiO) (ammonia LOD is 10 ppb) (Sun and Dutta 2016). *Helicobacter pylori* infections are the cause of gastritis or a peptic ulcer and can be detected by the presence of n-butanone in the breath. Chemoresistive graphene and ZnO nanorod electrodes can diagnose *H. pylori* by detecting n-butanone, with LOD of 500 ppb (Weng et al. 2016). Hydrogen sulfide (H_2S) and nitric oxide (NO) are biomarkers for asthma and lung injury, respectively and can be detected using a high performance chemiresistive electronic nose based on an array of metal-catalyzed thin films, metal oxide thin films and nanostructured thin films (H_2S LOD is 534 ppt and NO LOD is 206 ppt) (Moon et al. 2016). Trimethylamine is a biomarker for chronic kidney disease and can be detected using gas chromatography with mass-spectral detection coupled with thermal desorption method, with LOD of 1.76 ppb (Grabowska-Polanowska et al. 2013). Diagnosis of ovarian carcinoma can be done using a chemoresistive flexible gold nanoparticle-based sensor array that detects biomarkers of ovarian cancer, including cyclooctatetraene, hexamethylacetone, 2-ethylhexanol, 2-heptanone, menthol and hexadecane, with LOD of 400 ppb (Kahn et al. 2015).

4.5.2 Skin Perspiration Sensors

Glucose and acetone, biomarkers for diabetes, can also be detected in skin perspiration using mid-infrared pulsed photoacoustic spectroscopy (glucose LOD is 50 mg/dl) (Pleitez et al. 2013) and chemoresistive metal oxide semiconductors (MO_x) with zeolite concentrators (acetone LOD is 10 ppb) (Yamada et al. 2015), respectively. Optical coherence tomography can be used to detect carbon dioxide, a biomarker for respiratory monitoring, with LOD of 60 ppb (Chatterjee et al. 2015).

4.5.3 Digestive System Sensors

Lactic acid and pyruvic acid are biomarkers for gastric cancer and can be detected using an electrochemical L-lactic acid sensor based on immobilized ZnO nanorods with lactate oxidase, with LOD of 0.1 μM (Ibupoto et al. 2012). Esophageal cancer (malonic acid and L-serine), gastric cancer (3-hydroxypropionic acid and pyruvic acid) and colorectal cancer (L-alanine, glucuronic lactone and L-glutamine) biomarkers were detected in serum samples using gas chromatography and mass spectrometry, with LOD of 50 μM (Ikeda et al. 2012). Amperometric biosensor based on nanoporous nickel/boron-doped diamond film technology is also used for the detection of L-alanine, a biomarker for colorectal cancer, with LOD of 0.01 μM (Dai et al. 2014).

4.6 Wearable Technology and Smart Clothing

Smart wearables, including smart watches and fitness bands, and sensor-integrated smart clothing have rapidly gained popularity, particularly in the sectors of personalized healthcare, fitness and sports (Ahsan et al. 2022). There are several types of wearable technologies that can be used to monitor different body parameters and biosignals such as smart jewelry, smart watches, fitness trackers, brain activity tracker, smart belt, smart shoes, smart socks, smart baby garment, smart T-shirt and smart leggings (Ahsan et al. 2022). The different bio-signals in the human body that can be detected using smart wearables can be classified as bioelectrical (electrocardiogram (ECG), electroglottograph (EGG), electroencephalograph (EEG) and electromyograph (EMG)), biochemical (glucose, lactate metabolites, etc.), bioacoustics (phonocardiogram), biothermal (surface temperature), biomagnetic (magnetoencephalography, magnetogastrography, magnetoneurography and magnetocardiogram), biomechanical (blood pressure and murmurs, rubs and gallops) and bio-optical (optical parametric generation) (Ahsan et al. 2022; Muhammad Sayem et al. 2020).

Several smart clothing has been developed that has sensors and signals attached to them, including ECG, EMG, EEG, triaxle accelerometer and gyroscope, and

acromion sensor that monitors burn rate, energy, sweat, temperature, breathing patterns and physical stress levels (Meyer et al. 2010), heart rate variability and mental stress (Joshi et al. 2016; Zaffalon Júnior et al. 2018), sleep disorders (Liang and Nishimura 2017), respiration rate and blood pressure (Abtahi et al. 2015; Brady et al. 2005), rehabilitating shoulders (Wang et al. 2017) and rehabilitation process of osteoarthritis patients (Spulber et al. 2015). Ambient, physiological and motion sensors and signals are also found in smart T-shirts to detect inactive lifestyle using machine learn (Kańtoch 2018).

Smart T-shirt garments, consisting of knitted sensors, and shimmer sensors to detect ECG and accelerometer data, have also been developed specifically for the elderly to monitor heart rate, heart attack and stroke symptoms (Burns et al. 2012; Frydrysiak and Tesiorowski 2016). Smart socks contain Lilypad Arduino sensors that can monitor temperature, oxygen saturation, heart rate and heart rate variation (García et al. 2018). Wearable computers and smart clothing are also equipped with textrodes and motion sensors to monitor physiological and neuropsychological conditions and musculoskeletal fatigue limits (Scataglini et al. 2015; Friedl 2018).

5 Technological Advances for the Preventive Medicine and Healthcare Practice for Future Smart Society 5.0

For the fact that the recent Covid pandemic contact-tracing activities enabled health personnel to reach normally hard-to-reach populations, it gives promise that the political will to commit the right resources can help to predict or identify where the disease risks are and what health prevention interventions are needed to respond to mitigate the risk for preventive medicine even for the poorly, disadvantaged communities. The latter require all possible strategies and interventions for disease prevention.

5.1 Use of Technology for Continuous Contact Between Individuals and Healthcare Providers for Preventive Medicine

One of the pitfalls of (traditional) effective preventive medicine is its dependency on the uptake, responsibility and ownership by individuals, at preclinical and subclinical phases where individuals presume a state of well-being and therefore do not feel the need to engage in health-check activities. Of importance in this is the level of literacy in general and health-illiteracy. To bridge this gap, technologies that will enable continuous communication loops between an individual and the healthcare system, big data analysis application from sources such as wearable technologies that monitor health indicators (Fig. 1) such as blood pressure, cholesterol and

biomarker levels can be used. For super Society 5.0, early inception of data collection (from birth), exploiting the power of technological and computational advances, information explosion and big data analytics can provide opportunities for early warning signs in disease prevention and the feedback loop from healthcare provider will ensure that the individual receives relevant information for corrective prevention behavior change wherever they are, at all levels of literacy.

Finally, integration of data collected from birth to death, that includes personal genomic profile, EHR, daily monitoring data from wearable technologies including lifestyle and environmental pollutant exposure and sociodemographic data to formulate P4 medicine (personalized, predictive, preventive and participatory) medicine (Hood 2013). This approach for the smart society (Society 5.0) will enable prediction of disease susceptibly, early detection of pathological changes for early treatment and the appropriate implementation of primary and secondary prevention of disease. Regular interval feedback interactions between individuals and healthcare providers, facilitated through an electronic feedback application for interpretation of data analyzed through machine learning will ensure that all individuals are constantly updated about their health status as interpreted and warned by the healthcare providers. It is assumed that as more individuals engage in disease prevention activities and take responsibility for their overall well-being, the health system and healthcare personnel will no longer be overburdened. Subsequently more time and effort can be spent in P4 activities (Fig. 1).

At population level, the data can be collated for population public health for both communicable and noncommunicable diseases to achieve maximal benefits, wide coverage and hence higher impact to prevent both communicable and noncommunicable diseases (Canfell et al. 2022a).

6 Limitations and Challenges

6.1 Adverse Effects of Excessive Technology Use

One of the drawbacks of the 4IR advances is technology addiction. This has been linked with a variety of negative outcomes ranging from eyestrain associated with head and neck pains, mental disorders such as impaired brain and cognitive development, impaired emotional and social intelligence, attention deficit hyperactive disorder, depression and anxiety, social isolation (Small et al. 2020). In young children, poor language development has been reported (Duch et al. 2013). Other challenges are associated with prolonged sedentary lifestyle due to long hours on the internet and smartphones with consequent diseases of lifestyle such as obesity (Aghasi et al. 2020). This suggests a double-edge sword where on the one hand the technology advancements may provide improvements in disease prevention and quality healthcare; on the other hand, unintended adverse effects result in more negative health outcomes.

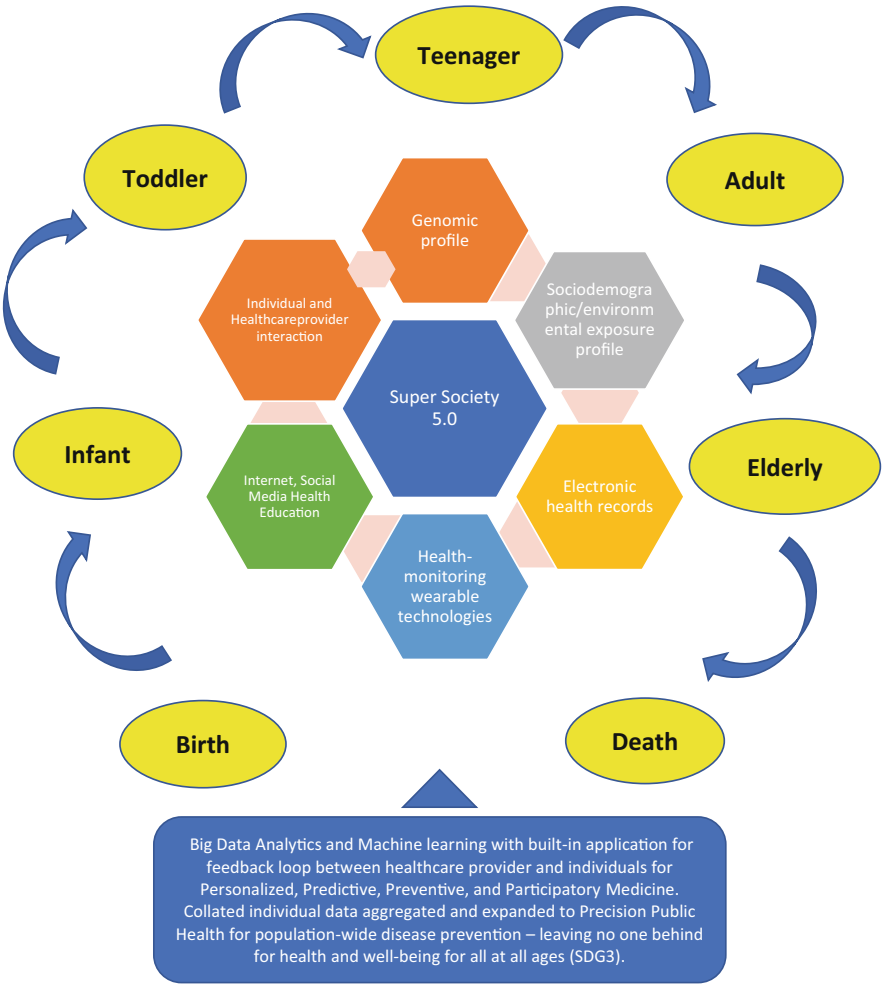

Fig. 1 Schematic presentation of the tenets of preventive medicine approaches for Society 5.0

6.2 AI-Based Applications, Including Surgical Robots, Preventative Health Software Applications (Diagnostic, Drug Discover and Telemedicine) and Sensor Technologies for Biomarker Detection in Biofluids

The high financial cost associated with the use of AI-based applications (surgical robots, biomarker sensor technologies, and diagnostic, drug discovery and telemedicine software applications) is a major challenge, which will have a negative impact on people from rural communities and low-income backgrounds who do not have medical aid insurance and do not have access to a suitable smartphone, cellphone,

tablet, internet or Wi-Fi to purchase and download these healthcare software. Furthermore, the majority of underdeveloped and developing countries are exposed to poverty and do not have adequate healthcare facilities and infrastructures to support the growth of technologically advanced AI-based preventative medicine practices which is a serious concern. As a result, there is an urgent need for more cost-effective solutions to tackle this issue. There is also a severe lack of research funding in underdeveloped and developing countries, which requires immediate attention from first-world research and innovation funding stakeholders to assist LMICs medical doctors, scientists and computer and software engineers and programmers in developing simple and cost-effective AI-based healthcare software's. Another issue is that almost all AI-based healthcare software developed to date has been transcribed into English which prompts the need for these software to be translated into all languages spoken globally.

6.3 Limitations and Adverse Impact on Biology and Human Behavior for Wearable Technologies

The neurological negative effects of technology gadgets causing brain and behavioral disorders (Small et al. 2020) raise concerns for wearable technologies. To date, little is known about how these smart wearables and other similar direct human contact technologies affect human biology and behavioral patterns. The majority of smart wearable devices communicate via Wi-Fi or Bluetooth which can be a health hazard. These devices transmit data via wireless technologies, which generate radio waves. The radio waves, however, can be hazardous to the users and those around them (Excellent Webworld 2022). Exposure to extremely high radiofrequency radiation intensities can cause biological tissue heating and an increase in body temperature. Tissue damage in humans could occur as a result of the body's inability to deal with or dissipate the excessive heat that could be generated (Federal Communications Commission 2022). Radiofrequency radiation emitted from mobile phones and computers was significantly associated with breast cancer development (RR = 2.057; 95% CI = 1.272–3.327) (Shih et al. 2021). Wearable technologies can also have a negative impact on human behavior by producing attention deficit and aggressive individuals who are overly reliant on social notifications and nudges to execute daily tasks and activities (Ranchordás 2020).

There are also several challenges and limitations associated with wearable technology and smart clothing that need to be addressed and improved on as follows:

6.3.1 Technical Issues

Noisy physiological signals from sensors due to motion artifacts can lead to inaccurate predictions of health status. Discontinuous sensor signals can also occur due

to malfunctioning of sensors and inappropriate attachment of sensors to clothing. Sensors in smart clothing lack flexibility, foldability and adjustability, which could lead to inaccurate physiological data collection. Wearable devices lack self-powering and utilize several technologies, wireless networks and GPS which makes them more prone to shorter battery life and power failure. Smart clothing lacks a suitable user interface and universal operating system software which pose a challenge in presenting the monitored physiological parameters to the end-users. Security and privacy of big data is another concern since wearable technology are prone to be hacked by cybercriminals, leading to a breach in users personal data and information (Ahsan et al. 2022; Fernández-Caramés and Fraga-Lamas 2018; Chen et al. 2017; Brioude et al. 2007; Fernández-Caramés et al. 2018; Bove 2019; Carpi and De Rossi 2005; Chen et al. 2016).

6.3.2 Durability

Smart clothing is particularly susceptible to frequent failure due to complex processing techniques used in sensor development and embedding, which raises concerns about its dependability in use. They also have a shorter lifetime in the market due to the short lifespan and durability of most sensors and materials used to manufacture them, and are difficult to maintain since human sweat and thermal regulation, and washing with water can damage the embedded electronics (Ahsan et al. 2022; Fernández-Caramés and Fraga-Lamas 2018; Chen et al. 2017; Muhammad Sayem et al. 2020; Paul et al. 2014; Chen et al. 2016).

6.3.3 Social Acceptability, Especially for Low-Income Individuals

A major issue with these advancements is the huge financial burden associated with purchasing wearable technologies and smart clothing, which will negatively impact individuals from low- and middle-income households. Furthermore, the majority of people from poor socioeconomic backgrounds and residing in rural areas do not have access to the internet and Wi-Fi which is a challenge since wearable technology and smart clothing heavily rely on connectivity networks to communicate the monitored physiological parameters to the user. Another challenge is the lack of awareness about the latest technological developments in preventative medicine, the high cost associated with purchasing smart fabric and the need for smart clothing to be fashionably trendy to appeal to the younger generation, as well as to suit different cultures, ethnicities or dress codes (Mokhtarian and Tang 2013; Ching and Singh 2016; Chen et al. 2016; Ahsan et al. 2022).

The current global energy crisis, caused by energy supply underinvestment, Russian-Ukraine conflict and weather extremes, have led to “affordability crisis” caused by record high energy bills and “energy supply crisis” owing to lack of fuels and power (S&P Global 2022). Higher energy prices have contributed to excruciatingly high inflation, pushed families into poverty, forced some factories to reduce

output or even shut down, and slowed economic growth to the point where some countries are on the verge of a severe recession (International Energy Agency 2022). The dwindling global energy supply will adversely impact the 4IR's Big data and AI, advancements for the Precision Public Health and faster attainment of SDGs. Also, AI-based healthcare software and Wi-Fi heavily rely on constant power to function which is a serious concern and issue to address.

Furthermore, the advantages and convenience brought in by technological advances, big data and AI also bring about a myriad of challenges that are not yet fully understood by medics and academics and clarified by lawmakers. One such issue is lack of clarity on who owns the patient health records data, how and when can it be used, should it be governed by propriety law or ethics bodies, particularly when there are issues of tech companies commercializing healthcare data (Liddell et al. 2021). The blurred legal framework on patients' rights and ownership, ethics of data usage and commercialization is also getting out of control with resultant class action, such as that between Google and University of Chicago where patient data was shared without adequately complying with the ethics of privacy (protection of patient data) (Wakabayashi 2020).

In summary, the overall limitations for taking full advantage of the 4IR's Big data and AI, advancements for the Precision Public Health and faster attainment of SDGs (a better Society 5.0 for all at all ages) particularly for LMICs are the prohibitive cost of resourcing this noble initiative, advanced data storage/cloud space infrastructures required to safely and securely store Big data generated from AI-based software and poverty. Another limitation is health illiteracy. People with limited health literacy are more likely to have chronic medical conditions and challenges in managing them, tend to avoid vital medical tests, less likely to follow treatment regimes, have a higher rate of hospital and emergency room stays and have higher mortality rates (Liu et al. 2020). Based on human rights, particularly the right to access to health, if all governments were to approach preventive medicine exclusively by 4IR and AI, under the current inequities, those who need these health interventions most, would be inadvertently excluded.

7 Concluding Remarks

The current cost of 4IR technological advances makes them exclusive for the rich populations. They are financially prohibitive, unscalable and therefore unsustainable particularly in LMIC where they are most needed. If governments in these countries make collective and conscientious efforts to invest more in preventive medicine exploiting the power of modern technology, AI and big data analytics, the long-term return on these investments outweighs current financial burden of disease treatment risks. Through very early detection, control and prevention of disease, healthcare costs will be kept at minimum. Important innovative actions are required, in the contexts of the inclusivity principle of SDGs plus literacy levels and economic challenges of LMICs. With appropriate level of commitment and careful budget

planning, the full potential of opportunities offered by the 4IR, CPS and big data analytics can achieve unmeasurable long-term benefits in prevention of disease and reduction of healthcare costs for LMICs. This can be achieved through application of smart society principles both at individual (personalized, predictive, preventive and participatory medicine (Hood 2013) as well as precision public medicine (Canfell et al. 2022a, b). While this ideal is pursued, careful consideration for issues of human rights and privacy, security, safety, oversight, resource allocation and energy crisis must be attended to.

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Internet of Things in Society 5.0 and the Democratization of Healthcare

Demetra Demetriou, Kgomotso Mathabe, Georgios Lolas, and Zodwa Dlamini

Abstract The application of the fourth industrial revolution will create a new society known as Society 5.0. This revolution will raise our standard of living and will solve many challenges currently faced. It will allow people to have access to medical advancements at a low cost. Innovations in medical science and technology allow patients to communicate with doctors anytime and anywhere. Simulators, such as virtual reality (VR) surgical simulators, will enable more advanced examinations and diagnoses. The knowledge and data can be combined into a sharable database improving medical technology and healthcare. Internet of Things (IoT) is a wireless, connected and intercalated system of devices that can send, store and collect data. IoT with the use of artificial intelligence (AI) will improve diagnostic accuracy. Through these technologies, healthcare and patient care can be improved. Medicine will become more precise, patients will become empowered, the value of medicine and medical care will shape delivery and digitalization will transform healthcare. Digitalization will allow patients to have a customized computational model of

D. Demetriou (✉) · Z. Dlamini
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: dd.demetriou@up.ac.za; zodwa.dlamini@up.ac.za

K. Mathabe
Department of Urology, Faculty of Health Sciences, Steve Biko Academic Hospital, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: kgomotso.mathabe@up.ac.za

G. Lolas
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa

Biomedical Design Integrate Computational & Mathematical Modelling Approaches (InCELLiA), Lavrion, Greece

Department of Internal Medicine, National & Kapodistrian University of Athens, Athens, Greece
e-mail: glolas@med.uoa.gr

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themselves that will allow doctors to anticipate illness, guide therapy and improve diagnosis and prognosis. Expanding precision medicine will enable doctors to make highly specific diagnoses. Healthcare will be anticipatory in Society 5.0 and will be available anytime transforming care delivery. In this regard, the lay public will be able to have access to medical information that is evidence-based, personalized via AI algorithms and often outside the control of the healthcare system, representing the "democratization of healthcare." The challenge faced with using IoT is accessibility of data that can be misused to violate human rights and values such as privacy, security and safety in many countries especially those countries with low resources. There is also a major energy and resource crisis, especially in South Africa, that can lower the sustainability and use of IoT.

Keywords Internet of Things · Artificial Intelligence · Society 5.0 · Healthcare · Democratization of Healthcare · Technology · Empowered · Innovations · SDG · Human rights · Privacy · Safety · Security · Oversight · Energy and resource crisis

1 Introduction

Evolution is a natural process of the world and leads to the improvement of life and technologies. The progression of information and communications technology (ICT) is leading to major changes in industry and society (Fukuyama 2018). The history of each Society and the available healthcare has guided the way forward. Each Society strives to be better than the previous offering improved healthcare and survival in the medical field. Society 1.0 is known as the hunting society. People hunt and gather and coexist with nature. This was the birth of human beings. Society 2.0 is known as the agrarian society. These groups are based on nation-building, increasing organization and agricultural cultivation. It was also the start and development of irrigation techniques and the establishment of settlements. Society 3.0 is the industrial society that promotes industrialization through the industrial revolution. This Society provided the invention of steam locomotives and mass production. Society 4.0 is an information society that includes the use of AI and big data. This Society provided the invention of computers and the start of information distribution. Society 5.0 is a super smart society using advanced AI and robotics to improve living (Fig. 1). Developed countries are already implementing Society 5.0 technologies (UNESCO 2019) whereas developing countries still need to acquire the technology for Society 5.0 devices (de Hoyos Guevara et al. 2020). The progression of Society 5.0 is not synchronized and there is no linear progression of all at once.

Society 5.0 is a Japanese concept of a technology-based, human-centered society. Society 5.0 is an upgrade on the existing society that will better human existence through technology. It will rise from the fourth industrial revolution and show humans and machines coexisting together. Although Industrial Revolution 4.0 and Society 5.0 show a relationship, they address different issues. In Industry 4.0 (4IR), intelligence and knowledge are achieved by humans with the support of technology. In Society 5.0, intelligence and knowledge will come from machines at the service of

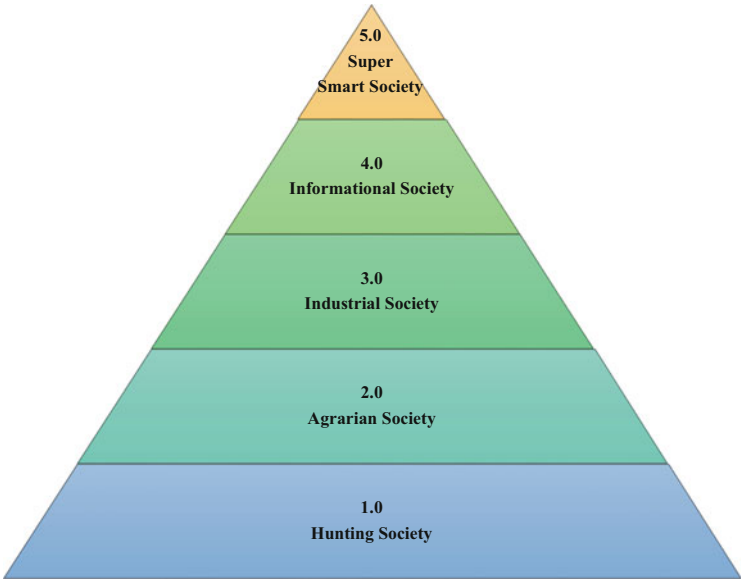

Fig. 1 The evolution of Society. Society 1.0 is known as the hunting society. People hunt and gather and coexist with nature. Society 2.0 is known as the agrarian society. These groups are based on nation-building, increasing organization and agricultural cultivation. Society 3.0 is the industrial society that promotes industrialization through industrial revolution. Society 4.0 is the information society that includes the use of AI and big data. Society 5.0 is the super smart society using advanced AI and robotics to improve living

people. Technology such as AI will infuse all areas of life including science, healthcare, law, environment and ethics (Sharp 2020). Society 5.0 is known as the Super Smart Society and this is already seen in the use of Smart Watches that monitor heart rate, sleep and blood oxygen levels. Innovations in medical science have been transforming society to allow people to live longer and healthier lives; for example, biometric data are gathered continuously every day through devices such as smart watches that can alert the user of an illness before there is any outward sign. This can enable them to receive prompt medical attention.

A major catalyst in the progression toward Society 5.0 is the Coronavirus (COVID-19) pandemic. During this pandemic, several aspects of life relied on technology. Formal educational classes from primary school to university and work were traditionally held on physical premises. During Covid 19, educational classes and work were done online and changed the way we communicated (Sarfraz et al. 2021). Other technologies in addition to AI that will be included in Society 5.0 are big data, Internet of Things (IoT), sharing economy, digital platforms, virtual reality and the robots (Sharp 2020; Sarfraz et al. 2021). The data collected will be converted to a modern type of intelligence through AI and improve human lives and sustainability. Japan is the lead runner in Society 5.0 due to its technological and innovative advancements and designs. Medical diagnostics and AI are used for

contact tracing and data collection as seen with Covid-19. Current digital tools have shown favorable results in managing outbreaks of infectious diseases (Kostkova et al. 2021; Verma and Mishra 2020). Enhanced human application through society 5.0 can improve the management of the scope, speed and impact of disease outbreaks (Sarfraz et al. 2021). Multidisciplinary collaboration will improve patient care and patient experience. This will allow the patient to become more empowered by having physical and virtual care when needed. This will also allow doctors and other healthcare providers to increase the value that improves healthcare.

1.1 Internet of Things in Society 5.0 and Healthcare

Internet of Things (IoT) is a connected, wireless and intercalated system of devices that can store, send and collect data over a network that avoids computer-to-human involvement or human-to-human (Kelly et al. 2020). IoT influences our lifestyle from the way we behave and react. IoT is adapted in many applications and the importance is growing in our daily lives for example we can control air conditioners with our smartphones. In simple terms, IoT is a giant network of connected devices. These devices collect and share data about how they are used and the environment. They work using sensors that are embedded in every device. The sensors emit data about the status of the device. IoT is the platform for the device data and allows devices to communicate with each other. The data are emitted to IoT security platform that integrates the data from various sources and further analysis is performed. The required data are extracted after the analysis. The results are shared across devices.

In healthcare, IoT can be any device that can collect health data and that will be able to connect and upload the data to the Internet (Dang et al. 2019). These devices include smart cell phones, smart watches, implanted surgical devices and digital medications to name a few. IoT can be used to predict and diagnose health issues and treat and monitor the patient in or out of the hospital. IoT can support healthcare systems to improve and democratize patient care. Some of the services provided by IoT in healthcare include eHealth, community-based healthcare, mobile health (mHealth) and smartphones. These systems can be used by medical staff to track and monitor health progress remotely, allow early detection of diseases, and improve disease identification and self-management (Dang et al. 2019; Saarikko et al. 2017; Nazir et al. 2019; Yuehong et al. 2016). Many health delivery services have made the switch to technological-supported health delivery systems due to Covid-19 (Fisk et al. 2020). For this reason, it is key to know how IoT technologies can support the healthcare system and improve the safety and effectiveness of the system (Ye et al. 2020).

1.1.1 IoT-Based Healthcare Construction

There are three basic levels which include the perception level, network level and application level (Sethi and Sarangi 2017). Perception and identification technologies are key in IoT. The perception level is the sensing system that collects the data. Sensory devices that can capture changes in the environment include infrared sensors, cameras, radio frequency identification (RIF) and GPS to name a few. These devices allow perception via object-, location- and geographical identification that is converted into digital signals (Sethi and Sarangi 2017; Wu et al. 2010). Using these sensory technologies, treatments can be monitored in real-time. Table 1 shows examples of devices that can improve and support healthcare services. The network level is data communication and storage of data. This level includes wireless and wired networks that processes the information from the perception level and stores the information. The information is communicated over various frequencies including technologies such as Bluetooth, RIF, Wi-Fi, 5G and wireless sensor networks (Sethi and Sarangi 2017; Li et al. 2018). The information is stored at a cloud-based (centralized) or local (decentralized) location. Cloud-based computing is flexible, ubiquitous and can be scaled to size (Darwish et al. 2019). The cloud can support electronic medical records (EMRs), medical IoT devices such as smartphones, patient portals and therapeutic strategies (Dang et al. 2019). Local or decentralized processing and networking can improve the scalability of IoT. Edge cloud is a new concept that allows the processing of data in a decentralized approach that reduces the required amounts of data (Sethi and Sarangi 2017; Pan and McElhannon 2017). The application level applies and interprets data and is responsible for application-specific services (Sethi and Sarangi 2017). These applications use artificial intelligence to improve diagnosis, prognosis and treatment (IBM 2018). IoT-based healthcare and the use of AI and deep learning can assist medical professionals to predict diseases and improve diagnosis and management (Tobore et al. 2019).

IoT allows data to be collected, communicated and stored and enables data analysis and smarter healthcare that can improve diagnosis, risk identification, treatment monitoring and management. Smart healthcare services can use the information from IoT, big data, AI and deep machine learning to provide a more personalized, efficient and convenient system (Tian et al. 2019). IoT improves the efficiency and quality of the ecosystem of service delivery like assessment management, hospital management, optimization of resources and workflow of staff (Thangaraj et al. 2015; Yu et al. 2012).

1.1.2 Health Service Improvement Through IoT

Primary healthcare is becoming more accessible. However, disease prevention must be a focal point to decrease the burden of disease. IoT can improve population health and transition the healthcare model to a hybrid of primary, secondary and tertiary healthcare. There is a demand for easy access to health information and many

Table 1 IoT devices that can support health service delivery systems

IoT device	Description	Uses
Vital sign patches.	To track and monitor respiratory rates, heart rates, sleep cycle, temperature, etc.	One pilot trial followed patients that were discharged from emergency. The patients had infections, heart failure, chronic obstructive pulmonary disease or asthma. The study showed fewer negative events and lower healthcare costs via IoT (Levine et al. 2020). The patches will be investigated for their effectiveness and will potentially have further applications for hypertension, type 2 diabetes mellitus, asthma, sleep apnea, etc.
Inhalers that are Bluetooth-enabled.	A Bluetooth sensor will be used coupled with a mobile app that will allow predictive analysis and provide feedback.	Used for asthmatic patients or for respiratory conditions. IoT devices can improve healthcare utilization through self-management and symptom identification (Merchant et al. 2016, 2018).
Therapeutic extended or virtual reality.	Virtual reality, mixed reality or augmented reality can be used to visualize data collected from sensors from IoT.	Virtual reality has become increasingly popular as it is portable, vivid and immersive. This can be used for a range of outpatient and inpatient applications (Birckhead et al. 2019; Eckert et al. 2019). Augmented reality and mixed reality applications have been suggested to outperform traditional service methods including central vein catheterization, anesthesia and acquisition of anatomy knowledge (Gerup et al. 2020). Other virtual reality applications have been applied in various diseases (Tashjian et al. 2017; Chirico et al. 2016; Lohse et al. 2014; Valmaggia et al. 2016) and is suggested to assist in obesity prevention and management (Persky 2011).
Digital medications.	An external body sensor, for example a wearable sensor patch, which receives information from an ingestible sensor	The smart medication interacts with a wearable patch and communicates with a mobile app. Information is stored on the cloud. A mobile app can also be used to remind patients to take their medication and share information with others (Plowman et al. 2018).
Smart voice assistants.	Provides support to users through vocal conversations. These devices include Siri, Alexa, Google Home and Amazon.	The hand-free feature of smart voice assistants assists various groups for example the elderly, disabled or technologically impaired users

(continued)

Table 1 (continued)

IoT device	Description	Uses
		(Dojchinovski et al. 2019). The interactive conversations with the smart voice assistants enables an engaged and patient-centered usage (Laranjo et al. 2018). The conversation agents can provide answers to health-related questions without human contact, collect data, assist with self-management activities, etc. (Ilievski et al. 2019).
Wearables.	Devices worn by the user for example glucose monitors can be used to dosage and time and recommend accurate dosage type.	Examples of wearables include smart insulin pens continuous glucose monitors (Sangave et al. 2019), smart watches, loneliness detectors (Doryab et al. 2019), fall detectors like iFall (Sposaro and Tyson 2009), wearable blood pressure monitors (Kakria et al. 2015) and wireless electrocardiogram monitors (Majumder et al. 2018). These IoT compatible devices can improve insulin administration and decrease medication errors (Sangave et al. 2019).
Social robots.	AI system that can interact with humans through social rules (Chen et al. 2018).	Robots in the hospital settings are used to provide navigation information, collect patient data and to detect abnormal actions (Van der Putte et al. 2019; Wan et al. 2020). In home settings, health robots can detect unhealthy behaviors, assist in treatment and therapies and manage medication (Baur et al. 2018; Tao et al. 2016; Nijholt et al. 2018; Moyle et al. 2013).
Smart cameras.	Changes in the environment can be captured by smartphone cameras.	Smart cameras are associated with smartphones. Data are downloaded to an app. This can assist the healthcare delivery system via diabetic wound analysis (Bhelonde et al. 2015), heart rate, skin and dry eye disease monitoring (Ashique et al. 2015; Połap et al. 2018; Shimizu et al. 2019).

smartphone users want to download a health-related app for self-management (Pai 2015). AI has provided point-of-care health information which can assist with medical and lifestyle advice. Established AI bots include Your Md, Woebat, HealthTap and Babylon that provide instant medical advice based on symptoms (Nadarzynski et al. 2019). However, the accuracy has not been approved

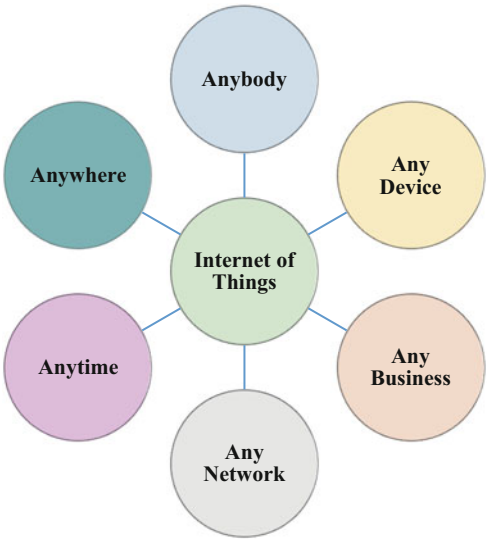

Fig. 2 IoT meaning to Society 5.0. The IoT can come from anybody, any device, any business, any network, anytime and anywhere. Using the IoT devices from Table 1, data is collected and stored on the cloud. The data is accessed and analyzed, and decisions are based on the information. Medical staff will be able to make evidence-based decisions to promote health, diagnosis, prognosis, treatment and monitoring

(Wisniewski et al. 2019). There is a need for a reliable digital, evidence-based app and resources (Borycki 2019). IoT also offers the opportunity to learn from and link nonhealth IoT technologies to provide support, monitor daily activities and encourage lifestyle changes. Nonhealth and health IoT data provide valuable information regarding surveillance on a population level, accidents, environmental conditions and risk factors which can be difficult to collect through human reporting systems (Pacheco Rocha et al. 2019; Lai et al. 2020). Through data linkage and IoT, professionals will be able to make evidence-based decisions to promote health, safe transportation systems, quality public services and smart healthcare (Pacheco Rocha et al. 2019; Wray et al. 2018; Palmieri et al. 2016) (Fig. 2). An IoT-based healthcare system allows the overall healthcare systems to evolve past the traditional model of service delivery to a more coordinated, continuous and proactive, continuous approach (Korzun 2017). It provides improved high-quality care that is less invasive than traditional methods. Improved changes in the healthcare system are also very attractive to policy makers as they can enhance the health system field's efficiency (Dauwed and Meri 2019) and can provide model flexibility based on the individual's need or population-wide need. IoT uses AI to improve the accuracy of results.

1.1.3 4P Medicine (Personalized, Predictive, Participatory and Preventive) Using IoT Services

The goal of medicine, that is personalized, predictive, participatory and preventive (4Ps), has been advocated by Leroy Hood and others. The 4Ps are summarized in Table 2. Systems approaches in medicine and biology provides consumers, physicians and patients with personalized health and disease information at the cellular,

Table 2 The 4Ps

	Goal	IoT application	References
P1—personalization	The goal of personalization is to identify tailored treatment based on the genetic profile of each individual. Other factors will also be considered like patients' abilities, needs, lifestyle, social contexts, family history and psychological aspects. This will improve treatment outcomes and survival rates. Disease risks can be discovered and precautionary steps can be taken to optimize wellness.	IoT will allow the capturing and collection of data that can be accessible to the patient and medical staff. The data can be used to design treatment that is personalized to the patient. This is also known as precision medicine.	Pravettoni and Triberti (2020), Jarow (2018), Sebri and Savioni (2020)
P2—Predictive	The goal of predictive medicine is to use genetic and laboratory tests to predict the onset of a disease and the involved risks. Techniques such as AI, biomedical imaging instruments and machine learning can be used.	The data in the IoT system can be used to design predictive models that can be used to assess risks and provide treatment solutions.	Tuena et al. (2020)
P3—participatory	The goal of participation is to involve individuals and to empower them. They will be able to manage their health status that will allow communication between the patient and the medical staff.	The IoT system will allow the data to be accessible to the patient and will allow the patient to be more involved in their healthcare. The patient will be able to ask questions and learn more about their health.	Kondylakis et al. (2020)
P4—preventative	The goal is to define interventions to a disease before it occurs. Environmental, socioeconomical and psychological factors can also be considered.	The data in the IoT system from various devices can be used to assess risks and provide treatment or lifestyle intervention before the disease occurs.	Monzani and Pizzoli (2020)

organ and molecular levels (Flores et al. 2013). The information collected by the IoT system makes disease care more cost-effective as medical care will be personalized and the cause might be treated. Patients will be more encouraged to be involved in their medical care and can observe lifestyle decision impact. Predictions models can be designed based on the IoT system data that will assist in the prediction and possible prevention of diseases.

1.1.4 Democratize the Healthcare System with IoT

New demands around health, safety and public health have been put on connective technologies and smart devices (Dodge 2020). In the ambient assisted living (AAL), IoT devices have gained prevalence (Incki and Ari 2018). AAL can be defined as "the use of communication technologies (ICT) and information in daily living including the use in a working environment that enables social connection, remaining active for longer and to live independently" (Monekosso et al. 2015). Improved computing capacity will allow for full operational systems and specialized software in the IoT system. These improvements will allow expedited data processing without compromising the safety and integrity of the data collected (Incki and Ari 2018). The goal in designing any IoT solution is to create a system that guides and simplifies decision-making by collecting data from various connected devices, compiling it and proving the right information to the right person at the right time (Dodge 2020). IoT will also be democratized as it will be available and accessible to the public. The democratization of healthcare will allow the empowerment of the patient, prove convenience and knowledge, and allow the patient to become responsible for their own care (Chemweno 2021). Data democratization can overcome barriers, improve health structures and assist communities with health challenges (Chemweno 2021). Data democratization and healthcare democratization will allow people to prioritize essential resources like employment, food, childcare and education as the data will be available using IoT systems.

Artificial Intelligence and Society 5.0

Society 5.0 framework is based on data captured by real-world sensors and sent to the virtual cloud world for AI-based analysis, which will return to the real world in physical form through robots, machines and motor vehicles (Garg et al. 2022). Objects, people and systems will be connected in Society 5.0. Hopeful new values will be created through social innovation, elimination of regional, age, gender and language disparities and enable the delivery of personalized products and services that meet many individuals and potential needs. Society 5.0 involves autonomous manufacturing in general and for specific products with human intelligence and AI as a backbone technology (Mourtzis et al. 2022). As a human-centric design solution where humans and robots collaborate, Society 5.0 has constantly gained more attention during the last years, aiming to solve the challenges of the Society 4.0 (Mourtzis 2021; Fukuyama 2018).

1.2 Internet of Things and the United Nations Sustainable Development Goals (UN SDGs)

The Internet of Things (IoT) can make significant contributions to support the implementation of the SDGs regarding social and environmental terms. Pay-as-

you-go and low-cost IoT can be potential solutions to achieve SDGs by 2030 (López Vargas et al. 2020). IoT can assist to achieve sustainable and stronger development; allow the opportunity for economical and human development while the impact in developing countries must not be overlooked (Rahim 2017). Developing countries are shown to be ideal for IoT innovation, can support economic growth, and contribute to cultural, environmental and social development (Barro et al. 2018). IoT development has allowed for the management and monitoring of renewable energy systems that improved the electrical access (Biggs et al. 2016; Ramanathan et al. 2017). IoT has the potential to predict and minimize the destruction of natural disasters (Pelc and Koderman 2018) like tsunamis and earthquakes (Biggs et al. 2016) that can avoid serious injuries and save lives.

The benefits of IoT falls into the UN SDGs. Specifically, IoT implements SDG goals 3 (Good Health and Well-Being), 6 (Clean Water and Sanitation), 14 (Life Below Water), 15 (Life on Land) and 17 (Partnership for the Goals). Goal 3 aims for good health and well-being. IoT allows the capturing of data on all devices and allows model predictions to improve health and well-being. Sensors of various devices will upload the data that can be analyzed. Smart watches for example can detect irregular heart rate and can notify medical staff of potential risk. This will improve treatment and save lives. There is, however, a need for additional resources such as engineers and technicians, capacity building and a working power supply and back-up solutions. Goal 6 aims to ensure clean water and sanitation. IoT will allow the monitoring and management of water, sanitation and electrical systems and technologies (Biggs et al. 2016; Ramanathan et al. 2017; UN ESCAP 2018). IoT will allow all the data captured by sensors to be analyzed and will provide reliable information about the water resources state, usage, wastewater generation and treatment (World Water Assessment Programme 2020). For example, sensors within the water filtration system will detect any debris, incorrect pH level or soil level. Other sensors will detect incorrect temperatures used for water cleaning. All the information will be loaded into the cloud and adjustments can be made based on the analysis results. IoT is already implemented by using low-cost reverse osmosis systems with smart controllers that allowed effective distribution of water to rural areas and allowed the guarantee and monitoring of water quantity and quality in real-time Jiangsu, (2020). IoT can thus assist healthcare systems by minimizing diseases, improving survival rates of patients and decreasing the burden on hospitals due to safer water, better waste management and providing healthier lifestyles in general to the population.

IoT can be used to improve life on land and in water (Goal 14–15) by allowing predictive modeling based on the capturing of data by various devices. Actions can be taken to avoid catastrophic events and improve the health of all living organisms on land or in the water. Sensors of various devices can detect various changes in the atmosphere, ground and water. The data will be captured across all devices. Changes can be made using smart devices and controllers that will allow the management of sustainable marine and terrestrial ecosystems. A balanced ecosystem will decrease the potential of harmful diseases and will improve health. The healthcare system will benefit from sustainability and decreased burden on the system. IoT will also allow

the growth of partnerships worldwide to increase the collaboration between people, science and technology (Goal 17). The IoT allows all data to be captured and stored and will be accessible across the Internet. This will allow world contribution based on data analysis and the partnerships will allow improved ideas for healthcare and healthcare management.

2 Challenges of IoT and Society 5.0

Cloud-based use of IoT has a few challenges including support effectiveness, human rights violations such as safety and security, reliability, transparency and energy consumption. The gathering, storage or distribution of data is one of the major concerns. Data must not be shared with third parties and private information must be protected. Cloud storage will also need adequate storage space and excessive data accumulation can be difficult to navigate. A major issue is that disclosed information can potentially be used to identify an individual (Bader et al. 2016). This will violate human rights such as safety, privacy and security. Although breached confidentiality is a major concern, the value must be considered (Lee et al. 2020). There are various factors that affect clinicians' acceptability of technology-supported programs. These factors include accuracy, ease of use, compatibility, knowledge, attitudes, external factors like patient–clinician interaction and organization and reimbursement (Gagnon et al. 2016). Low-income countries may also not have access to IoT devices leading to a recourse crisis for these countries. Regarding privacy and security, IoT can undergo cyber-attacks due to wireless communications and low energy. The National Institute of Standards and Technology (NIST) has drafted a security guide and recommendations for IoT devices; however, some guidelines may be unclear (NIST 2019).

There are also issues regarding the standardization and interoperability of IoT and healthcare protocols. Manufacturers and industry partners must still reach a consensus regarding standards for machine-to-machine communication and wireless communication protocols (Rubí and Gondim 2019). Historically, remuneration for technology-assisted healthcare has been challenging and differs between countries (Tuckson et al. 2017). Guidelines and policies on cyber-security, interoperability, protocols and reimbursements must become key precedences to ensure the effective, low-cost and successful use of IoT healthcare models in the medical field. IoT utilizes cutting-edge communication technologies and needs a lot of high transmission bandwidth, storage space and cloud computing. IoT devices use high amounts of energy in filtering and transmission of data. Studies have shown that IoT devices waste up to 30% of energy (Shah et al. 2022). IoT devices can result in an energy resource crisis due to their demand and waste. Energy management is an important factor to consider when developing IoT devices. Smart environments also need a lot of sensors in different places. These sensors are very expensive. Zouai et al. proposed a new approach using an IoT robot to oversight the smart environment to reduce this cost. The robot will carry a range of different sensors that will be able to

sense the surrounding environment and will send data to the various points and devices (Zouai et al. 2019). This application can also be used in hospitals and other healthcare facilities.

Challenges of Society 5.0 include legal, safety, ethical, security, privacy, human rights violation, societal issues, energy and resource crisis. Companies must be able to adapt quickly to Society 5.0 and all the technological advancements. This is not always possible and the financial implications might be too much in the beginning. People will also be able to live longer as they will have better medical care and decreased stress levels. This will place a burden on healthcare resources as unique needs will have to be met. In 2018, around 35 million people aged 65 and over in Japan, were representing over 28% of the total Japanese population (Sharp 2020). The aging of the Japanese population is still rising and it will increase the pressure on the public healthcare system. Energy resources can also be depleted due to the high demand of technologies such as IoT and living resources. Available energy resources will not be able to cover the required energy output demand for living and industrial consumption which will lead to a bigger energy crisis that is currently experienced. Another issue is the overreliance on technology. People will be thinking and problem-solving less on their own. There are also concerns about privacy, surveillance and manipulation of data when using big data and algorithms. AI is also a relatively new concept and the social implications of AI are unknown. There is also a concern for job security as robots will be doing the work intended for humans. This will lead to an increased unemployment rate and stress will increase leading to a decay in health. Humans and technology are becoming more involved and can result in issues related to liability and responsibility. Society 5.0 must be implemented in an ethical way. If handled correctly, the challenges can be overcome.

3 Benefits and Future Perspectives

The use of IoT in medicine will reduce the cost of doctors' visits and travelling and will relieve the pressure off hospitals to concentrate on emergencies (Shehabat and Al-Hussein 2018). IoT will also improve patient outcomes as it will be used to monitor the patient or to detect early diseases and health issues. IoT can improve medical research and enhance collaboration and communication between medical researchers and medical staff. It can also assist with managing the information (Shehabat and Al-Hussein 2018). IoT devices will be able to track and monitor respiratory rates, heart rates, sleep cycle, temperature and glucose levels to name a few (Levine et al. 2020). It can allow the patient or doctor to receive the information and treatment to be applied faster. This will improve patient outcomes and care. IoT can also benefit people with disabilities such as hearing or sight disabilities. People who are hearing disabilities make use of internal or external devices that can be implanted to improve their hearing (Rghioui and Oumnad 2018). Another option is the use of a wireless low-cost glove that is designed to help the deaf communicate with others (Rghioui and Oumnad 2018). The smart voice assistant will also be able

to assist sight-impaired individuals by allowing a hand-free feature (Dojchinovski et al. 2019). IoT can be used for the monitoring of patients which will improve patient care, especially after surgery. Sensors will also allow patients to move freely while they can be monitored. Although there are challenges, the benefits outweigh the challenges and will lead to an improved healthcare system.

Although there are challenges regarding IoT energy waste, if properly and effectively used, the challenges can be overcome. IoT can assist in better energy resource consumption. IoT is key in the transfer of energy and power to smart devices and buildings. IoT can be used to efficiently power buildings and reduce the consumption (Pan et al. 2015). IoT-based smart decisions can be taken to efficiently monitor and control devices and scalable architecture (Nandury and Begum 2015). IoT can assist Smart grid (SG) to enable the flow of data and electricity within the electricity system networks (ESN) and its clusters (Kumar et al. 2020). SG can replace the conventional fossil fuel-rich grid with the distributed energy resources (DER), thus improving the energy resource crisis (Kumar et al. 2020). IoT enables data monitoring, data sensing and data storage that can be used for efficient decision-making and control of SG. This can lead to enhanced availability, reliability, resilience, sustainability, security and stability. Improved energy consumption will benefit the healthcare system as it will allow healthcare systems to be fully functional at a lower energy demand.

Society 5.0 will enhance all industries in the world. It will solve many challenges that are currently faced. Society 5.0 will improve the lives of humans and improve patient care and healthcare. It will raise living standards. For example, stress will be decreased, patients will have access to medical advancements at low costs, and human abilities will be expanded through AI and robots which will allow people to be more fulfilled. Society 5.0 will provide technological support for the aging population. It will assist people to stay healthy by example innovative walking aids. Society 5.0 will also allow important information to be easily shared between medical professionals. This will reduce reliance on hospitals and hospital visits. People will have more control and will be empowered. Society 5.0 will be able to influence the population migration. For example, automated transport will be enabled which will allow low-income people to travel and get the needed healthcare. Smart sensors will also enable patients to receive warnings before symptoms may be apparent.

4 Conclusion

Advanced information technologies have provided the opportunity for innovation in our daily lives. IoT is an evolving technology that allows improved solutions in healthcare like the integration of devices, accurate medical record keeping, sampling and identification of diseases' causes and risk factors. IoT's sensor-based technology provides the ability to reduce the risk of surgery and aids with example COVID-19 type pandemic. Medical students can also be trained more efficiently for disease

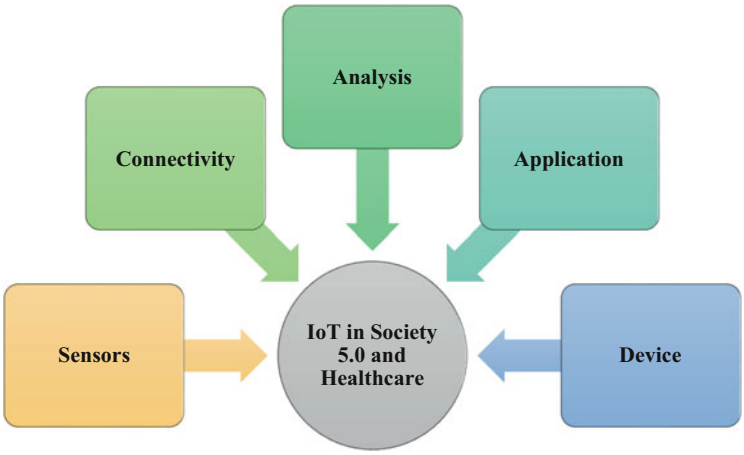

Fig. 3 IoT in Society 5.0 and healthcare. The device captures the information through the sensors. The data are connected to the cloud and are stored on the cloud. The analysis is done based on the received data and stored data. The results are used to improve the diagnosis, prognosis, treatment and monitoring of the patient. The device captures new data with the treatment provided and new information is received on the cloud for analysis

detection and treatment possibilities. IoT can allow healthcare systems to predict health issues and improve diagnosis, prognosis, treatment and monitoring (Fig. 3). Although there are challenges regarding human rights such as privacy, safety and security, as well as energy and resource challenges, the value of IoT outweighs the challenges. IoT implementation in healthcare will rely on a code of practice for the privacy, management, confidentiality and cyber-security of data. There are still gaps for research to address like how IoT devices can be interoperable with local and international health systems and designed with standardized protocols and on the efficiency of storage and cloud-based solutions to name a few. The goal of Society 5.0 is to enable a society where people enjoy life and prosper. Economic growth and technological development aid in this goal. Despite the challenges, the possible advancements made by Society 5.0 and the impact that it will have on democratizing healthcare outweigh the challenges. Society 5.0 will lead to a healthcare system that is predictive, preventive, personalized and participatory rather than reactive as it is nowadays. It can prolong life expectancy and fulfillment.

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Merging Cyberspace with Physical Space to Improve Cervical Cancer Management and Women's Health in Lower-Middle-Income Countries

Langananani Mbodi, Sheynaz Bassa, Mmamoletla Kgoebane-Maseko, Henry A. Adeola, Ravi Mehrotra, and Zodwa Dlamini

L. Mbodi (✉)
Department of Obstetrics and Gynecology, Gynecologic Oncology Unit, University of the Witwatersrand, Parktown, Johannesburg, South Africa

Department of Obstetrics and Gynecology, Charlotte Maxeke Johannesburg Academic Hospital, Parktown, Johannesburg, South Africa
e-mail: langananani.mbodi@wits.ac.za

S. Bassa
Department of Radiation Oncology, Faculty of Health Sciences, Steve Biko Academic Hospital, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: sheynaz.bassa@up.ac.za

M. Kgoebane-Maseko
Department of Anatomical Pathology, Faculty of Health Sciences, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: mw.kgoebane-maseko@up.ac.za

H. A. Adeola
Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, University of the Western Cape and Tygerberg Hospital, Cape Town, South Africa

Division of Dermatology, Department of Medicine, Faculty of Health Sciences and Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa
e-mail: henry.adeola@uct.ac.za

R. Mehrotra
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa

Indian Cancer Genomic Atlas, Centre for Health, Innovation and Policy Foundation, Pune, India
e-mail: ravi.mehrotra@gov.in

Z. Dlamini
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: zodwa.dlamini@up.ac.za

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Abstract The society we envision to live in for the future is one where scientific and technological innovations lead to human health innovations that merge cyberspace and physical space. In women's health, this can be compared with an autonomous driving of these cyber services toward improved women's health and early identification of diseases where strategies and services are decentralized such that women of all ages, languages, and citizenship lead high-quality lives. Imagine a system where women's health information is collected and processed, and such results are applied in the real world whether rural or urban. With the current advancement in technology, access to smartphones and other intelligent gadgets, such ideas should be explored in lower-middle-income countries (LMICs) for managing cervical cancer, a leading cause of death among women. Women, in this age of advanced healthcare services, should not be dying from preventable cancers such as cancer of the cervix. Besides advancements in primary prevention strategies such as HPV vaccines, the disease is often preceded by pre-malignant lesions which, when identified early, can be removed entirely and their development into invasive cancer arrested. This dismal picture can be improved by merging cyberspace information with day-to-day physical space. Applying Society 5.0 to a subunit of society such as a village or a suburb in a metropolitan city can potentially offer solutions in our setting. This chapter discusses the opportunities for employing technological innovations in Society 5.0 to improve cervical cancer management and women's health in South Africa, as an example of lower-middle-income countries. For the SDGs targets to be met in the LMICs, there is a need to simultaneously address challenges such as the energy crisis and bureaucratic issues such as those affecting oversight by government departments as they may deter the implementation of some of Society 5.0 programs. Not only is preventing and treating cervical cancer a human right but also a reproductive health right that requires adequate resources distribution, protection of women's privacy, and maintaining security to their personal information that may be collected during periods of piloting and implementation of research programs that are aimed at finding solutions for cervical cancer programs in LMICs.

Keywords Society 5.0 · Next-generation healthcare · lower-middle-income-countries · Cervical cancer · Artificial intelligence · SDGs · Rights · Energy crisis · Privacy · Oversight · Security · Safety · Resource crisis

1 Introduction

Global cancer statistics (GLOBOCAN 2020) estimated that in 2020, there were 19.3 million new cancer cases reported and 10 million cancer-related deaths, globally. Cervical cancer was recorded as the fourth commonest cancer with 604,000 new cases and 342,000 cervical cancer–related deaths worldwide. Globally, cervical cancer is known as the fourth leading cause of cancer-related deaths in women (Sung et al. 2021).

The global general cancer burden is expected to reach as much as 28.4 million cases in 2040, which is an increase of 47% from 2020 records. A large increase in the burden of disease is expected in transitioning (developing) versus transitioned (developed) countries (64% to 95% and 32% to 56%, respectively) due to demographic changes. However, factors such as globalization and the growing economy, which may contribute to the increase in risk factors, may further exacerbate the problem. For developing countries to attain sustainable cancer care including prevention services, infrastructure development is pivotal, and these strategies will also be critical for global cancer control (Sung et al. 2021).

During their migration, humans went from being hunter-gatherer societies (Society 1.0) that were burdened by disease and dependent on herbs and natural immunity to fight diseases; to an agricultural society (Society 2.0) that depended on farming, farming innovations, and technology that designed drought-resistant crops and genetic modifications which resulted in animals that produced gallons of milk and bulk of meat; through to an industrial society (Society 3.0) that manufactured machinery that did a bulk of work; and to the latest information technology society (Society 4.0) that can access the entire world and almost do anything from the palm of their hands (Deguchi et al. 2020). In all these stages, each society had strategies to screen and manage disease in keeping with the skills and expertise of that society's era. Specifically, each society has ways and means to preserve health, be it through screening, prevention, and treatment of that organ disease, even though the terminology and phrases used to describe such may have changed over the years.

The society we envision for the future (in fact, we are already living in it) is one where scientific and technological innovation leads the human innovations that merge cyberspace and physical space. In women's health, think of this as autonomous driving of these cyber services toward improved women's health and early identification of diseases where strategies and services are decentralized such that women of all ages, languages, and citizenship lead high-quality lives (Deguchi et al. 2020).

In many developed countries, the implementation of an effective screening program hastened the decline of cervical cancer incidences, such as those in Europe, Oceania, and Northern America, even though there was an observed increase in diagnosis at a younger age which may be attributed to changes in sexual behaviors with a resultant increase in HPV infections (Bray et al. 2005). The reduction in new cervical cancer rates was also observed in countries such as the Caribbean and South Americas, whereas the majority (seven of eight) of sub-Saharan countries reported a uniform rise in the rate (Jedy-Agba et al. 2020).

Cervical cancer is one of the cancers that are considered almost completely preventable through a highly effective primary (HPV vaccine) and secondary (screening) prevention strategies. However, less than 30% of LMICs have implemented national HPV vaccination programs in comparison to what is implemented in high-income countries, where more than 80% of these countries have National HPV vaccination programs (Sung et al. 2021). The age-standardized incidence and mortality rates for cervical cancer are relatively higher in most African

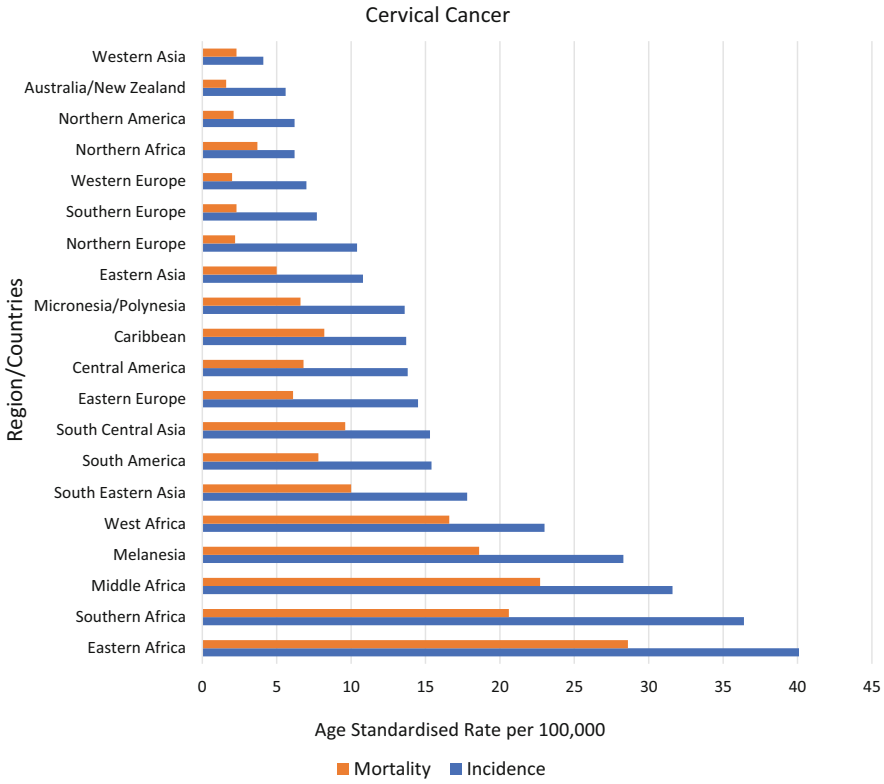

Fig. 1 Region-specific incidence and mortality age-standardized rates for cervical cancer in 2020. Rates are shown in descending order of the world (W) age-standardized incidence rate, and the highest national age-standardized rates for incidence and mortality are superimposed. Adapted from GLOBOCAN 2020 (Sung et al. 2021)

regions compared to other regions and the world (Fig. 1), and the reasons for such disparities are poorly understood.

1.1 What Does Merging Cyberspace with Physical Space Imply?

Cyberspace can be defined as a digital space where real-world data are collected and analyzed by machines/computers to drive solutions. This is where virtual life or events are converted into useful information. In the context of Society 5.0, this real-world data is analyzed in cyberspace using artificial intelligence (AI) and mirrored to the real physical world. Therefore, merging these two will imply a smooth flow from

the physical world to the cyber world and back from the cyber world into the physical world (Deguchi et al. 2020).

1.2 What Makes Society 5.0 the Hope for Women's Health in LMICs?

Imagine a system where women's health information is collected and processed, and such results are applied in the real world whether rural or urban. With the coverage of the current advancements in technology, access to smartphones and other intelligent gadgets, such ideas should have long been alive (Adel 2022).

2 The Societal Problem of Cervical Cancer

It is unfortunate that in this day and age of advanced healthcare services, many women still die from preventable cancers such as cancer of the cervix. Besides advancements in primary prevention strategies such as HPV vaccines, the disease also has premalignant lesions which when identified early can be completely cured and development into invasive cancer can be arrested. However, such is not the case in most developing societies in both urban and rural areas, rich and poor. There are many possible reasons why the health sector and society have not succeeded in stopping the deaths from this disease. These range from perceived lack of resources, misplaced human resources, blocked access to entry into health systems, poor reporting and delay of results, and a lot of patients on the waiting list for surgery. However, the proposed concept of merging cyberspace and day-to-day physical space in Society 5.0 offers new hope for women's health in Africa. Unfortunately, many lower- and middle-income countries continue to plan and execute health programs in the same way that did not yield many results in the past 50 years, thus, failing to acknowledge the evolution and development of human societies and the technological advancements that permit pulling the future to today and bringing tomorrow to now.

3 The Sustainable Development Goals and Society 5.0

Antonio Guterres, the Secretary-General of the United Nations, on the launch of a report on the socioeconomic impacts of COVID-19 in March 2020 said that "Everything we do during and after this crisis [COVID-19] must be with a strong focus on building more equal, inclusive and sustainable economies and societies that are more resilient in the face of pandemics, climate change, and the many other global challenges we face" (United Nations 2020a). There was a slow decline in the

probability of dying from cardiovascular disease, cancer, diabetes, and chronic respiratory disease in people between the ages of 30 and 70 from 22% in 2000 to 19% in 2010 and 18% in 2016 partly due to a shortage of services to prevent diseases with severe disruption to these services seen during the COVID-19 pandemic. The worst affected regions were the LMICs. The implementation of the SDGs (with specific reference to goal 3) was therefore an essential priority. This included the full range of essential health services, from health promotion to prevention, treatment, rehabilitation, and palliative care. If LMICs were to be covered by the year 2030, strategies that include the use of technology, advanced preventive programs, and merging cyberspace with physical space should be part of the solution (United Nations 2020b). The SDGs were aligned with Society 5.0 actions as a universal call for ending poverty for countries including LMICs, the protection of the planet, and to guarantee the enjoyment of peace and prosperity by all people by 2030. Using Society 5.0 to improve women's health through AI-based cervical cancer screening particularly speaks to SDG number 3, which focuses on good health and well-being (Narvaez Rojas et al. 2021; WHO 2021).

4 What Are the Society 5.0 Solutions to Cervical Cancer? (Some Insights)

Applying this to a subunit of society such as a village or a suburb in the city can offer solutions to the problems in lower-middle-income country settings.

4.1 Information Gathering

The screening of cervical cancer has tremendously evolved over time (Table 1), and current approaches such as nucleic acid testing (DNA, RNA, mRNA, etc.) have led

Table 1 The evolution of cervical cancer screening throughout the years through Societies (WHO 2020; Forslund et al. 2019)

Year/period	Cervical cancer screening activity
1928	Dr. Papanikolaou—uterine cancer can be discerned from a vaginal smear
Later	Dr. Aurel Babes and the invention of the Pap smear
1943	American Cancer Society endorses Pap smear
1955–1980	The incidence rate of cervical cancer drops by 70–80%
1988	First clinically available HPB test (viral Pap)
1996	Liquid-based cytology from Hologic (thin prep)
1996	SurePath, FDA approved by Becton Dickinson
2003	HPV DNA testing
2011	HPV RNA testing
2018	mRNA E6/E7

to the accumulation of big data that is potentially amenable to AI and data analytics. The advanced use and ethical sharing of information between government agencies and departments such as Statistic South Africa, information on shopping trends, school and university information, driver and vehicle licensing services information, etc., may be applied to either villages or suburbs isolated from major metropolitan cities. "From crucial information about medication and its effects, right through to daily goals and aspirations, it will help to ensure that everyone can be treated as an individual" (Mohamoud 2020). Information such as age, smoking, sexual behavior, drinking and risks for unsafe sex, access to healthcare, use and access to the internet and emails, and ownership of smartphones or any other intelligent gadgets may be gathered to the benefit of the society as a whole. Such information may be synchronized with information available within the district or regional health facility for processing and developing risk profiles for individuals, districts, or regions. This data is collected from the real world and processed by computers/machines (Adel 2022).

4.2 Information Processing

The processing of this information may be initiated by retrospective access to the data, profiling and characterizing the women who have had the disease (precancer and cancer). Such information can then be used in collaboration with statistical computations and AI systems to develop a risk score for developing cancer, estimating the progression from normal to abnormal cells (precancer) based on individual characteristics and the score and estimating the rate of progression from precancer to cancer based on these individual factors. Instead of generalizing the entire population, these factors and scores can be individualized to a specific female/woman (Pravettoni and Triberti 2020; Loppolo et al. 2020).

4.3 Application to the Real World

Such information can then be used in government budgets and planning for the region/district and resources (such as vaccines, screening kits, colposcopy services, and theater booking) can be mobilized as and when needed for that suburb. With this information, smart resource management can be done without increasing expenditure and with minimalizing any unaccounted expenditure or corruption (The Academy of Medical Sciences 2019).

Individual women can then be informed through any available services such as box office, email, cell phone, or direct contact when they are due for a screening or when they are at the most risk for the development of abnormal cells or cancer; and if there is a need for theater, such can be booked without them having to join long

queues in healthcare facilities. Such implementation is not out of this world and will use the technology we have and the cyberspace that currently exists to solve real-life problems in real time (The Academy of Medical Sciences 2019; Fardazar et al. 2021).

Then perhaps one may ask how the rural areas will benefit from this Society 5.0 innovation. They will benefit in two ways. Direct: If multiple individuals within the rural village are considered high risk for disease development or are due for another screening, such information gathered centrally can be synthesized into services offered to them as a subgroup. Self-applied test kits, for example, can be sent through e-hailing vehicles, ten or so patients test and give the sealed kit back to the e-hail driver who will deliver directly to a laboratory, and tests are processed and results sent to women in real time. This solves the challenge of access and financial resources (Mahdavi et al. 2018; Fardazar et al. 2021). In our opinion, governments do not have to employ 20 healthcare workers to provide such services as cervical cancer screening. The use of the e-hailing system or related services also saves on transportation costs for the specimen to the laboratories, as well as for the patients. An indirect benefit is that when provincial and district governments save money by offering such services in the urban areas, more resources are made available for use by remote regions and can therefore be redirected.

4.3.1 Rapid HPV DNA PCR Machine

In the theme of Society 5.0 aiming to solve social issues from a new perspective, different aspects of health such as screening programs will be connected and technology will integrate big data, the Internet of Things (IoT), and artificial intelligence to develop digital and physical infrastructure for services such as cervical cancer screening (Narvaez Rojas et al. 2021).

With regards to health, it is estimated that by 2065, most populations will have more than 35% of people who are above the age of 65 years. Not only will this result in a reduction in the workforce but also an increased incidence of age-related malignancies. Therefore, screening for malignancies becomes important to all. The LMICs are already burdened by malignancies and will need to increase screening and prevention efforts to reduce the impact (Narvaez Rojas et al. 2021). This will require rapid, reliable, and affordable technology.

5 How Will Society 5.0 Benefit Women's Healthcare in LMICs?

In digital healthcare, Society 5.0 affords an alternative option where technology affords support and essential healthcare medical systems for the benefit of society with regard to the quality of healthcare services (Narvaez Rojas et al. 2021).

Table 2 Main disruptive technologies of the Fourth Industrial Revolution and their impact on women's health (cervical cancer)

Features	Description of general development	Impact on cervical cancer screening and treatment
Artificial intelligence	Algorithms of machine learning and automated decisions	Hand-held cervical screening equipment for triage
Advanced mobile world wide web	Smartphones, 4/5G	Easy access to applications and information regarding choice on management, triage decision, and disease staging by clinicians in remote areas
Internet of Things	Wireless sensors, monitoring of digital and physical information	Allows for prediction model analysis to improve screening and treatment applications
Big data	Data science, analytics	New diagnostic technologies and monitoring of cancer, proteomics in screening and risk monitoring
Blockchain	Cryptocurrency and digital mining	Digitalizes transactions and payments related to cervical cancer management and removes access to funds delays in remote settings
Smart environment	Controlling and decision by machines or human commands	Biomarkers and sensors can pick up the presence of environmental carcinogens and toxicity
Ubiquitous computing	Global access and storage (cloud)	Access to data for cancer-related studies, use of patient data stored for monitoring of disease and screening follow-up
Wearables and devices	Remote health monitoring, diagnostics and decisions, and emergency notifications system	Monitoring of well-being of patients undergoing treatment of cervical cancer including deterioration in patients who are for palliative care and need treatment plan changing

The collection of data, storage, and analyses in a cloud infrastructure is presented in an affordable systems product that LMICs can afford to purchase and maintain for the benefit of the citizens. With this system, information regarding cervical screening status, results, follow-up trends, appointments, and any new information processed can be sent to their district and will ensure timeously compliance to screening such as cervical cytology and prevention strategies such as HPV vaccination (Narvaez Rojas et al. 2021).

Some of the disruptive technological advances seen in the Fourth Industrial Revolution (Table 2) and some applications relevant to cervical cancer prevention, screening, and management and development of research will be key if all societies including LMICs are to advance and benefit from Society 5.0 (de Hoyos Guevara 2022).

Table 3 Comparison between Industry 4.0 and Society 5.0 (Adapted from Deguchi et al. 2020)

Title	Industry 4.0 (Germany)	Society 5.0 (Japan)
Design	(a) High-Tech Strategy 2020 Action Plan for Germany (b) Recommendations for implementing the strategic initiative INDUSTRIE 4.0 (Industry 4.0 Working Group, 2013)	(a) Fifth Science and Technology Basic Plan (released 2016) (b) Comprehensive Strategy on Science, Technology, and Innovation for 2017 (released 2017)
Objectives	(a) Smart factories (b) Focuses on high-tech manufacturing	(a) Super-smart society (b) The focus is on society as a whole
Key issues	(a) Cyber-physical systems (CPS) (b) Internet of Things (IoT) (c) Mass customization	(a) High-level convergence of cyber-space and physical space (b) Balancing economic development with a resolution of social issues (c) Human-centered society

The WHO Global Strategy 2030 to accelerate the elimination of cervical cancer and achieve a cervical cancer-free society by the end of the century requires efforts from various strategies and role players. This includes the plan to achieve a 90% full vaccination of girls with an HPV vaccine by 15 years of age, 70% of women to have been screened using a high-performance test done at ages 35 and 45 years, and lastly, a 90% of those identified with cervical disease (premalignant or malignant) to receive treatment (90% of women with precancer treated, 90% of women with invasive cancer managed) (Sung et al. 2021).

As society moves or upgrades from Society 4.0 to Society 5.0, there will be a transition from currently known dimensions to newer dimensions (Polat and Erkollar 2021). There are some key differences between Industry 4.0 and Society 5.0 (Table 3). The former advocated for smart factories while the latter called for a super smart society. Their scope of deployment of cyber-physical systems differs in that Industry 4.0 deploys in a manufacturing environment whereas Society 5.0 deploys across society as a whole (Deguchi et al. 2020).

Society 5.0 has the potential to resolve multiple challenges in many aspects of human life such as mobility, agriculture, food, manufacturing, disaster control, energy, and most importantly healthcare. The concept fully integrates with a sustainable society where everyone can live a safe and fulfilling life empowered by digital solutions and an integrated approach to health challenges. This will surely allow governments the opportunity to develop a robust framework for a smooth transition from Society 4.0 into Society 5.0, enriched with new-age digital technologies (Deguchi et al. 2020; United Nations 2021). The model is likely to benefit South African society through processes as described in Fig. 2.

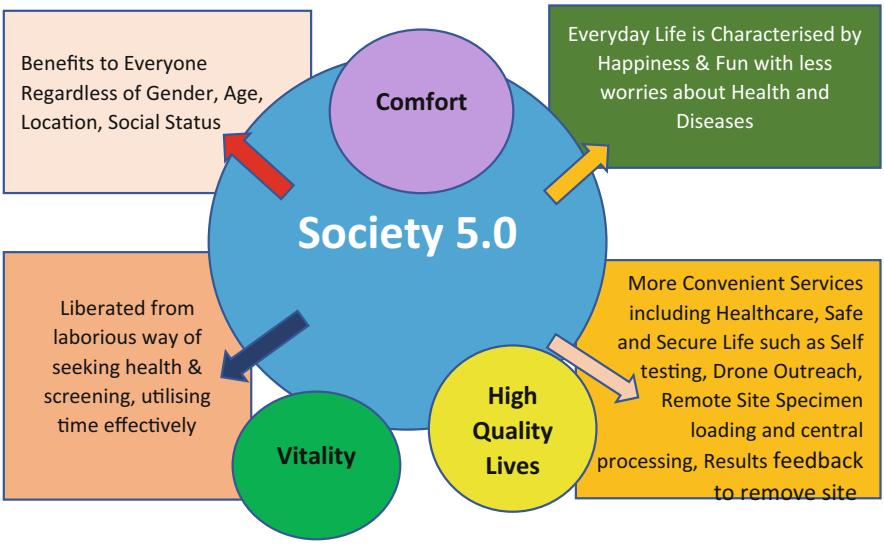

Fig. 2 Vision of a sustainable society where everyone can live a healthy, safe, and fulfilling life

6 How Will Cervical Cancer Screening Be Affected?

6.1 Introduction

As the third most common cancer in women globally, effects have been put to increase and improve screening and vaccination programs in developed countries. There is a wide disparity in the burden of disease between women in developed countries and women in underdeveloped or developing countries. Such has become more profound recently (Sung et al. 2021). Human papillomavirus (HPV) is categorized as low-risk (Lr) or high-risk (Hr), depending on the oncogenic potential of the strain or sub-strain. The majority of cervical cancer diseases are attributed to the infection with the Lr HPV. Sexual contact is often necessary for HPV transmission, and it is the most common STI in the world. Incidences of the disease are highest during teenage years and in 20–30-year-olds. These ages are associated with risk factors such as the early age of sexual debut and multiple sexual partners (Bedell et al. 2020).

When there is immune competency, most young women will be able to mount an effective immune response and clear the HPV infection or reduce the viral load to less than detectable levels within the 24 months period. Tobacco use, immunosuppression, low socioeconomic status, and long-term use of oral contraceptives are associated with the persistence of the disease. HPV consists of a circular, double-stranded genome containing nine open reading frames. "Early" (E) genes control DNA maintenance, replication, and transcription (Fig. 3). E1 and E2 are expressed at high levels early in HPV infection and allow for viral replication within cervical cells. "Late" (L) genes encode capsid proteins (Bedell et al. 2020).

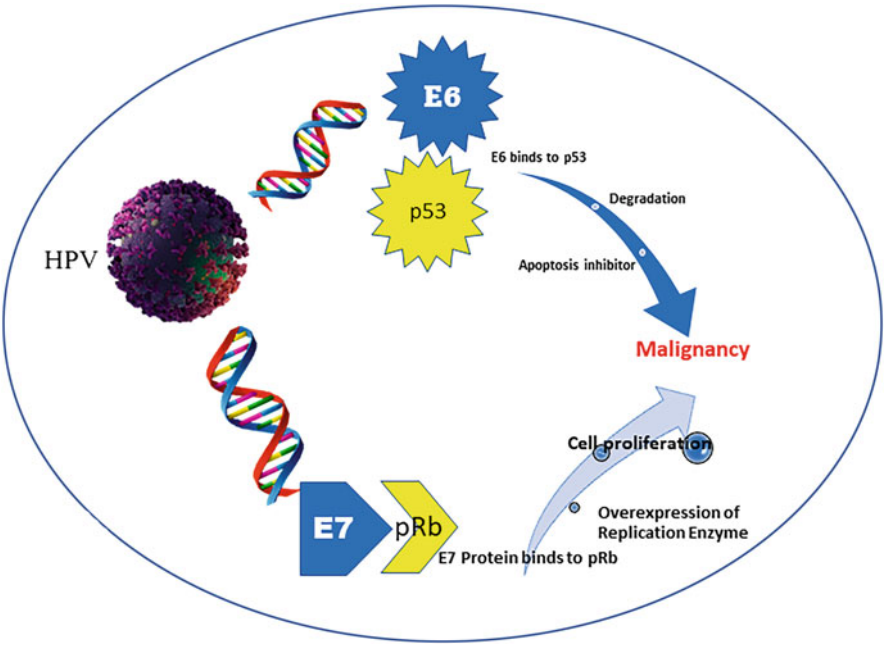

Fig. 3 The role of HPV E6 and E7 in cervical cancer carcinogenesis

6.2 Medical Laboratories in Cervical Cytology and HPV Screening in the Context of Vision 2030 and Society 5.0

Lower-middle-income countries face many challenges that hamper progress in the eradication of HPV infection and treatment of its sequelae (Catarino et al. 2015). Among these is a desperately under-resourced healthcare system. The doctor-to-patient ratio in South Africa stands at 26 per 100,000 1: 3846. The nurse-to-patient ratio is calculated at 1: 213. A cytotechnologist screens approximately 60 cervical smears daily in the public sector, well above recommended daily case numbers with potentially high error rates (Ahmed and Davids 2021; SANC 2020). The lack of improvement in these statistics and lack of innovation means that sub-Saharan Africa continues to under-diagnose and undertreat HPV and cervical cancer. This is further complicated by an entrenched undercurrent of poorly managed HIV infection (Marima et al. 2021). With adequate funding and resourcing, local vaccinology will manufacture HR HPV vaccines. Following the COVID-19 pandemic, governments in Africa are investing in prefilled vaccine manufacturing and rollout.

A Society 5.0 ideal in this space will see individuals self-vaccinating, in a similar way that patients are self-administering insulin and heparin in the comfort of their own homes. Family-centered vaccination by parents for their children and school-driven vaccination drives are initiatives that will reduce much pressure on the health

Table 4 Challenges that may impact South Africa's Vision 2030 in the context of Society 5.0

Challenges	South Africa's Vision 2030, in line with the Society 5.0 approach
Low laboratory equipment capacity	Repurposing of oversupplied PCR testing equipment as well as accompanying skills left behind by the COVID-19 pandemic.[a]
Low laboratory staff capacity	Use of automated cytology screening tools such as BD's FocalPoint GS. Such tools save laboratory human capacity valuable screening time, affording staff more time to focus on difficult positive cases.
Low healthcare professional capacity	Self-testing: Placing testing into the patients' hands provides much-needed relief in terms of health professionals' capacity.[b]
The human condition	Adequate sex education. Equal responsibility for sexual health is shared by both sexes. Eradicative HPV vaccination drives. Education on the use of existing smartphone technology towards sharing health information amongst individuals and health-care professionals, placing the responsibility of individual's health back into their hands.
Current and historical economical inequality	National Health Insurance.
HPV screening is riddled with diagnostic pitfalls which include transient infections, contributing to over-diagnosis and potential over-treatment and inaccurate statistics	Extension of basic HPV PCR screening to include a full cytological evaluation. This can be achieved by the addition of preserving media to self-testing kits: • Diagnosis grading of intraepithelial neoplasia • Diagnosis of in-situ and invasive malignancies • Diagnosis of concomitant infections such as trichomoniasis, candida Enduring that protocols are properly applied to avoid over-treatment.

[a]Lozar et al. (2021)
[b]Arbyn et al. (2018), Bishop et al. (2019), Hitti (2020), Saville et al. (2020), Smith et al. (2016)

system. Some contextual challenges for the realization of Vision 2030 and Society 5.0 in South Africa are presented in Table 4.

The WHO's approach: The current approach to cervical screening for HPV as mandated/guided by the WHO in their 2020 report assessment has placed HPV PCR as an adjunct step in the algorithm for screening and treatment for cervical Hr HPV. In accommodation of the larger developing world, the visual inspection with acetic acid (VIA) step is retained due to its affordability and wide availability and sensitivity. The addition of HPV-PCR as an adjunct in the algorithm was informed by the need to re-purpose/utilize the massive roll-out of PCR that was stimulated by the COVID-19 pandemic (skilling, software, hardware, and consumables) (WHO 2021).

South Africa has done away with the VIA step because patients already receive Pap testing at primary health-care level facilities. Because of the pandemic, even the poorest third-world countries now have PCR testing facilities (WHO 2021).

6.3 *HPV Self-Testing Devices Are Already in Use on the Continent*

Human papillomavirus self-testing is an important screening tool for the early detection of HPV infection and the development of benign and malignant HPV-associated lesions. Some of the self-testing HPV devices are described in Fig. 4a–d.

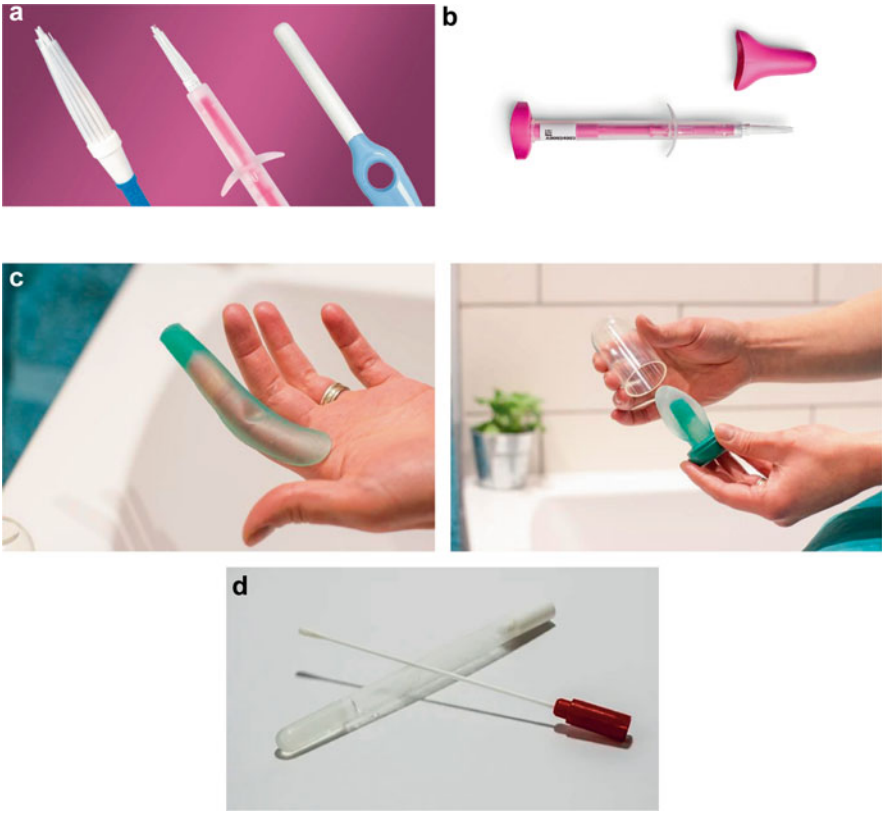

Fig. 4 (**a**) Various HPV self-testing medical devices available on the market (Rover) (Bishop et al. 2019). Images used with permission from Rovers® Medical Devices (www.roversmedicaldevices.com). (**b**) Evalyn® Brush used in Kenya (by Rover) (Bishop et al. 2019). Image used with permission from Rovers® Medical Devices (www.roversmedicaldevices.com). (**c**) Matter's Sukha concept enables women to carry out smear tests at home. Images used with permission from Matter (matter.co.uk). (**d**) Widely used dry swab already piloted in Australia (Arbyn et al. 2018; Bishop et al. 2019; Saville et al. 2020; Smith et al. 2016)

6.4 *Newer Cervical Screening Technologies That May Benefit the LMICs*

6.4.1 HPV DNA

The Hybrid Capture II HPV-DNA Assay (Digene) is the first FDA-approved test for the detection of Hr HPV. To date, four other tests have received FDA approval: Cervista HPV HR (Hologic), Cervista HPV 16/18 (Hologic), Cobas HPV test (Roche Molecular Systems), and APTIMA HPV Assay (Gen-Probe). These have expanded the scope in an era where HPV is used as a primary screening modality. The HPV testing machine is costly and needs laboratory processing, and time to obtain results. However, for LMICs, there is a newer variant of the test, the Hybrid Capture II HPV DNA test that has been designed to work in low-resource settings (the careHPV testing system, QIAGEN, Germantown, MD, USA). It is simple, fast, low-cost, and robust (Bedell et al. 2020). There is also a low-cost PCR-based testing system (AmpFire human papillomavirus detection system, Atila Biosystems) that is not only rapid in analyzing specimens but also more sensitive (Fig. 5). It is approved for use in China and Europe but not yet in the USA. This will also be ideal for LMICs such as South Africa (Bedell et al. 2020).

6.4.2 HPV mRNA Technology

The new focus is on the use of HPV mRNA tests for oncoproteins E6 and E7 messenger RNA detection as an alternative to HPV DNA. The HPV infects the basal cell layer and uses the double-stranded DNA at its core and a protein coat (capsid). The HPV DNA tests detect viral DNA through a hybridization technique or a highly conserved region of the L1 capsid protein or E genes using PCR whereas the HPV mRNA tests detect transcripts of the viral E6/E7 oncoproteins (WHO 2021).

Fig. 5 AmpFire human papillomavirus detection system, Atila Biosystems (Bedell et al. 2020)

Oncogenesis is a result of persistent infection from any of the high-risk genotypes of HPV. This is essential for cervical oncogenesis. The viral particles enter the basal layer of the cervical epithelium and integrate their DNA with the host cellular DNA. As it persists, the E6 and E7 oncoproteins are expressed. These proteins are primarily responsible for neoplastic transformation (WHO 2021).

The E7 protein binds and degrades retinoblastoma (pRb), the tumor suppressor protein, which initiates uncontrolled activation of the cell cycle. The E6 protein degrades p53 (another tumor suppressor protein) and inhibits apoptosis (programmed cell death) and upregulates telomerase activity. The results are cell cycle deregulation and cellular immortalization which kickstarts the process of carcinogenesis. The level of E6 and E7 expression increases as the grade of cervical intraepithelial dysplasia worsens. These changes in HPV mRNA expression of E6/E7 oncoproteins directly underlie the neoplastic phenotype. Detection of HPV E6/E7 mRNA of these two oncoproteins could be more specific than viral DNA (WHO 2021).

6.4.3 Digital Colposcopy

Advances in technology have led to the development of digital optical technology and the manufacturing of highly portable digital colposcopes (Fig. 6) with ultra-high-resolution benefits to manipulate the picture such as magnification and transfer. The gadget and its portability are useful tools for the visual inspection and treatment of premalignant lesions in rural settings (Liu et al. 2016).

When using digital colposcopy software, it is possible to connect through a smartphone which further enhances the image and offers ease of image transfer to a higher center for interpretation. An example is a technology used in the Enhanced Visual Assessment System (MobileODT, Israel) which utilizes the advanced optics found in Android smartphones and is easily available even in low-resource countries (Bedell et al. 2020; Liu et al. 2016).

6.4.4 Self-Sampling for HPV

Self-sampling is an acceptable method in lower-middle-income countries and has been accepted well in rural areas such as the Kwazulu-Natal in South Africa. The specimen is collected with either a swab or brush. Several pilot studies have shown the benefits of using a tampon for specimen collection. The use of the Dacron swab makes testing easy as this device is used in combination with the color indicator cards (Mbatha et al. 2017). Since its introduction, self-testing has been reported to be less sensitive (11% reduction) to the clinician-collected sample with regards to a DNA test and detection of high-grade cervical lesions (Gravitt and Rositch 2014). However, recent studies have shown that self-collected vaginal samples, cotton swabs, and Dacron swabs have an overall sensitivity of 0.74 and specificity of 0.88 when compared with the clinician-collected samples and at times the two are

Fig. 6 Digital colposcopy

comparable (Mbatha et al. 2017). A study in a lower-middle-income country, Ghana, reported that because the prevalence of high-risk HPV is higher in HIV-positive women, acceptance of the self-test helps reduce the weight of visiting a facility and delayed referral for management as these patients are known to progress rapidly from severe dysplasia to malignancy (Asare et al. 2022). We believe that in LMICs, there are barriers that need to be overcome such as personal preferences, environmental factors affecting access, and other barriers including religion. If women are to benefit maximally from the legacy facilities retained after pilot studies or larger studies, these barriers must be overcome.

6.4.5 DNA Methylation

DNA methylation (DNAme) of host cell DNA is another alternative triage tool for Hr HPV-positive women. DNAme has a major role in gene transcription and in genomic stability. Aberrant methylation leads to the silencing of tumor suppressor genes, cell immortality, and malignant transformation. When used for screening triage, it will be an added advantage that it is automated, objective, and run on the same sample as the HPV assay. Some of the genes that have been shown to have elevated methylation profiles in cervical cancer are CADM1, DAPK1, and RARB. Its disadvantages are that it does not cover other HPV types such as 18, 31, 33, and 45 and the high cost (Lorincz et al. 2013).

Elevation of methylation of the HPV 16 L1 and L2 is associated with high-grade cervical intraepithelial neoplasm (CIN) and invasive cancer. Although further studies are required to validate this for clinical practice, there is indeed a known association between specific patterns of DNAme in HPV16 L1 and L2 and high-grade CIN. When rolled out for clinical use, it will help in reducing the waiting period for results and reduce the false negative rate (Lorincz et al. 2013).

6.4.6 The Use of Gene-Xpert

Xpert® HPV is a qualitative, in vitro test that detects HPV in liquid-based cytology (LBC) specimens collected in PreservCyt®. It is able to detect DNA of different Hr HPV types of up to 14. It is quick and results may be available in 60 minutes (Fig. 7). Due to the prevalence of TB in Southern Africa and Africa in general, many health facilities in South Africa have a Gene-Xpert machine. Therefore, its use in screening for cervical cancer is a good step forward toward reducing morbidity and mortality. Each HPV test can be completed in around 1 hour (Cubie and Campbell 2017).

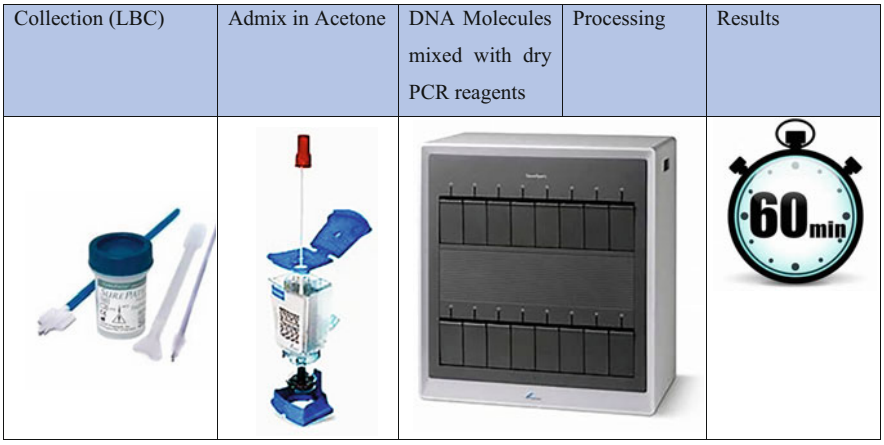

Fig. 7 The Gene-Xpert machine HPV testing process

Although currently, the positivity is about 19.9%, in the detection of HPV graded as "other," it is more than such detection on HPV 16 or HPV 18/45 (64.4% versus 24.2%) for each of HPV 16 or 18/45. The test identifies HPV 31-related types (HPV 31, 33, 35, 52, or 58) mostly in HIV positive people (43.4%). It also has the advantage of ease of use by non-laboratory staff with minimal training, has a rapid turnaround time, and gives reproducible results in about an hour with the added bonus of partial genotyping (Cubie and Campbell 2017).

6.4.7 HPV First Void Urine Testing

Urine "liquid biopsy" for human HPV DNA testing has been reported to have a reasonable correlation with that which is collected from the cervix. The ease of sampling and higher acceptability by women due to its non-invasiveness makes it a perfect test for use in LMICs. The test is performed on the first-void urine and is able to detect cervical cells that were shed off into the vagina and have become a contaminant on the labia (Pattyn et al. 2019). During voiding, these cells are admixed with urine, making it possible for testing HPV DNA on this first void specimen (Vorsters et al. 2014). However, there are challenges related to the standardization of urine collection, storage and preservation, and processing techniques. This technique is predominantly still being piloted, and hopefully, we will have answers that address these challenges and improve the efficacy of the test.

6.5 Radiotherapy Management in LMICs

Surgery has an established role in the curative treatment of cervical cancer. However, a large number of women present with advanced or inoperable diseases for which radiotherapy has an established role in both cure and palliation. The availability of gynecology oncology and radiation oncology services is, however, limited in lower-middle-income countries. Even in LMICs with limited gynecology oncology services, patient access to services is limited by poverty and access to tertiary care facilities (Zubizarreta et al. 2014).

Approximately two-thirds of low-income countries and up to one-third of middle-income countries do not have radiotherapy facilities. The figures for Africa are significantly worse with 80% of low-income countries (LIC) and 44% of LMICs having no radiotherapy facilities (Zubizarreta et al. 2014). Between 4000 and 7000 new units are required to meet the needs of LMICs currently.

Concurrent chemoradiotherapy remains the standard of care for locally advanced cervical cancer. Cisplatinum 40 mg/m2 has been the most common agent studied and a dose-response has been found to impact disease-free survival with a cumulative dose of 200 mg required to meet the threshold for clinical benefit.

6.5.1 Radiotherapy Access in LMICs

There is a dire shortage of radiotherapy resources across the African continent. Even with the upscaling of HPV vaccinations, there will remain a significant burden of cervical cancer requiring radiotherapy treatment (Rodin et al. 2021). At least 5000 new megavoltage radiotherapy units are required to meet the needs of the African continent (Ngwa et al. 2022). Less than half the continent has brachytherapy equipment and like megavoltage units, most of these are concentrated in certain parts of the continent (Tumba and Theyra-Enias 2022). The mere provision of equipment will not address the problem. Human resources include radiation oncologists, medical physicists, radiotherapists, and oncology nurses. Staffing numbers are determined by patient workload and equipment availability. Based on the current equipment needs in Africa, ~50,000 individuals will need to be trained to meet current recommendations (Rodin et al. 2021).

6.5.2 Technological Advances to Deal with LMICs' Radiotherapy Needs

Hypofractionated Radiotherapy

Hypofractionation for pelvic malignancies has proven to be an acceptable form of treatment. The process of delivering higher doses per fraction while reducing the total dose and overall treatment time is an attractive one, especially in centers where resources are limited. Clinical evidence has confirmed the safety and efficacy in breast, prostate, and rectal cancers (Kapiteijn et al. 2001; START Trialists' Group 2008). In rectal cancer, 25Gy in five fractions has been confirmed in early stage, resectable, as well as locally advanced disease (Kapiteijn et al. 2001). Data has been lacking on cervical cancer but there are ongoing randomized studies in this regard. Nonetheless, hypofractionated cervical cancer radiotherapy is practiced in LMICs driven by need as opposed to clinical evidence (Rodin et al. 2021).

7 A Vision for the Future in LMICs

For LMICs, a process where screening a woman at just one time in her life after the age of 35 will be beneficial. Evidence suggests that it decreases the risk of dying from cervical cancer by 70% with the risk of cancer-related death reduced by 85% if the screening is done every 5 years (Bedell et al. 2020) The future where testing is rapid, low-cost, high volume, and self-administered with multitudes of tests a day is not impossible using the above-mentioned technologies. It is not hard to imagine a future where screening programs utilize rapid, low-cost, high-volume, self-swab HPV testing of thousands of women per day. Although these modern tools utilize minimal energy and some are operated and rechargeable batteries, there is still a need

for a secured energy supply. In most LMICs' government systems, there is a crisis in energy supply, and many villages and other establishments still do not have at least a reliable supply of electricity if at all (Jamal 2015). The screening could be done by nurses, midwives, or trained local healthcare workers and images interpreted by artificial intelligence software (Bedell et al. 2020). Not least, drones have been used in healthcare and have proven to assist in breaking the divide and giving the opportunity to patients who have limited (or would rather not directly seek) access to healthcare facilities.

8 Challenges to Implementing Programs for Improving Women's Health in LMICs

For Society 5.0 to work effectively in improving the screening and treatment of women's malignancies, there should be a good and collaborative working relationship between national and local governments. The current red tape in many LMICs hinders progress in developing services such as building an inter-sector information integration architecture and striking a balance between protection and access to personal information. For innovation to be successful, ease on existing national and district regulations should be imposed (Deguchi et al. 2020).

Currently, the rural regions of these LMICs have little identifiable data management systems and such should be established. The urbanized part of the LMICs has some regions with data managed both privately and publicly and these should be consolidated, leveraged, and coordinated with the resultant building of inter-sector information integration architecture (Deguchi et al. 2020).

The existing national and local government policies in existence will need to be enforced together with resolutions of social issues. The generation of data, analysis, and synthesis should not be done only by private companies that are conducting research, piloting projects, and building infrastructure for these studies. Governments should also play a role. However, in most LMICs, governments often fail to do so, and health data will be owned by private companies with no guarantee of citizens' safety (Deguchi et al. 2020).

9 Conclusion

LMICs will benefit from pilot studies done by big pharma and manufacturers with regard to equipment. The pilot of cervical cancer screening tools such as those used in self-collection when combined with mobile stations for pilots, use of drones, and smartphone technology will solve the problems experienced by patients with regard to access to results, follow-up plans, and referral for treatment. Africa and other LMICs are not without resources but have resistance from bureaucrats and political

leaders who in most instances do not share the vision with healthcare workers on the ground. The WHO 2030 plan and its accelerated approach to address all the SDGs is possible in LMICs. The sharing of skills and training of fellow clinicians in the identification and management of precancer and cancer patients will be made possible and easy by aspiring toward Society 5.0. The implementation strategies of Society 5.0 will see LMICs improve drastically with regard to screening and treatment of premalignant lesions and improve the outcome of cervical cancer management, via integration of the cyberspace with physical healthcare space for better women's health.

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Artificial Intelligence–Enhanced Drug Discovery and the Achievement of Next-Generation Human-Centered Health System

Sikhumbuzo Z. Mbatha, Thanyani V. Mulaudzi, Zukile Mbita, Henry A. Adeola, Jyotsna Batra, Kim R. M. Blenman, and Zodwa Dlamini

Abstract Conceptualized in Japan, Society 5.0 sets an ambitious goal of advancing the human endeavor from the current information-intensive society to a knowledge-intensive society by creating a human-centered society based on the integration of cyberspace with real-world physical space, exploiting the powers of artificial intelligence technologies for the betterment of all human life at both individual and societal levels. It is a society that uses technological advancement objectively to

S. Z. Mbatha (✉)
Department of Surgery, University of Pretoria, Hatfield, Pretoria, South Africa

Department of Computer Science, School of Engineering and Applied Science, Yale University, New Haven, CT, USA
e-mail: sikhumbuzo.mbatha@up.ac.za

T. V. Mulaudzi
Department of Surgery, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: thanyani.mulaudzi@up.ac.za

Z. Mbita
Department of Biochemistry, Microbiology and Biotechnology, University of Limpopo, Sovenga, Mankweng, South Africa
e-mail: Zukile.Mbita@ul.ac.za

H. A. Adeola
Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, University of the Western Cape and Tygerberg Hospital, Cape Town, South Africa

Division of Dermatology, Department of Medicine, Faculty of Health Sciences and Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa
e-mail: henry.adeola@uct.ac.za

J. Batra
Centre for Genomics and personalized Health, Queensland University of Technology, Brisbane, Australia

Translational Research Institute, Queensland University of Technology, Brisbane, Australia

School of Biomedical Sciences, Faculty of Medicine and Health, University of New South Wales, Sydney, Australia
e-mail: jyotsna.batra@qut.edu.au

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provide an equitable and fair distribution of the world's resources, circumventing the current inter-personal and global-regional based disparities and inequalities. Such a society will be incomplete without a human-centered health care system, designed to understand patients holistically and provide suitable comprehensive solutions to a patient's health needs. Artificial intelligence (AI) in the drug discovery process uses machine learning and deep learning computational models that enhance the understanding of disease heterogeneity, identify dysregulated molecular pathways, and find the right therapeutic target as well as the appropriate drug candidate during the discovery and design process; thereby, improving efficacy and speed of drug discovery. AI can use deep learning algorithms to analyze vast amounts of data from scientific text and publications relating it to a patient's clinical data and laboratory characteristics and thereby identify suitable candidates for inclusion in a particular clinical trial. AI can also predict the responses to therapy including drug-drug or drug-food interactions. Another crucial aspect of achieving a human-centered health care system will be the protection and upholding of basic human rights as enshrined in the UN's Universal Declaration of Human Rights. Drug development has notable impact on some of these rights and now even more so with the incorporation of AI and machine learning. In this chapter, we outline a brief overview of some of the uses of AI in the drug development process. We discuss the possible influence of AI-enhanced drug discovery in a human-centered health care system with special reference to the drug discovery process, the challenges of availability of therapeutics, especially in low- and middle-income countries, and the challenge posed by the energy crisis on big pharma. And finally, we touch on the human rights issues posed by AI in drug discovery.

Keywords Society 5.0 · Drug discovery · Machine learning · Human-centered design · Deep learning · Artificial intelligence · Right to access medicines

K. R. M. Blenman
Department of Computer Science, School of Engineering and Applied Science, Yale University, New Haven, CT, USA

Department of Internal Medicine, Section of Medical Oncology, School of Medicine, Yale Cancer Center, Yale University, New Haven, CT, USA
e-mail: kim.blenman@yale.edu

Z. Dlamini
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: zodwa.dlamini@up.ac.za

1 Introduction

From time immemorial, human society has gone through a number of eras characterized by massive paradigm shifts and evolution from one era to the next. Human beings started their journey as mere hunter-gatherers (Society 1.0), then settled into agrarian communities (Society 2.0), and eventually progressed to start large industries during the industrial revolution phases (Society 3.0) which culminated in the information age (Society 4.0). Some argue that perhaps now we are also at the precipice of another jump from the information-gathering and information-consuming society to an information-application society characterized by the integration of artificial intelligence (AI) in our everyday lives (Society 5.0). Japan has now set a challenge to the world by conceptualizing what is commonly called Society 5.0. The ideals and ambitious goals of Society 5.0 is the advancement of human endeavor by creating a human-centered society, moving from the current information-intensive society to a knowledge-intensive society, by the integration of cyberspace with real-world physical space and exploiting the powers of AI technologies for the betterment of all human life at both individual and societal levels (Tokyo 2020). It is a society that uses technological advancement objectively to provide an equitable and fair distribution of the world's resources, circumventing the current inter-personal and global-regional based disparities and inequalities (Tokyo 2020).

One of the fundamental tenets of a human-centered society is the creation of human-centered health care systems. A health care system based on the fundamental appreciation of human emotions, thought processes, and people's behavioral tendencies as far as their health is concerned, while at the same time optimizing and encouraging human-centered behavior among all health care providers and health care facilities (Searl et al. 2010). A health care system designed to understand patients holistically and provide suitable comprehensive solutions, delivering products and services that cater to the patient's health needs in a meaningful and pleasurable experience (Melles et al. 2021). Central to the delivery of any health care is the provision of safe therapeutic agents to the right patient, at the right time via an effective and safe dose. The human-centered design includes the design of policies, strategies, services, and products that are effective; accessible; sustainable; lead to improvement in the well-being of humans; enhance user satisfaction; and counteract possible adverse events on human health, safety, and performance (Melles et al. 2021). Health care provision almost always involves the prescription of drugs either as the main treatment of the disease or part thereof. To this end, it is important that clinicians provide effective and safe drugs that are easy to administer and improve patient compliance. Drug discovery is a complex and tedious process, where a traditional workflow can take 12–14 years costing on average more than 2.6 billion USD (Manish Vyas et al. 2018). Though recently, due to the COVID-19 pandemic, we have seen faster time to market of drugs and vaccines in effort to fight the pandemic with much faster repurposing of already existing agents and the FDA more rapidly issuing emergency use approval (EUA) for a number of drugs. For

example, the combination drug consisting of monoclonal antibodies Casirivimab and imdevimab used to treat mild to moderate SARS-CoV-2 infection by targeting the spike protein was issued the first EUA in November 2020 (Gao and Sun 2021). The efficacy of Casirivimab and imdevimab combination to decrease the development of symptomatic disease or reduce the duration of symptoms was tested in a Phase III clinical trial, that started enrolling on July 13, 2020, and lasted for seven months to January 28, 2021, and follow-up ending on March 11, 2021, having only enrolled only 314 participants (O'Brien et al. 2022). Artificial intelligence can be successfully applied at different phases of drug development to enhance efficiency and speed while significantly lowering costs. AI can be employed at various phases of the drug development process, for example, cell target classification and sorting, the prediction of a drug's physical properties, prediction of toxicities, prediction of the 3D structure of a drug, and prediction of drug-protein interactions (Chan et al. 2019). For drug discovery to enhance the envisaged human-centered society, the fundamental question will be on which areas of drug discovery should be the main focus, especially since recent research experience suggests that computational methods fare better with chemistry than they do with biology in a sense that specific chemical reactions are constant and predictable whereas biological systems may respond differently to the same chemical compound due to a variety of factors like patient physiology, genomics, previous environmental or chemical exposures, etc. (Bender and Cortés-Ciriano 2021). Hence, the application in a systems-oriented manner of novel in silico AI approaches to drug discovery and administration will tremendously improve precision health, particularly in resource-limited settings.

2 Drug Discovery

The process of drug discovery starts by identifying a disease process which may be either new or existing, that requires pharmacological therapy. The needed therapeutic agent may be unavailable as in the case of new disease or in a case of existing disease. The available agents may be inadequate due to a variety of reasons, including lack of safety, poor efficacy, toxicity, or poor compliance, as a result of cumbersome dosages. The initial phases of drug development and one of the most important steps involves generation and analysis of data to identify a suitable drug target, which can be either a receptor, a protein, a gene, an RNA, or a disease pathway that if inhibited or activated will result in a desired therapeutic effect (Hughes et al. 2011). The biological target, which is involved in a dysfunctional biological process leading to a disease state, is often identified during basic science research (Mohs and Greig 2017). Table 1 summarizes the drug development process. New drug discovery projects are associated with high attrition rates due to the ever-rising cost of research and development, coupled with low success rates. For example, only around 11% of new compounds complete development and get approval from regulators, while approximately 62% of new drug candidates fail in phase II and III clinical trials. Another major hurdle in drug development is the

Table 1 Drug development process: Overview summary of the process of drug development project from initiation to FDA approval

Activity	Aim and description	Examples, time, and cost	References
Target identification	Identify molecular compound or pathway involved in the disease process that can be targeted with a drug. Involves data mining of a wide range of biomedical data.	Genes, pathways, proteins, or RNAs: lncRNA, miRNA, ceRNAs	Hughes et al. (2011), Jayarathna et al. (2022)
Target validation	Employ various techniques to interrogate that the target will respond to a drug with safe therapeutic benefits. Multi-validation approaches are preferred.	Antisense technologies. Monoclonal antibodies assessment. Chemical genomics assess genomic response to chemicals	Hughes et al. (2011)
Hit discovery	"Hit"—The first compound that shows activity against a targeted protein or pathway, often found by screening chemical libraries or computer simulations.	Obtained via virtual, traditional high-throughput, or fragment-based screening = small molecules (<1000 Dalton)	Mak and Pichika (2019), Zhu et al. (2013)
Lead compound identification	A chemical compound that has the potential to be developed into a new drug and is used as the basis for structural chemical modifications.	Compounds with molecular weights below 500 and logP values below 5	Mak and Pichika (2019), Hefti (2008)
Lead optimization phase	Drug candidates are designed from the lead compound maintaining its favorable properties while improving on its deficiencies.	High throughput DMPK (drug metabolism and pharmacokinetics) screening	Deore et al. (2019)
Pre-clinical testing	In vivo animal studies to evaluate drug candidate safety and efficacy and in vitro studies.	Assess pharmacokinetics and pharmacodynamics of drug and monitor toxicity Timeline: 1–2 years	Deore et al. (2019), Matthews et al. (2016)
Clinical trials (0–IV) on human subjects	Phase 0 – first-in-human, micro-dose studies, and few volunteers to clean pharmacokinetic data. Phase I – assess safety and dosage. Phase II – assess efficacy and side effects. Phase III – assess efficacy and adverse drug events in larger groups over longer periods.	Timeline: 6–7 years	Deore et al. (2019), Matthews et al. (2016)
Regulatory approval	Application for regulatory approval once the drug has passed Phase III.	Timeline: 1–2 years (FDA)	Matthews et al. (2016), Deore et al. (2019)
Clinical trial –Phase IV	Phase IV – post-approval monitoring of drug performance in real-world setting.	Thromboprophylaxis in esophageal cancer patients (TOP-RCT) – ongoing trial	Zhang et al. (2016), NIH (2022)

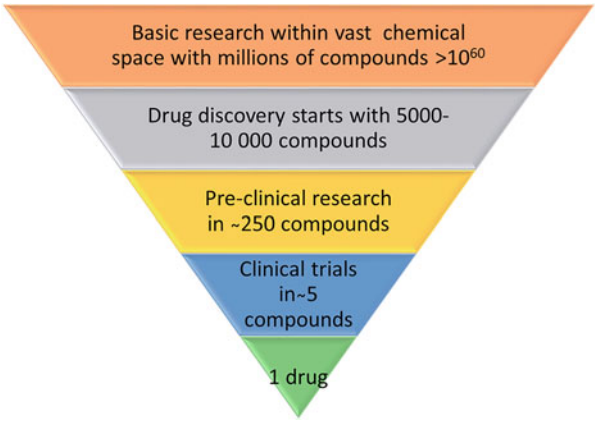

Fig. 1 The funnel-shaped flow of chemical compounds from hypothesis generation to the final approved drug

vastness of chemical space, which is composed of more than 10^{60} molecules (Mak and Pichika 2019). To get one drug approved, approximately 5000–10,000 compounds have to be tested and enter the investigation and development pipeline, significantly increasing cost and time (Deore et al. 2019). Figure 1 shows the funnel-type progression of chemical compounds through the drug development process. A wide variety of molecular structures or ligands can be targeted for drug design based on their level of complexity and the desired pharmacological drug effect. G protein-coupled receptors (GPCRs), for example, have become some of the most commonly targeted protein families because of their involvement in multiple physiological functions and rich ligand space owing to their structural and functional complexity (Díaz et al. 2019). Understanding the physical interplay between therapeutic agents and the intended targets in a living ecosystem is crucial during the drug development process and also remembering that the clinical outcomes observed may be the result of downstream effects (Zhavoronkov et al. 2020). Generally, the more nuanced the intended effect is, the more complex the molecular space that is required for drug design. There are various types of ligands that are targeted during the process of drug design, including full and partial agonists, neutral antagonist, full and partial inverse agonists, allosteric modulators, and biased ligands (Díaz et al. 2019).

2.1 Artificial Intelligence in Drug Discovery

Machine learning (ML) and in particular deep learning (DL) have proven useful in enhancing drug development. Drug discovery proceeds in a feedback loop mechanism of design, make, test, and analyze (DMTA) cycle ensuring that developers can adapt, recover, and learn from mistakes during the process. Machine learning methods that utilize active learning (AL) are well suited to this feedback loop

mechanisms (Smith et al. 2018). AI technology is becoming more and more useful in the pharmaceutical industry due to the advancement and exponential growth of big data; AI is used to predict whether treatment will be successful in a patient, to assess for potential repurposing of existing drugs, and to evaluate the drug's safety and efficacy (Patel and Shah 2022). Machine learning involves the use of algorithms to identify patterns within given data sets. Deep learning uses artificial neural networks (ANNs) comprising of interconnected sophisticated computing elements comparable to the human brain neural network that mimic the functioning of the human brain and thus have an ability to learn and deduce new data and solve problems by recognizing patterns in the input data (Paul et al. 2021). AI learning requires harnessing and understanding volumes of data derived from basic science, clinical research, and clinical practice. This data is typically sourced from hundreds of sources and presented in different formats. Cognitive computing solutions, like IBM Watson, are empowered to understand technical, industry-specific information and use advanced reasoning, predictive modeling, and machine learning techniques to enhance research. They were specifically designed to combine and interrogate big datasets and understand various types of data such as laboratory results in a structured database or the text of scientific publications (Chen et al. 2016). The main benefits of using AI in drug development are in drug design, poly-pharmacology, drug repurposing, and drug screening. Predicting drug properties helps to reduce the rate of inappropriate clinical trials and unsuitable participants, which would be beneficial from both financial and ethical standpoints (Patel and Shah 2022). With drug repurposing and reevaluation using AI tools, we can develop better and improved medicines than currently available, medications that offer benefits in terms of potency, safety, tolerability, and convenience without the need to manipulate new biological targets that are dissimilar to those directly affected by existing medications (Mohs and Greig 2017). Machine learning models such as support vector machines, k-Nearest Neighbors, Naïve Bayes, and Random Forest have been utilized for some time in drug discovery. However, recently deep learning or deep neural networks (DNNs) have risen to prominence because of the superior computational power and flexible architecture which allows the generation of models that can perform single-task or multitask machine learning as well as predict drug-target interaction more accurately (Ekins et al. 2019). The advantage of deep learning is its capability to adapt to a wider class of chemical compounds and modeling tasks allowing for a more efficient use of data (Jiménez-Luna et al. 2021). Figure 2 depicts the role of artificial intelligence in the drug discovery process over time, while Fig. 3 highlights some of the areas where artificial intelligence can be successfully employed during drug development.

2.1.1 Artificial Intelligence in Identifying Potential Drug Targets

Artificial intelligence is useful in identifying potential biological entities that can be used as targets for drug development. For example, IBM Watson as a cognitive learning computational model was used to accurately predict and rank RNA-binding

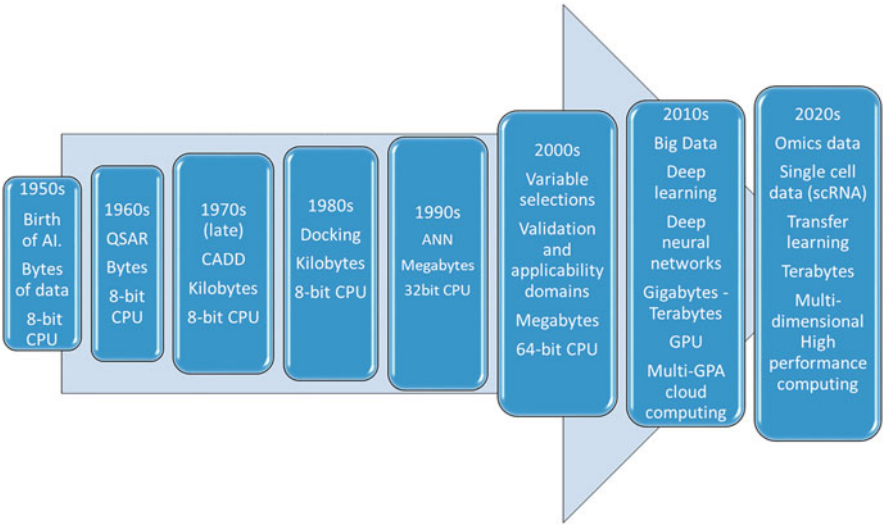

Fig. 2 Artificial intelligence in drug discovery: Depicts the progress of AI application in drug discovery over the years, showing increases in computing power and data. CPU – central processing unit, GPU – graphics processing unit, QSAR – quantitative structure-activity relationship, CADD – computer-aided drug discovery, ANN – artificial neural networks, scRNA – single-cell RNA sequencing data (Zhu 2020; Wang et al. 2019; Cai et al. 2020)

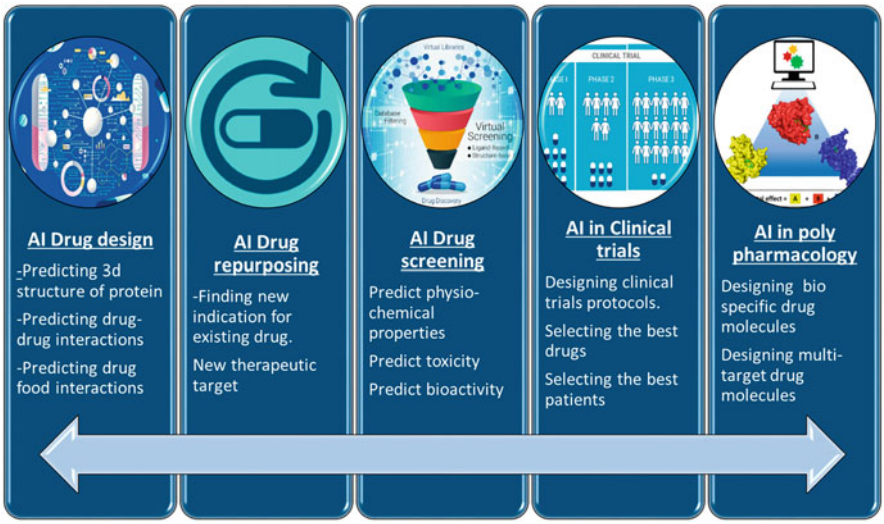

Fig. 3 Depicting some of the areas where AI can be integrated into the drug discovery process. Adapted from Paul et al. (2021)

proteins (RBPs) that are altered in amyotrophic lateral sclerosis (ALS) by mining scientific publications and extracting domain-specific text features to identify new connections between the entities of interest. Eight of the top ten altered RBPs as ranked by IBM Watson were validated with immunohistochemistry and RNA and protein analyses of the lumbar spinal cords of ALS patients and normal non-neurogenic controls. ALS is a devastating neurodegenerative disease that is putatively caused by alterations in RBPs and at present has no treatment (Bakkar et al. 2018).

Applying multiple supervised and unsupervised machine learning algorithms on molecular data, Sinkala et al. (2020) sub-classified pancreatic cancer into two distinct subtypes that upregulate different kinases. Subtype-1 tumors showed upregulation of m-TOR signaling pathway–associated kinases like MTOR-pS2448, GSKB-pS21-S9, and PDK-pS241 whereas subtype-2 tumors display upregulation of the cell cycle–associated kinases like CDK1-pY15, p27-pT158, and p27-pT198. Most of these kinases are potential targets for small molecule inhibitors. The small molecule inhibitors are currently being tested or used in some anticancer clinical trials (Sinkala et al. 2020). ML can analyze multiple complex pathways to identify appropriate potential targets. For example, competing endogenous RNAs (ceRNA) have been identified as important post-transcriptional regulators of gene expression via the microRNA-mediated mechanism and may play a prominent role in the molecular pathogenesis of hormone-dependent cancers (Jayarathna et al. 2022). Jayarathna et al. utilized a supervised machine learning algorithm called Cancerin to identify regulation-factor-mediated ceRNA networks in five hormone-dependent cancers; they identified cancer survival significant ceRNAs *BUB1* and *EXO1* for invasive breast carcinoma, adenocarcinoma of the colon, uterine corpus endometrial carcinoma; and ceRNA *RMM 2* for prostate adenocarcinoma, adenocarcinoma of the colon, and uterine corpus endometrial carcinoma. These ceRNAs provide potential targets for drug development against these hormone-dependent cancers (Jayarathna et al. 2022).

2.1.2 Artificial Intelligence Tools in Pharmaceuticals

A number of AI-based tools that function in the pharmaceutical industry have been developed, and these include the following:

- IBM Watson

  IBM Watson is a supercomputer developed by International Business Machines (IBM) which has a combination of AI and sophisticated analytical software. Watson can be utilized in various domains, including medicine, life sciences, engineering, law, and finance. It collates data into what is called Watson corpus and groups databases relevant to each domain into domain-specific corpuses. It then uses deep natural language processing and machine learning capabilities to teach itself and make a meaningful conclusion in a cognitive fashion from the vast data (Chen et al. 2016). Its health application called Watson

Health was designed to analyze structured and unstructured data from a patient's medical records, scientific publications, and other relevant data (i.e., clinical research trial data and basic science research) and thereby assist clinicians by providing possible appropriate options for further treatment or disease management of a patient. Watson has information from literature curated by Memorial Sloane Kettering Cancer Center, over 200 textbooks, 12 million text pages, and over 290 medical journals (Manish Vyas et al. 2018; Paul et al. 2021). However, while Watson Health is excellent at the interpretation of well-organized curated data it has had difficulties with the interpretation of very unstructured medical data from written medical notes and case reports and often confuses medical abbreviations used by clinicians because it fails to decipher the medical context when an acronym is used; MD Anderson data found that despite training Watson still could not interpret unstructured medical language as well as human beings could (Schmidt 2017).

- Robot pharmacy

  While employing AI to develop innovative medicines is helpful, we also need to consider access and the appropriate administration of these drugs. In the real-world setting almost half of all medications are inappropriately prescribed, dispensed, or sold, while at the same time only about 50% compliance rate is seen among patients (Leisinger et al. 2012). Technological companies have developed AI technology in the form of Robot pharmacies to improve safety and efficiencies in drug dispensing, with improved dose preparation and the ability to keep track of all medications dispensed and stored in the facility. UCSF Medical Center uses robotic technology for the preparation and tracking of medications and their system purportedly performed much better than humans at delivering accurate medication to correct patients after preparing more than 350,000 doses (Manish Vyas et al. 2018).

  Although Robot pharmacies have been proven to significantly reduce medication errors, they do have disadvantages and limitations. These include high initial set-up cost coupled with expensive up-keep that may lead to job losses to offset those costs, an unexpected failure of the computer program controlling the pharmacy with disastrous consequences especially with IV preparation systems, etc. Mechanical errors do also occur, which included vials or fluid bags that fall outside the weight parameters, failure of the robot to successively grip or hold a vial due to manufacturing defects, incorrect measurements of syringes or other items, faulty needles, and failure to recognize barcodes and correct medication vials (Alahmari et al. 2022).

2.1.3 Artificial Intelligence in Drug Screening/Virtual Screening

Artificial intelligence, ML, and DL through superior computational modeling have the ability to identify and validate chemical compounds, assist in the hit discovery, peptide synthesis, evaluation of physiochemical properties, drug monitoring for efficacy and effectiveness, and drug repurposing. AI models can also identify

potential toxicity problems that may occur as a result of off-target interactions (Gupta et al. 2021).

Virtual screening (VS) is a computational technique used to search a large library of chemical compounds in order to identify those that are likely to bind to a specific drug target, usually an enzyme or receptor (Gimeno et al. 2019). Traditionally screening for lead compounds involved in vitro high-throughput screening of all the chemical space for existing compounds in a particular collection, which is very time- and resource-heavy while producing a low number of hits (Carpenter and Huang 2018; Mcinnes 2007). Virtual screening introduces the possibility to screen both existing molecules as well as those that are not physically present in the collection of interest, but can be purchased or synthesized, while at the same time introducing the increased computational ability to predict binding affinity which enables scientists to test only a relatively small subset of compounds in low or medium throughput assay format (Mcinnes 2007).

Virtual screening for potential drug candidates minimizes time and cost associated with early drug discovery, by accurately predicting the ligand–protein binding potential between a chemical compound and target protein in silico, thus minimizing the need for costly in vitro/in vivo experiments. VS facilitates faster hit identification and validation and lead optimization. VS methods can be ligand-based (LBVS) or structure-based (SBVS) or a combination of both, with SBVS having emerged as one of the most promising techniques (Maia et al. 2020; Negru et al. 2022). VS sequentially selects the compounds that have a higher susceptibility to bind to the target protein with the least amounts of adverse reactions. This process can filter out from 500 compounds down to only 5 compounds that will proceed to in vitro experiments (Maia et al. 2020). In SBVS, the protein structure is known and available and it's docked into the environment of the biochemical target, and the compound library of small molecules is explored using computer algorithms and scoring functions (mathematical algorithms) to assess the binding affinity strength between the docked compound and the target. A number of docking software programs are available with different conformational sampling algorithms and a variety of scoring functions. In LBVS, biological data is evaluated to identify known active or inactive compounds that will be used to retrieve other potentially active molecular scaffolds based on similarity measures (evaluates the database for the nearest-neighbor molecules most likely to exhibit the needed bioactivity against the bioactive reference structure), common pharmacophores (a 3D molecular structure that is needed for a ligand to interact with target receptor binding site), or descriptor values (Lavecchia and Di Giovanni 2013).

Pal et al. in their study to identify potential anti-cancer agents that may target GPR12 0, a G-protein coupled receptor that is over-expressed in colorectal cancer cells, virtually screened approximately 350,000 well-characterized and drug-like molecules from the SPECS database against GPR120s and finally only selected 13 hit-compounds which needed in vitro testing. In the end, they identified a potential chemical scaffold for future CRC anti-cancer drugs named *dihydrospiro (benzo[h]quinazoline-5,1′ -cyclopentane)-4(3H)-one* (Pal et al. 2021).

Virtual screening will undoubtedly be further enhanced by the machine learning ability to not only predict drug–protein interactions but also to accurately predict the three-dimensional structure of proteins. The revolution in protein structure prediction is the advent of AlphaFold2 system developed by DeepMind, and it is an artificial neural network system that predicts protein structure with a median accuracy of 1.5 ångströms. AlphaFold2 considers both local and long-range interactions in protein molecules. It uses computational algorithms that efficiently capture long-range interactions on the basis of fundamental aspects of protein geometry and repeatedly applies these operations to refine its structure prediction, while also applying structured machine-learning approaches that deduce protein structures by identifying patterns of mutation in proteins that evolve in common temporo-spatial environment and thereby identifying amino-acid residues that are closely related to each other. It may predict approximately 60% of all human-protein regions (Alquraishi 2021).

2.1.4 Artificial Intelligence in Prediction of Physiochemical Properties

A crucial step in drug discovery and design is to define the relationship between chemical structures and biologically active physiochemical properties because they indirectly affect the drug's pharmacokinetics and its target receptor family. Physicochemical properties include solubility, partition coefficient (logP), degree of ionization, and intrinsic permeability of the drug (Paul et al. 2021).

Quantitative structure–property relationship (QSPR) methods involve supervised learning methods designed to extract and predict often complex relationships between the physicochemical properties of interest and the molecular structure of chemical materials (Le et al. 2012; Zang et al. 2017). Zang et al. developed QSPR models for in silico prediction of six physicochemical properties (logP, logS, logBCF, BP, MP, or logVP) by analyzing the binary molecular fingerprints from diverse data sets of environmental organic chemicals. The data sets used were obtained from Estimation Program Interface (EPI) Suite. They used unambiguous machine learning algorithms, namely multiple linear regression (MLR) which produced a linear model to describe the relationship between a physicochemical property and molecular fingerprint bits, partial least-squares regression (PLSR) generated linear statistical models based on the fingerprint bits and the physicochemical property being predicted, random forest (RF) is a nonlinear consensus method based upon an ensemble of decision trees, and support vector regression (SVR), which was shown to be superior to the other three approaches, modeled a nonlinear relationship between the property and molecular descriptors (Zang et al. 2017).

"Quantitative-structure activity relationship (QSAR) modeling is a computational approach through which quantitative mathematical models can be created between chemical structure and biological activities" (Gupta et al. 2021). The mathematical model helps in identifying a chemical entity from molecular databases that can be used as a drug compound, which is then sent for laboratory synthesis followed by in vitro or in vivo testing (Gupta et al. 2021). Many systems-oriented, multiscale

mathematical models using ordinary and stochastic differential equations (ODE and SDE) have been formulated to determine the therapeutic efficacy of combinatorial administration of cancer drugs (Goldie et al. 1988; Sun et al. 2016; Malinzi et al. 2021). The merits of these higher order abstraction mathematical models have been demonstrated in various experimental scenarios to be able to significantly mitigate the prohibitive cost and human effort required in the drug development pipeline, as well as determine the optimal combination of drugs, which minimizes toxicity and other adverse side effects (Malinzi et al. 2021). These emerging novel mathematical oncological approaches would be potentially beneficial for optimal and cost-effective oncological care in resource-limited health care settings.

2.1.5 Artificial Intelligence in Predicting Drug-Drug and Drug-Food Interactions

Drug-drug interaction (DDI) and drug-food interaction (DFI) can lead to a significant decrease in drug efficacy, compliance, and safety with increased risk of adverse events. Furthermore, pharmacogenomics which deals with individual genomic differences in metabolism of drugs can affect the efficacy and precision of pharmacological agents in treating various diseases (Ryu et al. 2018). Available computational models that are used to predict drug–drug interactions can be divided into three categories namely similarity-based methods, networks-based methods, and machine learning methods. ML methods improve DDI prediction by integration of multiple aspects of data from a single source or multiple heterogeneous data sources, with ensemble learning, kernel methods, and deep learning used predominantly to integrate data from heterogeneous sources. However, data integration has a downside of increasing data complexity and a potential to drown data regarding the underlying molecular perturbations that result in DDI (Mei and Zhang 2021). In an attempt to improve on these data integration shortcomings, Mei and Zhang developed a machine learning framework that uses drug target gene profiles and signaling pathways as the basis of learning and prediction of DDI; they employed l_2-regularized logistic regression model (Mei and Zhang 2021).

Artificial intelligence can be used not only to predict potential drug-drug and drug-food interactions, but also suggest alternative drug pairs that produce minimal side effects and are more effective. Ryu et al. (2018) presented a computational model called DeepDDI that employed machine learning and DNN to predict and classify drug-drug interaction for a given drug pair. As system inputs, they used the names of drugs and their chemical compound's structural information, provided in simplified molecular-input line-entry system (SMILES). DeepDDI outputs were presented as readable human sentences that describe changes in pharmacological effects and/or the risk of adverse drug events because of the interaction between two drugs in a pair. DeepDDI produced specific information on drug interactions with high accuracies of 84.8–93.2% in predicting drug-drug interaction and drug-food interactions (Ryu et al. 2018).

2.1.6 Drug Repurposing

Drug repurposing is an approach of assessing whether an existing drug, which may or may not have been approved for original intended use, can be repositioned and used for another new indication. It offers a cost-effective and rapid solution to drug development, bringing much needed therapeutics to patients quicker and at less cost than designing a new drug (Zhou et al. 2020).

Ge et al. (2021) used an integrative network combining machine learning and statistical analysis model to identify potential drug targets for the treatment of SARS-CoV-2. They used a network-based knowledge mining algorithm called CoV-DTI and used a deep learning–based relation extraction method named BERE among other methods. Their study demonstrated that poly-ADP-ribose polymerase 1 (PARP1) inhibitor CVL218 exhibited significant antiviral activity against SARS-CoV-2 and therefore could be used to treat COVID-19. CVL218 demonstrated inhibitory activity against the replication of SARS-CoV-2. Its antiviral mechanism was shown to be potentially mediated by binding and interaction with the nucleocapsid protein of SARS-CoV-2. At the time of their study CVL218 and other PARP1 inhibitors either already had FDA approval or were being actively tested in clinical trials as potential antiviral therapeutic agents (Ge et al. 2021).

2.1.7 Clinical Trial Design and Artificial Intelligence

Significant cost and time in the drug development pipeline are consumed by the clinical trial phases (Ekins et al. 2019). This phase can take up to 57% (1.46 of 2.56 billion USD) of the total budget cost and last for 7–10 years. Therefore, failure in clinical trials impairs investment into the trial itself and also negatively affects pre-clinical development costs. The major reasons for failures during trials are poor patient selection and recruitment, as well as ineffective patient monitoring during trials (Zhavoronkov et al. 2020). AI can improve the success of clinical trials. For example, for patient cohort selection natural language processing (NLP) and computer vision algorithms such as optical character recognition (OCR) can be used to automate and compile patient data from “omic” data, electronic medical record (EMR), handwritten paper copies, digital medical imagery, and biomarkers, thereby improving clinical trial enrichment and patient cohort composition (Harrer et al. 2019). IBM developed the AI-based clinical trial matching system called Watson for Clinical Trial Matching (WCTM) that helps to match patients to clinical trial by analyzing and integrating the large quantity of structured and unstructured EMR data, creating detailed patient profiles of clinical findings and comparing them to trial eligibility criteria in ongoing clinical trials (Zhavoronkov et al. 2020). A study by Beck et al. evaluated the performance of WCTM in a cohort of 239 breast cancer patients and found that WCTM correctly identified 91–95% of eligible patients in three out of the four trials and reduced screening time by 78%, and they concluded

that WCTM assisted and expedited matching patients with correct clinical trials (Beck et al. 2020).

2.2 Challenges

The sheer scale of the large chemical space plus data sets of millions of compounds that are held by pharmaceutical companies for drug development coupled with the rapid growth, diversity, and uncertainty of this large data poses a significant challenge to computing power of traditional ML tools and AI. For instance, some computational models can predict large numbers of compounds or simple physicochemical parameters but fail to predict complex biological and pharmaco-genomic properties, such as the efficacy and adverse effects of compounds (Paul et al. 2021).

Artificial intelligence models and tools rely heavily on the availability of credible medical data. One of the challenges is the accessibility of EMR data. EMR formats tend to differ widely between institutions and regions and are sometimes not compatible with each other; some records are not digitalized or even electronic and exist in a decentralized environment with no data exchange. Strict legal regulatory frameworks on data collection also limit access to patient data by third parties, with even patients themselves having difficulty accessing their own records (Harrer et al. 2019). Properly kept EMR will be particularly useful in low- and middle-income countries (LMICs), especially in Africa, where infectious diseases have become the leading cause of death, with HIV and multi-drug resistant TB being the major culprits, followed by trauma deaths. Patients with infectious diseases require continuous treatment and long-term care, necessitating an efficient record-keeping system. Some of the challenges negatively affecting widespread use and implementation of EMR in LMICs are related to poor bandwidth availability and access to the internet in health facilities, low levels of computer literacy and lack of motivation to use the system correctly, and concerns from clinicians about medico-legal litigation (Ohuabunwa et al. 2016). For most LMICs, EMR adoption and implementation is limited to specific disease programs such as HIV and TB in small regions of the country. Effective implementation is influenced by the availability of funding (which commonly comes from external donors) and poor involvement of stakeholders, and therefore evidence-based strategies need to be developed to enable EMR integration in the national health care systems of LMICs (Kumar and Mostafa 2020).

Despite an enormous amount of extremely valuable chemical and biological data being now publicly available together with screening data, most of this data is kept in different databases using different formats and generally is not AI model ready or machine readable. Therefore, this data needs to be properly curated and prepared before the machine learning models can be used (Ekins et al. 2019). Over and above that in resource-constrained settings, the feasibility of deploying AI for drug delivery is limited by factors such as lack of stable power supply, human resources, and computer infrastructures.

Another challenge that AI faces is the interpretation and analysis of unstructured medical data because the quality of data varies and different medical institutions sometimes use medical terms differently (Schmidt 2017).

Major global events of the past three years have led to unprecedented multi-pronged crises. The COVID-19 pandemic and subsequent shutdowns have led to shortages of raw materials and the Ukraine-Russia war has worsened the situation leading to an energy crisis that has negatively impacted not only Europe but the entire globe. Big pharma is faced with escalating energy costs and costs of raw material, such that a lobby group, Medicines for Europe, has warned that European pharmaceutical companies may have to stop producing cheaper generic drugs (Hawkins 2022). The increase in energy and resource costs will push drug prices higher, limiting the availability of medicines, especially in under-resourced countries. Companies are now having to change their business models in order to accommodate the energy crisis, such as looking at alternative energy sources in particular renewable energies (Stewart 2023).

3 Achieving a Human-Centered Health System

A human-centered health system has people as the focal point of all care solutions. It is a system that seeks to gain deep understanding of people's needs and design solutions by seeing the world through the eyes of all people involved (patients, caregivers, clinicians, nurses, pharmacists, and all the involved stakeholders). It incorporates the experiences and insights of patients, citizens, and the workforce. Human-centered health design involves empathy and prototyping, requiring input from both patients and clinicians, which results in greater satisfaction, better health outcomes, and proper allocation of resources (Naar et al. 2018).

The most expensive part of drug design is the conduct of human clinical trials. AI has the potential to lower this cost, but by supplementing trial designs with human-centered design (HCD), costs can be lowered even further. HCD has the ability to bring new ideas to entrenched problems by bringing in a strong human lens and integrating multiple stakeholder perspectives in program designs. The greater the engagement of stakeholders in a project the greater their continued willingness and motivation to engage and see the project to completion (Blynn et al. 2021). Bender and Cortes have argued that limiting the failure rate in clinical trial phases may be more important in terms of cost reduction than decreases in the cost of individual preclinical phases or the speed of completion of a phase. They also argue that it is crucial to improve the quality of decisions regarding which chemical compound will be the best to take forward in drug discovery projects, the best compound being the one that is most likely to provide the desired outcome in terms of efficacy and safety (Bender and Cortés-Ciriano 2021).

Artificial intelligence applications in drug discovery can increase access to medicine and improve the experience of patients, their families together with health care workers, and all involved in the health care system. Access to affordable, safe,

and effective medicine is a fundamental human right. To try and attain universal human rights and improve the lives of all the earth's inhabitants, in accordance with the United Nations developed sustainable development goals (SDG) that need to be achieved by the year 2030. Goal number 3 talks about "Ensuring healthy lives and promoting well-being for all at all ages" and particularly goal 3.8 seeks to "Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all" (UN-SDGs 2015). However, more than half of the people living in low- and middle-income countries do not have access to essential medicines for a variety of reasons including the high cost of medicines and poor health care infrastructure. New medicines are unaffordable for the majority of the population living in LMICs, while at the same time these countries have 75% of the world's poor, accounting for the majority of the global disease burden (Stevens and Huys 2017). Therefore, leveraging the AI's advantages of increased speed coupled with reduced cost of drug development will be paramount if we are to attain Goal 3 of SDGs. While governments are responsible for the health care infrastructure, pharmaceutical companies can play a key role in improving access to medicines; through innovation and enhancing research and development capabilities, they will be well poised to produce cheap and innovative medicines that improve quality of life (Leisinger et al. 2012). Improving access to essential medicines and vaccines coupled with their proper use will reduce unnecessary suffering and potentially save up to 10.5 million lives each year (Leisinger et al. 2012).

Artificial intelligence plays a crucial role in the development of a human-centered health care system, playing a role not only in the laboratory space of research and development but also during the implementation processes. For example, Beede et al. conducted a human-centered evaluation of a deep learning system by conducting a prospective sociotechnical study in a real-world clinical setting. The study evaluated the performance of the deep learning algorithm used to assess retinal images of diabetic patients for the detection of diabetic eye disease (diabetic retinopathy), but it also had an additional focus on the human aspects of deploying the DL algorithm. They assessed the experience of nurses, technicians, and indirectly of patients interacting with the system. They found that the system significantly improved the time to specialist referral recommendation from up to ten weeks for a referral recommendation to same-day immediate referral recommendation. However, the study did highlight human aspect challenges with respect to nurse and patient experience; nurses expressed frustrations with the systems' inability to grade "poor" quality images while patients complained about the logistical problems posed by the sudden need to travel to the far away referral center (Beede et al. 2020). Figure 4 demonstrates the interaction between drug discovery and artificial intelligence and how that can be integrated with human-centered design with the aim of achieving a human-centered health care system.

Artificial intelligence in the treatment of disease is not confined to drug discovery alone. In recent years, virtual reality (VR) simulations have emerged as a treatment for a variety of mental health diseases. According to the World Health Organization (WHO), mental health disorders affected 12.5% (1/8) of the world's population in

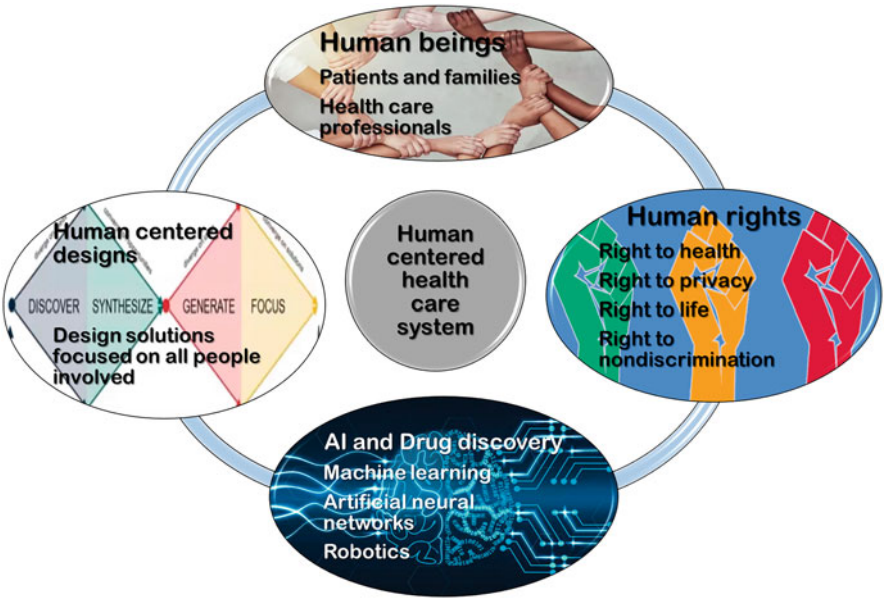

Fig. 4 Human-centered health care system. Requires putting people first. Applying human-centered design principles of empathy and prototyping in any project that will result in a health care outcome or health care experience

2019, with anxiety and depressive disorders being the most common conditions. Just in 2020 alone with the COVID-19 pandemic, there was an estimated increase of 26% in anxiety and 28% in depression (WHO 2022). Virtual reality provides an advanced human–computer interface that enables the creation of specific computer-generated virtual environments that are used to retrain the brain's reaction to the scenarios that lead to the mental disorder (Riva and Serino 2020). VR in vitro exposure allows for better control and standardization of the simulated environment for both therapists and patients compared to in vivo exposure (Guitard et al. 2019). VR exposure therapy combined with cognitive behavioral therapy has been used to successfully treat social anxiety disorder, depression, post-traumatic stress disorder, phobias, autism, and schizophrenia (Baghaei et al. 2021; Park et al. 2019).

4 Human Rights Impact of Artificial Intelligence and Drug Development

Another fundamental tenet of achieving a human-centered health care system will be the protection and upholding of basic human rights as enshrined in the UN's Universal Declaration of Human Rights. Drug development has notable impact on some of these rights and now even more so with the incorporation of AI and machine

Table 2 Impact of AI on human rights in relation to health care (Adapted from Mpinga et al. 2022)

Area	Impact of AI	Protected rights	Threatened rights
Health and health care	Improved diagnostics Improved access to care Increased safety in care Strengthening and precision in prevention Improved quality control of care Improving health promotion	Right to health Right to life Right to information Right to work Right to participate	Right to work Right to health Right to culture Right to life Right to non-discrimination

learning. These two fields raise certain challenges; drug development impacts the right to health and access to essential medicines, while AI and machine learning raise challenges with regard to privacy and security of citizens and protection from biases. Enhancing drug development with AI involves canvassing large amounts of sensitive and private medical data from large groups of patients be it in the initial phases of identifying a target disease or during the clinical trial phases, thereby raising concerns about the right to privacy (Noorbakhsh-Sabet et al. 2019). It is important, however, to underline that human rights are not necessarily always threatened but may be enhanced by AI as noted by Mpinga et al.; see Table 2 (Mpinga et al. 2022). The use of AI in the drug discovery and development process fast-tracks the process making it more cost-effective and efficient, thereby promoting access to medicines and the right to health. While on the other hand, selection biases of data points used to feed learning algorithms and the use of "limited" genomic and clinical trial databases from selected regions or ethnic groups may lead to the development of agents that may be unsafe to use in underserved under-represented peoples, thereby threatening their rights to health, safety, and life (Naik et al. 2022).

Pharmaceutical companies as main developers of drugs have an obligation to find a balance between their needs to protect their patents and profits on one hand, while on the other hand ensuring people's right to access safe and quality medicines by promoting transparency, monitoring, accountability, fair pricing, ethical marketing, and promulgating and adhering to regulations concerning drug safety and quality. Whereas governments have a legal obligation to ensure quality essential medicines are available, affordable, and accessible to their citizenry and they are duty-bound to prevent violations of human rights by pharmaceutical companies (Gruskin and Raad 2010). Two United Nations guidelines – the *Guiding Principles on Business and Human Rights* (2011) and the *Human Rights Guidelines for Pharmaceutical Companies in Relation to Access to Medicines* (2008) – appropriate a moral obligation and responsibility to pharmaceutical companies to make essential medicines including vaccines are available, particularly to patients in LMICs (Santoro and Shanklin 2020).

5 Conclusion

Enhancing human-centered health care is about improving the quality of health care offered to all the world's citizens, regardless of race, gender, age, sexual orientation, or geography. Human-centered design needs to be integrated in all projects or innovation of any product or service that is intended to produce healthy outcomes and service experience. Incorporation of artificial intelligence in drug discovery will drastically reduce the cost and time to production of new, innovative, safe, efficient, easy-to-use medications, with minimal occurrence of adverse drug events. The ease of drug administration and less adverse events will surely improve the experience of not only the patients but also the clinicians and caregivers. And more importantly, pharmaceutical companies that lead drug development should realize that they have a moral responsibility to assist in the achievement of the right to access to essential medicines as a vital component of the fundamental human right to health. AI in drug discovery has the potential to transform the drug discovery process from a purely industrial design to hopefully a more human-centered design process.

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The Role of Digital Twinning, the Next Generation of EMR/EHR in Healthcare in a Society 5.0: Collecting Patient Data from Birth to the Grave

Rodney Hull, Nkhensani Chauke-Malinga, Guy Roger Gaudji, Kim R. M. Blenman, and Zodwa Dlamini

Abstract The U.S. FDA estimates that drug treatments may be ineffective in 38–75% of patients. This clearly demonstrates the importance of personalized medicine. Personalized medicine requires vast amounts of data, and a digital twin is an easy way to represent and use this data. A digital twin is a virtual copy of an individual generated using large amounts of highly descriptive data specific to that individual. To generate the most accurate digital twin, information should be collected from the individual's birth, and this record must be kept up to date. This digital twin will then be a digital version of the individual containing their full medical history, genetic information, family history, biometric data, demographic information, and details concerning their environment and exposure to risk factors for various diseases. Epigenomic, transcriptomic, proteomic, metabolomic, and microbiomic data should be collected at various times to identify potential risk

R. Hull (✉) · Z. Dlamini
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: rodney.hull@up.ac.za; zodwa.dlamini@up.ac.za

N. Chauke-Malinga
Department of Plastic and Reconstructive Surgery, Faculty of Health Sciences, Steve Biko Academic Hospital, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: ny.chauke-malinga@up.ac.za

G. R. Gaudji
Department of Urology, Level 7, Bridge C, Steve Biko Academic Hospital, Faculty of Health Sciences, University of Pretoria, Arcadia, Pretoria, South Africa
e-mail: guy.gaudji@up.ac.za

K. R. M. Blenman
Department of Internal Medicine, Section of Medical Oncology, School of Medicine, Yale Cancer Center, Yale University, New Haven, CT, USA

Department of Computer Science, School of Engineering and Applied Science, Yale University, New Haven, CT, USA
e-mail: kim.blenman@yale.edu

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biomarkers that have developed. When an individual requires medical treatment, the digital twin can be updated using the latest "omics" data. These digital twins can then be used as accurate virtual models to test patient responses to various treatment, or to monitor patients at risk, which will improve early diagnosis and ensure early treatment. In this way, the digital twin could contribute to the lifetime healthcare goals of healthcare in Society 5.0, leading to the goals of improving the life expectancy and vitality of an individual through personalized healthcare from the cradle to the grave. Digital twins can also be used to improve health delivery and the healthy layout of cities and attain a multitude of other sustainable development goals, through virtual modeling and optimization based on the use of these models. Despite the promise of digital twins in healthcare, there are barriers to their use and implementation. These include ethical issues, violation of privacy, abuse, and the creation of a population of hypochondriacs as digital twins can be used to overdiagnose conditions.

Keywords Digital twins · Human digital twins · Precision medicine · Personalized medicine · Precision public health in Society 5.0 · SDGs · In silico experiments · Ethical issues · Privacy · Energy crisis · Rights

1 Introduction

The emerging technology and practice of creating a digital twin has most often been employed by the industrial and engineering sectors (Wickramasinghe et al. 2021). A digital twin can be used to represent a physical object (or individual), process, or service as a virtual model consisting of both data and algorithms. They differ from traditional models in that they can represent unique features specific to the entity being modelled. Using technologies such as smart sensor technology, data analytics, and artificial intelligence, these models can be used to "test" their real-world counterparts in a digital virtual space and as these technologies improve, the predictions made through the use of digital twins will become more accurate. In the industrial engineering and commercial space this allows for prediction of system failures and the improvement of system performance or to innovate whole new approaches (Liu et al. 2019).

However, the creation of digital twins is now being applied to the field of healthcare and medicine, where it is being promoted as an exciting and promising approach that can further advance efforts in medical discoveries and improve clinical and public health outcomes (Schwartz et al. 2020). Some of these applications include modeling the management of diseases such as multiple sclerosis (Voigt et al. 2021), dementia (Wickramasinghe et al. 2022), cancer (Hernandez-Boussard et al. 2021), and cardiovascular disease (Sun et al. 2022). Digital twins can also be used for the testing and development of medical equipment in a virtual space, such as radiological devices (Pesapane et al. 2022), or as a means to perfect or develop new procedures, such as a model for surgical interventions (Kurakova et al. 2022). A digital twin is created using patient-specific data to create a virtual copy of the

patient. Additionally, these digital twins could be amalgamated into a digital representation of a population group. To create an accurate digital twin, detailed and up-to-date patient information is required (Batch et al. 2022). This digital twin can be used to monitor the change in the patient's risk of developing a disease across their lifespan and to decide on the best treatment for an individual. Simply put, this digital twin serves as a model of a physical entity and can be used to model the response of the physical entity to situations within the digital domain (Wickramasinghe et al. 2021). In the fields of medicine and public health, it can serve as the next development in electronic health/medical records for either an individual or an aggregate of records to model the response of a population. Modeling disease occurrence, spread, response to treatment, and outcome using digital twins would be required for a new era of precision medicine (Wickramasinghe et al. 2021; Björnsson et al. 2019). Healthcare in a Society 5.0–based healthcare system would involve a human-centered approach that is actively led by the patient focused on preventive care, but most importantly it is centered around the individual with personalized medicine, involving tailor-made solutions from treatment and diagnosis to assessment (Natakusumah et al. 2022). The importance of personalized medicine was demonstrated by a report from the FDA in 2013 which estimated that drug treatments were ineffective in 38–75% of patients being treated for a variety of conditions. This is due to standardized treatments being unable to account for individual variations (Parker 2005). This illustrates just a single problem that exists in healthcare that can be solved through the use of digital twins and the digitization of every individual patient. This chapter will discuss the development, application, and concerns around digital twins in Society 5.0 healthcare systems. In line with achieving the reforms necessary to implement Society 5.0 are the 17 United Nations sustainable development goals. These goals were agreed to by member states in 2015 and are meant to provide a blueprint for the development of a prosperous future for individuals and the planet. Healthcare is covered by SDG-3. This chapter will cover the use of digital twins in the realization of SDG-3, but digital twinning can be applied to most if not all these development goals, examples of which are given in Fig. 1 (Costanza et al. 2016).

2 History, Overview, and the Generation of a Digital Twin

The first practical use of a digital twin was in 2010 where NASA used digital twins to model spacecraft flight (Glaessgen and Stargel 2012). The digital twin model system consists of three components, the source, which is the physical thing being modelled, the digital twin, and the data which connects them. The source can be virtually anything ranging from an individual to a population to a city or even a manufacturing process. The twin that is created based upon this object or process is a virtual copy based on all the descriptive or quantitative data available to create the most exact copy. This data is collected from the source and used to create the twin (Grieves 2014). The use of the digital twin as a predictive model for patient

Fig. 1 The role digital twins can play in the realization of various UN sustainable development goals in relation to health. The creation of digital twins can be used to improve simulations and modeling that is performed prior to implementation of various strategies. This can help point out problems and predict outcomes

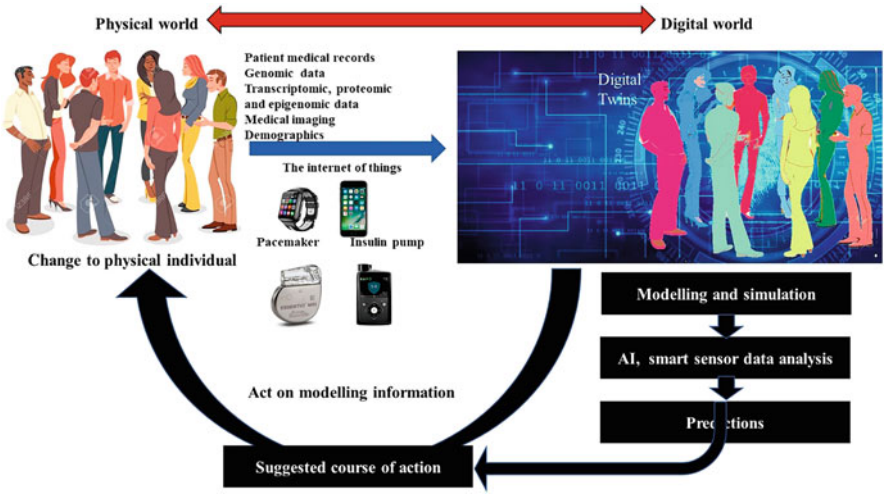

Fig. 2 The flow of information from physical objects to digital twins. Information is gathered from the physical object(s), in this case individual patients. This information can be gathered by medical professionals through clinical means or through the individual's interaction with devices connected to the Internet of Things. This data is unique to each individual and gives rise to a corresponding unique digital twin. These twins can be used to perform various simulations, the result of which can be used to implement changes in real life. This will change the status of the individual which will be reflected in new information gathered from the individual. This information is fed back into the digital twin. In this way, the AI algorithms can learn from those implemented changes and use this information to fine-tune its predictions

healthcare is becoming more accurate thanks to the aforementioned smart sensor technologies, data analytics, and artificial intelligence. This predictive information can then be applied back to the patient, changes can be implemented, and new data can be gathered and used to alter the twin to make new predictions. This creates a feedback loop of information between the patient and the digital twin where the digital twin can be said to be learning (Boschert et al. 2018) (Fig. 2). The modeling and simulations of a human body using a digital twin to improve diagnosis, prognosis, treatment, screening, and overall well-being can be more beneficial with the expansion of the source and scope of accessible data since the twin will become more accurate. Due to the bi-directional flow of data between the physical world and the digital twin, the twin is also capable of learning and developing (Björnsson et al. 2019; Tao et al. 2019a).

The bi-directional flow of information between a digital twin and its physical counterpart means that a digital twin is not a static copy or simple simulation model. Not only that but the continuous inclusion of updated information the idea of a digital twin is based upon means that the digital twin will change as their physical counterpart changes (Boschert et al. 2018).

A digital twin can be created not just of an individual, but of various tissues, body systems cell types, diseases, or populations. These different types of digital twins can even be created to model individual cells or even cellular components (Fig. 3). Not

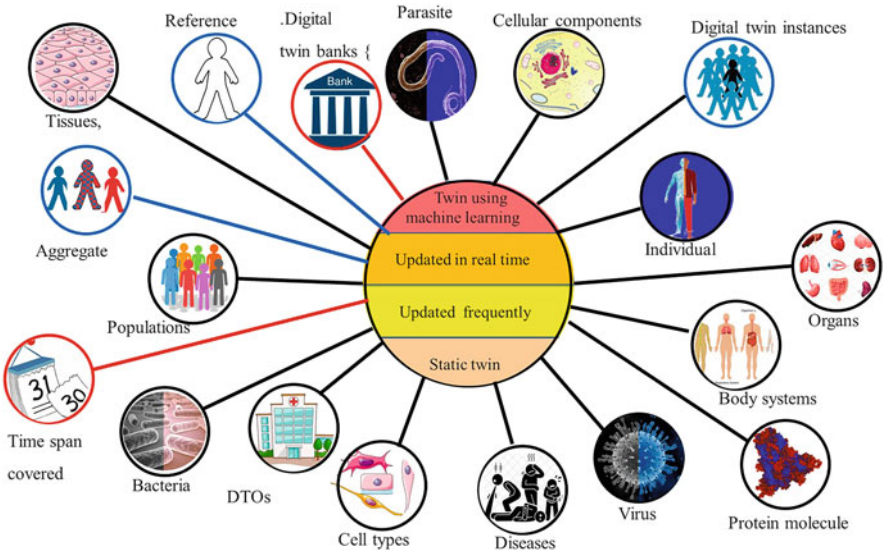

Fig. 3 Concepts in the design and creation of and types of digital twins. The various levels of complicity of a digital twin describe how often the twin is updated: never, frequently, or in real time. The most complex and useful twin for the highest accuracy modeling would be one where the twin is updated in real time and can use machine learning algorithms to learn from the changes brought about by interventions or changes to the real life individual. The *red* lines and circles indicate concepts such as the twin being a temporal entity and a repository of digital twins in the form of a "bank." The *blue* lines and circles represent the main types of digital twins while the *black* lines and circles represent the different applications of a digital twin

only can digital twins be created for a specific disease or disorder, but a twin could be created for the causative agent, bacteria, virus, or parasite. This twin could be used to model the effect of drugs, vaccines, or other therapeutic agents on these agents or even a population of these agents (Singh et al. 2021a). As previously stated, one type of digital twin is a digital replica of infectious or disease-causing agents, while another is the modeling of individual components. In its simplest form, this may only be a model of individual molecules. Protein modeling has been performed for many years and these are in fact digital twins representing the same physical characteristics of the real-life molecule (Fig. 3). These types of digital twins have recently been used to model the interaction between the spike protein of the SARS-coronavirus and digital twins of real-life individual's angiotensin-converting enzyme 2 (ACE2) receptors (Piplani et al. 2021).

One of the most basic types of digital twins is the reference digital twin, a template used to construct digital twins. As such they are also known as proto-twins (Popa et al. 2021). One of the major uses of digital twins in healthcare is the ability to test various treatments or scenarios of the same patient's digital twin at the same time. To do this, multiple copies of the same individual's digital twin need to be made. These digital twin copies are referred to as digital twin instances. In order to create a digital twin of a population of individuals an aggregate or composite twin

must be made by adding information from the individual digital twins that represent the individuals making up that population. This type of twin can be used for predicting the spread of a pandemic within an individual population (De Benedictis et al. 2022). Both aggregates and instances can be stored in organized repositories which can be combined with other similar repositories to create different aggregates or groups of instances. These repositories are known as digital twin banks (Garg 2021). A final type of digital twin that is useful in healthcare is the digital twins of organizations (DTOs). This could be a model of a hospital or other healthcare organization, a health department, or a referral chain between healthcare providers. This twin can be used to optimize their design and running (Callcut et al. 2021).

In addition to different types of digital twins, there are also different levels of sophistication, abstraction, and complexity for digital twins. These differences are due to the fidelity of the twin which is a measure of how much the digital twin reflects the current state of the real-life patient. This fidelity is therefore a measure of three different characteristics. Firstly, how much real-world detail is used to construct the digital twin. Secondly, if the digital twin is being updated with new information in real time using updated data from connected instruments (via the IOT), and finally, if the algorithm used to update the twin is capable of learning from the changing status of the patient using the new information (Gerber et al. 2019) (Fig. 3).

A final important concept for digital twins is that they are a product of the time the data used to create them covers in the physical world. In other words, was the data used to construct them recorded at an individual's birth continuing until they die or was it just between two specific dates? This information is important for aggregate twins as they can cover the period for which a population was exposed to the situation being modeled or the times they existed as a distinct population. This temporal delineation of the digital twin is known as the digital thread (Garg 2021).

Currently, there is no single software that is specifically designed to create a digital twin of an individual. Some of the software that has previously been developed or is in use to model either medical devices, specific organs, or the digital environment of an individual are listed in Table 1. A multi-purpose human/medical digital twin software development kit (SDK) has been developed and is available as of 2022. It is hoped it will become widely available at some point in the future to complement existing (generic) digital twin software tools (e.g., GE Digital 2022) and optimize them for medical and healthcare applications.

2.1 Data Used to Generate a Digital Twin

The collection of data is one of the most important concepts and barriers for the creation of an accurate digital twin. However, recent developments may make this easier. In particular, the Internet of Things may mean that data can be accurately gathered from everyday objects an individual uses and most importantly for healthcare from devices attached to or implanted into the human body. This would

Table 1 Software used to create digital twins relevant to healthcare

Company and software	Details	References
Semarx: The Human Digital Twin (HDT)	AI-based software that learns based on the users' interactions with the environment. The digital twin enables the user to optimize and automate their digital interactions based on their preferences and interests.	SEMARX (2022)
Twinbase	Open-source digital twin web server that stores digital twin documents.	Autiosalo et al. (2021)
Living Heart'	Transform a person's two-dimensional (2D) scan into a full-dimensional model of their heart. Allows for manipulation and testing using a virtual heart model.	Scoles (2016)
ALTAIR-One total twin	Medical device design by simulating and optimizing to improve device designers and manufacture. Leading to improved patient care and reduced costs.	Forward (2022)

allow for the acquisition of greater quantities of real-time, more accurate data than ever before, which can then be used to construct a more accurate digital twin (Jacoby and Usländer 2020). These not only include devices but also apps such as activity trackers, diet monitors, and telemedicine services (Björnsson et al. 2019). This ability to collect real-time data not only allows data concerning the health of an individual to be gathered but also environmental data concerning risk factors to which they may be exposed. The Internet of Things would also allow devices to communicate with each other concerning an individual who is using many connected devices. This remote monitoring and integration of data would allow for faster generation of digital twins in real time whilst continually updating with the most recent data concerning the status of an individual and allow for the generation of a more up-to-date digital twin. The collection storage and analysis of this data is assisted by other advancing technologies, with the aforementioned AI being the most important, but also including cloud computing (Kamel Boulos and Al-Shorbaji 2014).

Only the development of modern simulation capabilities and the ability to gather large amounts of data in the form of genomic, transcriptomic, epigenomic, proteomic, microbiomic and medical reports, among others, make the creation of a digital twin modeling something as complex as the human body even possible. This allows for the modeling of even complex molecular processes such as protein structures (Paul et al. 2021). The collection of these omics data should ideally begin at birth with the genome being sequenced. Mutations can be identified, and all this data will be used as the basis for the generation of the digital twin, along with basic demographic data and data concerning the family history of disease. At this stage, the collection of transcriptomic data would only be done in a future setting where this is easy, rapid, and routine as each tissue and cell type within the body would have a different transcriptome. Rather data like this will be collected at various points throughout the lifetime with clinical checkups and consultations. At various stages throughout the life of the patient, the genome can be sequenced again to track any mutations that have arisen in different tissues of the body. All this data can be used to

make a digital twin that best reflects the genetics of the individual (Telenti et al. 2016). Another form of omics data which is being increasingly studied is microbiomics. The population of the microbiome of an individual can give important insights into an individual's health and well-being. In the future, microbiomic data can be gathered at every doctor's visit. This will give the digital twin the ability to model an individual's changing lifestyle, diet, and health and allow for the modeling of the risk of developing specific disease due to these changes (Lloyd-Price et al. 2016).

At this moment, the generation of a digital twin that is fully capable of fully representing a physical object as complex and intricate as the human body is not possible. This is largely due to all the complex interactions between the various molecules, tissues, cells, organs, and body systems present. Modern medicine is still able to use the simplified twins we are capable of generating, such as pandemic modeling, drug design, and disease progression. However, without the ability to gather and utilize large amounts of specific data, these twins will remain simple approximations and will only give predictions of limited accuracy. Currently relying on omics data to generate a digital twin is problematic due to the cost associated with whole genome, transcriptome, or proteome studies. However, with the research costs of big data technologies constantly decreasing and the increasing availability of computing resources, obtaining this data for every patient will become more cost-effective. This would lead to the use of digital twins becoming the standard procedure (Lehrach et al. 2016).

3 The Role of a Digital Twin in a Society 5.0 Healthcare System

The aim of personalized medicine is to provide healthcare that is centered around the differences between individuals and populations and target these for care, diagnosis, prognosis, monitoring, and prevention. These differences include genetic makeup, lifestyle, and environmental factors. Digital twins give the ability to model how this unique makeup of an individual will affect the different aspects of healthcare (Harvey et al. 2012).

Digital twins can also be used to model many healthcare situations. These include determining drug interactions; the effectiveness of a treatment; the safety and outcomes of a procedure; the frequency and type of disease screening to be carried out; the most useful molecular markers to use for diagnosis, prognosis, and disease monitoring; as well as keeping an accurate and fully accessible complete medical ID. All these can be done in silico, improving care and optimizing resources (Kuchemüller et al. 2021; Sahal et al. 2022). Digital twins can also be used in medical research to lower costs, and partially replace laboratory experiments and the use of laboratory animals, with in silico simulations. Rather than using animals aggregate digital twins can be used to perform more personalized medicine research

(Kuchemüller et al. 2021; Piplani et al. 2021). By modeling the health and wellness of individuals and populations, digital twins can also be used to improve the working life span of an individual as well as increase efficiency and output by decreasing sick leave and incapacity leave (Tao et al. 2019b). The use of digital twins as virtual test subjects will also lead to a decrease in errors made in treating a patient and highlight any side effects or harm a treatment may cause. This will in turn result in a reduction in medicolegal liabilities (Benson 2021).

3.1 Digital Twins in Personalized Medicine

The "guardian angels" principle was proposed by Lehrach et al. (2016). These guardian angels were "virtual twins" of every European individual that could assist in establishing personalized healthcare and disease prevention in Europe. These digital twins will be created using data gathered from multiple sources including but not limited to -omics, imaging, clinical, and sensor data (Lehrach et al. 2016).

Personalized disease management using digital twins has been tested in various studies. Disease such as multiple sclerosis requires lifetime management to prevent or lessen the resulting neurological disability. This disease occurs in young adults and is a chronic multidimensional disease. This disease has been intently studied and large amounts of research data can be used to create digital models of the disease itself. These can be used in conjunction with the digital twin of the individual patient to model the progression of the disease and suggest the best actions that must be taken to minimize morbidity. This can be done by using the patient's genomic information and evaluating how it will interact with the molecular basis of the disease as well as the effect of the patient's environment, nutrition, and lifestyle on the disease (Voigt et al. 2021; Walsh et al. 2020). A large body of evidence support the link between endocrine disruptor chemicals (EDCs) and urogenital birth defects, diabetes, obesity, and metabolic syndrome worldwide and in South Africa. Digital twins can provide scientific data to address the current gaps in environmental policies and in the long term reach the SDG-3 goals with regards to maternal newborn and children deaths. Evidence shows that EDCs have a substantial impact on an individual's genome, transcriptome, proteome, epigenome, and metabolome (Bornman et al. 2017; Singh et al. 2021b). All this information is contained within the patient's digital twin (Voigt et al. 2021; Walsh et al. 2020).

3.2 Treatment Modeling

The guardian angel digital twin proposal previously described envisages the practice of generating a digital twin becoming the standard medical practice, leading to each individual in Europe having a digital twin which can be used to test all possible treatments and only prescribing the most predicted to be the most effective for the

patient (Lehrach et al. 2016). This process involves the generation of multiple twin instances. Each instance or duplicate twin is treated using a different drug or treatment option. Like the twin, these treatments are all virtual and are created based on known data concerning the treatment. This includes its pharmacokinetics, pharmacodynamics, the molecular pathways it affects, whole libraries of proteins and ligands that it may associate with, the models of these interactions, the treatment side effects, toxicity, and half-life. This data may also include case reports concerning the previous use of the treatment. All this data is tested against the digital twin using advanced AI algorithms. A different treatment is applied to each individual twin meaning that multiple treatment options can be tested simultaneously. The results can be used to select the best treatment option (Björnsson et al. 2019).

There are many ways these drugs can be tested in these simulations. One example is the use of protein–protein interaction (PPI) networks, constructed using a patient's proteomic or transcriptomic data as a map. Changes in protein expression caused by a treatment can then be mapped to the patients PPI to identify changes in the pathways the drug could cause when used to treat the patient (Zhou et al. 2014; Barabási et al. 2011). Another example could involve genetic changes detected in a patient. These alterations that lead to transcript and protein changes can be used to create a twin with the altered protein and protein expression patterns. A treatment targeting this protein can be used to treat the digital twin. The resulting effects on PPI and pathways can then be simulated in the twin.

Digital twins also show promise in the fields of drug discovery, drug development, as well as replacing or shortening animal and laboratory drug trials. By creating digital twins of target organs or through the use of aggregate digital twins, experimental drugs can be assessed for their effectiveness, toxicity, or pharmacokinetics, before further money is invested in them or further development takes place, thus saving time and money (Canzoneri et al. 2021; Portela et al. 2021). For example, a digital twin of the liver was created using knowledge concerning liver disease and the effect of drugs on the liver. This twin was used to simulate the development of various liver diseases, but also assess the response of both normal liver function and the response of liver disease to new experimental drugs (Subramanian 2020).

Digital twins of the human immune system have also been created; obviously the immune system is important in a wide range of disorders from autoimmune disease to infections. Because of this, a digital twin of this body system will be especially useful in modeling the ability of an individual's immune system to fight off an infection, screening individuals for autoimmune diseases and modeling the progression of a disease or condition. However, these twins are challenging to create due to the human immune system involving complex interactions between many different immune cells and tissues. It is also difficult to measure an individual's immune state. To construct a digital twin of an individual's immune system, data is collected from each level of the physiological scale from the whole body to the body systems, to the organs, to the tissues, to the cells, and to the molecular level. A digital twin of each of these levels of complexity is constructed and then these separate digital twins are integrated into a multiscale base model (Laubenbacher et al. 2022).

Even far simpler treatment options such as orthodontic treatment have been shown to benefit from the creation of simple digital twins. Using facial scans and three-dimensional (3D) imaging to create a digital twin of the patient's face and jaw, the correct measurements, and assessments of the alignment of the various structural components of a patient's face allow for more precise individual interventions to correct any issues with the alignment of the central incisors with the forehead (Cho et al. 2021).

3.3 Aggregate Twins and Digital Twin Populations: Whole Population Modeling

Society 5.0 aims to bring about a society that is a balance of economic, societal, and personal development, and relies on the interdependence of these factors. The recent COVID-19 pandemic highlighted how this delicate balance can be plunged into turmoil during a global pandemic. In many regards the pandemic highlighted the shortcomings of public health. As healthcare in society 5.0 is centered on the individual so public health in Society 5.0 should be centered on the individuals within that society (Natakusumah et al. 2022). Of greatest concern to public health 5.0 would be the interactions between people and the existence of patients with medical conditions within a community (Adel 2022). One of the main concerns of public health is to prevent disease outbreaks and to track the spread of diseases to try to limit or control that spread (Natakusumah et al. 2022). Aggregate twins can be constructed using the individuals of a particular population to give a digital representative population for the modeling of public health concerns. However, digital twins of entire populations may also be useful.

As already alluded to one of these concerns is tracking and managing disease outbreaks. Virtual systems capable of doing this more accurately than current models using standardized populations would be vital to allow public health sectors to be better prepared and to take meaningful action when the time comes. A model of a smart city or Society 5.0 city contained an integrated disease outbreak model (Deren et al. 2021). This model was constructed using data gathered in China during the COVID-19 pandemic. It made use of a digital twin of the patients at a particular time period in specific locations during the pandemic. It also used cloud computing and AI to analyze new data concerning a new or hypothetical outbreak to generate instructions on how to best stop the spread of the outbreak. The integrated model can trace the disease based on the locations of affected patients as well as identifying these patients' close contacts. When digital twins of different non-patient populations are entered into the model, it can assess the risk of the disease spreading through this population using the location, health status, and environment of these digital twins (Deren et al. 2021).

Another method making use of digital twins to monitor and control a disease outbreak uses digital twins of individuals based on their smartphones. The phones

collect basic data such as age, gender, and underlying health issues, which the user enters. The user can then also enter any symptoms they have and the results of any diagnostic test. These digital smartphone twins are location-linked with hospitals and medical centers that will use the information collected from the digital twins to plan for bed space, medical staff, and equipment. Once again close contacts can be identified using the smartphone location or recently visited locations (El Azzaoui et al. 2021).

Digital twins of cities have been created to help city planners improve the health of people living within those cities. These can range from access to people with special needs to removal of waste, pest control, the effect of heat waves as well as the effect of emissions from traffic and industries as well as the use of chemicals in agriculture. In South Africa, both agrochemicals and pest control insecticides, mainly for the control of malaria, have been found to leach into aquatic environments including freshwater supplies. These chemicals have been linked to endocrine disruption, interfering with normal hormone function (Horak et al. 2021; Patrick et al. 2016). Digital twins can be used to simulate the effect of these chemicals on individuals, but even more importantly they can be used to simulate the environments in which the chemicals are deployed. This will allow predictions of how these chemicals enter the water resources through runoff and drainage. These models can be used to change the way these chemicals are used, limiting their indiscreet or excessive use as well as allowing for the prevention of runoff or drainage. The current energy crisis has important implications for healthcare. The WHO states that "Access to clean, sustainable and affordable energy, outlined in the seventh Sustainable Development Goal (SDG 7), plays a crucial role in advancing health (SDG3)" (World Health Organisation 2023). Digital twins are already being used to create simulations of powerplants and energy grids to optimize maintenance, avoid waste, and predict failures. Industries can use digital twins to model their manufacturing process and assess their energy usage and waste. This includes providing predictions of energy lost to the production of heat as a by-product as well as modeling their creation of waste gasses such as CO and CO_2 (Sifat et al. 2022).

These models are not static simulations but mirror the movement and infrastructure of a city at different times of the day and the behavior of the city residents. These model cities allow various alterations both physical and administrative to be modelled in the virtual world (Deren et al. 2021). These cities also allow for modeling the effect new buildings will have on the health and well-being of the city residents. New buildings will alter the sunlight surrounding buildings receive and these changes caused by shadows can be modelled in various seasons and conditions (Patrick 2020). Reduced sunshine can lead to seasonal affective disorder, a condition that normally appears in the autumn and has symptoms including depression, low energy, listlessness, insomnia or over-sleeping, lack of hunger or dietary changes, and even suicidal thoughts (Kurlansik and Ibay 2012).

4 Issues with Digital Twins

There are many design criteria for creating a digital twin, many of which revolve around the data used to construct the model. These concerns and design criteria include the perceived accuracy of the data, the use of personal information, who is able to access alter or remove data, how visible the data is, and finally is the twin designed in such a way that it can be easily integrated into different healthcare computational systems. There are also issues of consent when it comes to the gathering and storing of data. How much needs to be disclosed to the real-life people the twin represents? (Schwartz et al. 2020) When it comes to data removal, whether due to the presence of incorrect data or data that violates an individual's privacy, who has the right to access and edit this data? One option to solve this is the creation of a modular digital twin, where related data sets are separated (Fig. 4). The twin only functions as a whole with all modules working together by each module communicating through a central data structure. This means new modules can be added or others edited without interfering with the twin as a whole. Additionally, access to edit the twin can be granted to different modules at different times (Masison et al. 2021) (Fig. 4). The safety of data is also a concern. To what extent should the data used to create a digital twin be encrypted and who has the right to the key to unencrypted data? If commercial companies are paid to host or curate the digital twins what is stopping them from selling this data to a third party? (Parmar et al. 2020; Fuller et al. 2020)

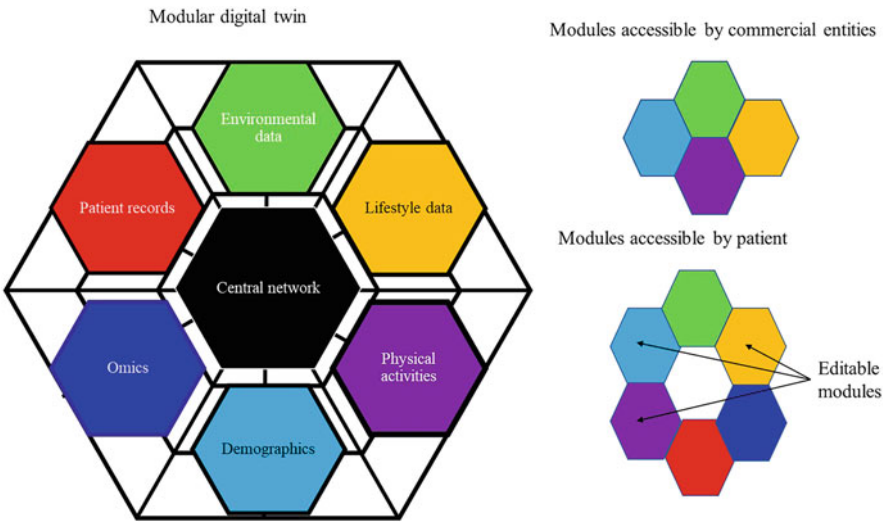

Fig. 4 Representation of a modular digital twin. Related datasets are separated but joined by a central network or framework to create the entire functional digital twin. Only certain modules are accessible to certain individuals. For instance, commercial entities such as insurance companies are only allowed to access modules such as demographic data, while an individual can access all modules but is only allowed to edit specific modules

Even some of the technologies used to implement digital twins have their own disadvantages and limitations. Since they are based on AI technology both the twin and the underlying AI algorithms require good quality accurate data. Questions surrounding the quality of data are important considerations for not only AI but data analytics as well. The intensive collection of data from individuals may itself pose an ethical risk as it can infringe on the rights of an individual who may not want their data collected but are not given the choice due to the automated collection of data that occurs with the IOT. It may also increase the risk of an individual's data being stolen through data mining inference attacks (Krumm 2007). The danger of hyper-collection of data may lead to the collection and inclusion of data that has no bearing on health, and this in turn can lead to overcomplications and incorrect results when the twin is used to model a healthcare scenario (Bagaria et al. 2020). This excess data collection may be exploited to collect data which can then be sold to other commercial entities such as insurance companies or retailers. This is known as data brokerage and healthcare data may be very valuable to pharmaceutical companies and marketing organizations (Prainsack 2017). Currently, health data is protected by law and legally informed consent is required from the patient to share this information. However, the networking of devices and databases in the smart society may render this legal protection obsolete. The maintenance and use of data also pose a problem since as software and hardware are upgraded, so digital obsolescence may result in data not being able to be transferred to the newer systems. This may result in the loss of data. Another problem is data transferability. This becomes a problem as data is collected by devices from different manufacturers using different analysis or operating software. This may lead to data being unable to be used or being entered into the analysis or AI software incorrectly (Sandborn 2007).

Smart sensors that can be used to gather data are likely to be expensive since the microchips need to contain both sensors and actuators, making them more complex. Another issue is that of sensor calibration. Currently, smart sensors need to be calibrated using an external processor. If this means an individual needs to take the sensor to a manufacturer or service partner, the end result may be devices that are not serviced regularly, correctly, or not at all. This may result in the collection of incorrect inaccurate data (Majumder et al. 2017). This may be problematic when it comes to data gathered through the IOT. For instance, if an AI were to monitor the information from a device such as a smartphone which gives the individual's location as a bar, it does not necessarily mean that the individual is consuming alcohol, yet an AI capable of learning may infer this (Rao and Mane 2019). The use of mobile wearable devices and smartphones to collect data is also a concern as the constant collection of data and real-time updating of a digital twin would be happening without the individual's consent. The individual may want the device and may want to wear the device but may not agree to the collection of data (Armstrong 1995). There are also questions around the accuracy of these devices (Falter et al. 2019; Marcus 2020).

Digital twins also face the same issues that AI does in mistrust and suspicion. It is human nature to fear the new and unknown. It is natural to doubt the accuracy of

predictions made by AI using digital twins because it is difficult to understand how AI has come to this conclusion. These concerns over mistrust in AI are valid and can be summed up by the black box problem. This problem revolves around medical professionals not being able to determine or understand how an AI came to its conclusion. This is especially problematic once the AI is fully automated using ML or DL. This may lead to doubt as to the accuracy of the conclusions reached by the AI (Sorell et al. 2022). One option would be to develop AI systems that explain their operations by creating an easy to understand log of the actions taken by the AI in constructing or modeling using the digital twin (Kwong et al. 2022). In addition to this, there has always been a mistrust of mechanization and automation, of these things replacing or rendering humans obsolete. It is important to remember that digital twins are tools to be used to make predictions and the decision to act on those predictions will ultimately reside with the humans using these tools (Fuller et al. 2020).

The digital twin also requires standardization, involving the actions of an organizing body comprised of all stakeholders such as industry, government, academia, and practitioners. Such organizing bodies already exist, such as the Swedish Digital Twin Consortium (2022) and the Digital Twin Consortium (2022). The Digital Twin Consortium is a collection of industrial, government, and academic members. These industry partners include software and hardware IT companies, companies from the aerospace and motor vehicle sectors, the agricultural sector, transportation, military, natural resource management, as well as the healthcare sector. The consortium aims to drive the adoption and development of digital twin technology (DigiTwins Consortium 2022). The STDC is more focused on the medical sector than the DT consortium. It is made up of partners from multiple disciplines within the healthcare sector. These include partners from healthcare, medical and technical faculties, and industry. The academic partners consist of multiple universities, hospitals, and medical institutes within Switzerland (Consortium.).

The mass of information contained within a digital twin and the extensive results generated when that twin is used to model a scenario, suggests that there may be an issue that could lead to overdiagnosis. Digital twins can be effectively used to give an early warning of a disease and allow for preventive healthcare. But this may also lead to overdiagnosis and overtreatment. For instance, if a patient possesses specific genetic biomarkers these may only indicate that the patient is predisposed to developing a disease, not that they have the disease (Mandl and Manrai 2019; Walker and Rogers 2017; Bunnik et al. 2015).

One of the main ethical issues concerning digital twins is how much control a person has over their digital twin, but this twin must be able to be accessed by and therefore managed by the healthcare system. The aforementioned regulatory organizations as well as governments must be responsible for data privacy and the protection of people's personal biological information (Bruynseels et al. 2018). There is also a fear that aggregate digital twins or populations of digital twins may lead to population-specific patterns being identified and this information being used to discriminate against groups of individuals, especially in those countries, such as the USA, where the majority of healthcare is privatized (Bruynseels et al. 2018). The

answer to all these problems most likely lies in the creation of new regulations. These new technologies require the creation of new laws specifically for the collection and use of information by AIs for the use of creating a digital twin and the use of this twin. In South Africa, the Protection of Personal Information Act 4 of 2013 ("POPI") came into effect on July 1, 2021. This act requires that all companies treat, handle, store, and protect the private information of other parties or their clients in a way that it cannot be misused, exploited, or divulged.

The major cost associated with digital twins is the creation of infrastructure to generate, capture, and integrate the data. There is also the initial capital cost of setting up digital information systems, which involves the cost of software to build the twin, AI systems to manage and integrate data being used to create the twin, servers or space on cloud storage, and finally, the training of individuals to run and maintain the system (Parmar et al. 2020). Currently, the costs involved with data collection and curation mean that for poorer individuals or in lower- to middle-income countries the use of digital twin technology for personalized medicine might not be a viable healthcare initiative. This could result in increased discrimination and inequity between the haves and have-nots. Countries like South Africa with their public and private healthcare systems may only be able to institute digital twin technology in the private healthcare sector (Bruynseels et al. 2018).

It has been suggested that like many medical advances, the use of digital twins should be pioneered using animals. Already digital twins have been used in the veterinary care of livestock, where digital twins were not only used to manage livestock but also to detect signs of distress and to predict and diagnose illnesses in the animals (Neethirajan and Kemp 2021).

5 Conclusion

Society 5.0 calls for the sustainable and more intelligent use of resources while it aims to improve the lives of those living in it through, among other initiatives, improved healthcare. One of the main tenets put forward by the concept of healthcare in Society 5.0 is the desire for personalized lifelong healthcare. Digital twins are simply the digitization of the individual based upon data collected throughout the individual's lifetime or over a given period of time. The integration of technology into our everyday lives makes collecting this data far easier and in conjunction with advances in the biomedical industry makes the creation of an accurate digital twin feasible (Fig. 5). An intelligent digital twin, combining data, knowledge, and algorithms (AI), has the capacity to accurately simulate public health and medical situations. These simulations will be individual or population specific as the digital twins reflect those physical entities. These simulations can include medical conditions, disease progression, drug interactions, treatment effectiveness, as well as the spread of a disease and make accurate predictions which can inform practices and assist in planning, diagnosis, prognosis, and the choice of treatment. They can also be used to model health-related situations that are in line

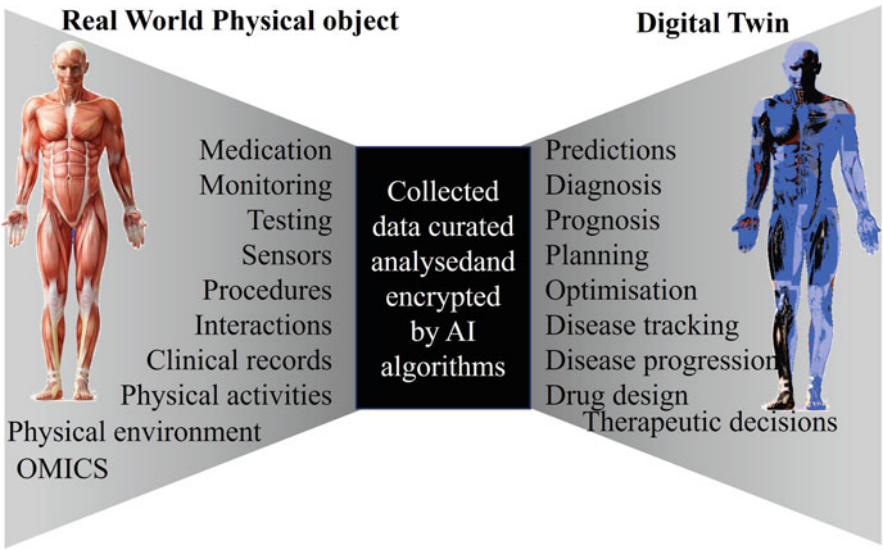

Fig. 5 A summary of digital twin technology in healthcare 5.0. A twin of the real-world patient is created through the collection of multiple forms of data, which is interpreted by an AI algorithm to create a digital twin. In healthcare the twin can be used as an individual, a group, as a population, or the characteristics of multiple twins can be combined to create an aggregate twin. These twins can be used in simulations of either conditions pertaining to an individual patient such as diagnosis, prognosis, or response to treatment or even to monitor the disease progression. Aggregate or populations of twins can be used to model public health initiatives and planning, to optimize the treatment of patients at a medical facility, or model the spread of a disease

with the UN SDGs. These include the layout of healthy cities, clean water and contaminants in drinking water systems, the effects of the energy crisis on healthcare and how to efficiently use limited electricity capacity in healthcare, as well as the alleviation of poverty. The use of digital twins in healthcare can help drive the transformation to healthcare 5.0 by providing truly personalized modeling of the patient.

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Integration of Cyber-Physical Systems in the Advancement of Society 5.0 Healthcare Management

Botle Precious Damane, Mahlatse Cordelia Kgokolo, Guy Roger Gaudji, Kim R. M. Blenman, and Zodwa Dlamini

Abstract Cyber-physical systems (CPSs) allow the integration of digital and physical systems to perform well-organized and precise tasks in several disciplines including medicine. Reliability, efficiency, and security are key players in achieving successful CPSs. Artificial intelligence (AI) systems can host and manage large data sets from different sources including omics and biomarkers bank used for the development of targeted therapies and accurate medical diagnoses. The inclusion of CPSs can advance the ability of AI systems to logically synergize digital

B. P. Damane (✉)
Department of Surgery, Level 7, Bridge E, Steve Biko Academic Hospital, Faculty of Health Sciences, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: precious.setlai@up.ac.za

M. C. Kgokolo
Department of Dermatology, Bridge A, Level 9, Steve Biko Academic Hospital, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: mahlatse.kgokolo@up.ac.za

G. R. Gaudji
Department of Urology, Level 7, Bridge C, Steve Biko Academic Hospital, Faculty of Health Sciences, University of Pretoria, Arcadia, Pretoria, South Africa

SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: guy.gaudji@up.ac.za

K. R. M. Blenman
Department of Internal Medicine, Section of Medical Oncology, School of Medicine, Yale Cancer Center, Yale University, New Haven, CT, USA

Department of Computer Science, School of Engineering and Applied Science, Yale University, New Haven, CT, USA
e-mail: kim.blenman@yale.edu

Z. Dlamini
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: zodwa.dlamini@up.ac.za

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platforms with physical elements and back, thus improving control and automatic actuation of health technologies. In a world where digitalization has become part of our daily lives, incorporating and actualizing new technologies for personalized and precision medicine can be achieved through CPSs. Input data can be communicated to computational platforms where patient environmental, health, and diagnostic information can be analyzed to assess the efficacy of precise medical therapies. Human-based technologies such as networks-on-chip (NoC) could allow constant communication between patients and healthcare providers as well as real-time monitoring of patient health status. However, the disadvantage of CPS is the vulnerability to cyber-based attacks which could be as a result of terrorism or organized crime thus compromising confidentiality and human rights. Should certain information regarding patients end up in the wrong hands, this information can be used to target, harass, or take advantage of certain groups of individuals. The inclusion of a security layer equipped with protocols such as open authorization, user-managed access, and self-sovereign identity in Society 5.0 ensures the incorporation of common global laws. This chapter will focus on integrating CPSs in Society 5.0 to improve accurate patient diagnosis, treatment, and monitoring in advancing healthcare management systems.

Keywords Cyber-physical systems · Metaverse · Robotics · Artificial intelligence · Healthcare management · Holography · SDGs · Human rights · Security · Confidentiality · Energy conservation

1 Introduction

The Fourth Industrial Revolution focuses on efficient and optimal industrial production and data management. It comprises cyber-physical systems (CPSs) in which the physical and digital worlds are intertwined by the industrial Internet of Things (IoT). The idea here was to create smart machines/factories that can be utilized in various sectors including health (Adebayo et al. 2019; Popov et al. 2022). Multilayered architectures for specific CPSs have three main layers which include the physical layer, the cyber layer, and the human interactive/decision layer. The physical layer comprises of two sublayers which are the sensor and the application layers. The cyber layer has two sublayers, which are the storage and the processing layers. The collected data is processed and analyzed using different algorithms (Edward et al. 2017; Pedro 2022). The development of network layer architecture for CPS security to protect and guard against cyberattacks serves as a crucial component of medical CPS (Chaganti et al. 2021). Future technological advancements have sparked the idea of smart or intelligent hospitals. Integration of artificial intelligence (AI) technologies for processing of high volume of patient information through big data systems to allow prompt decision-making is essential for the new concepts adapted to the upcoming new era referred to as Society 5.0 (Rovira-Simón et al. 2022). Most of the technologies used for monitoring patients' health status rely on embedded systems. The use of glucose/heart rate/blood pressure monitors, magnetic

resonance imaging (MRI), computerized tomography (CT) scans, positron emission tomography (PET) scans, and so forth have advanced medical diagnostics and monitoring (Lindén and Björkman 2014). Some of these systems permit remote monitoring of patients and all facilitate prompt diagnosis and treatment decisions.

However, future technologies continue to advance toward nano and smart technologies, including microchips. A link between innovative and social sciences is formulated and sustained with the intention of providing human-centered healthcare (Ioppolo et al. 2020). Society 5.0 is expected to most certainly bridge the gap between cyberspace and physical space. To achieve this, Society 5.0 will facilitate the realization of modern smart technologies through the integration of AI algorithms which facilitate big data analytics, IoT, metaverse, robotics, digital twining, blockchain, and networks-on-chip (NoC) for the optimization of personalized medicine. This chapter will explore some of these concepts in the context of CPSs in healthcare management. These technologies will be integrated into the healthcare management systems and in the process ensure cost-effectiveness and quality of life (Garg 2022). CPS is most important in modern-day medical practice where new effective human-centered healthcare management and service delivery are in high demand. The study by Sony et al. supports the idea that medical CPSs will provide high-quality, comprehensive, accessible, reproducible, more coordinated, and accountable human-centered healthcare service delivery (Sony et al. 2022) (Fig. 1).

2 CPS-Embedded Systems

Embedded systems require specialized skills for programming and installation of hardware components. Mobile medical systems can monitor health parameters such as temperature and heartbeat with a wireless microcontroller. The sensor signaling conditioning circuits have an embedded software algorithm responsible for monitoring the temperature, pulse rate, heartbeat, and blood pressure. Thereafter a record generated from the electrocardiogram (ECG) is displayed on the liquid-crystal display (LCD) screen (Reshma 2019; Fouad 2017). Data generated from these recordings is stored in the built-in erasable programmable read-only memory (EPROM) of the microcontroller. This ensures that data is not lost in case of power cut-off (Fouad 2017) or during loadshedding which frequently takes place in South Africa. Additionally, data can be processed using ARM7LPC2148 which is transferred wirelessly to LabVIEW software through ZigBee. The ZigBee technology is cost-effective and energy-conserving (Thirukrishna et al. 2021).

Some monitoring systems are designed to monitor both health and fitness status. This is mostly important in patients with metabolic diseases. Fitness or health status can be recorded and sent via text messages or email to relevant individuals who could then advise or take necessary action. In addition, blood glucose level and muscle condition data can also be recorded, displayed on the screen, and stored as patient history (Abdullah et al. 2015). The embedded systems can automatically send the recordings to an android phone of healthcare providers potentiating

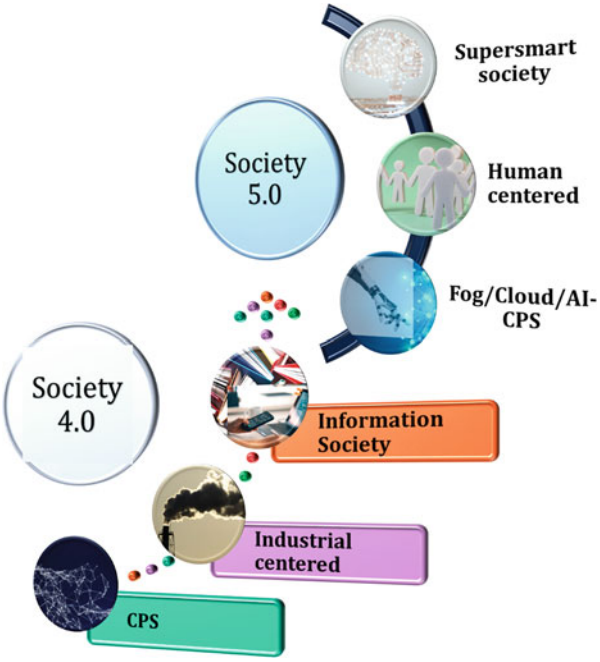

Fig. 1 Transitioning from an information society to a supersmart society. Whereas the concept of Society 4.0 brought a lot of technological advancements, it focused more on the manufacturing sector. The society depended more on machines to complete various tasks. However, Society 5.0 looks forward to integration and collaboration between humans and machines. Human emotion, cognitive skills, and analytical skills cannot be completely replaced by machines and the lack of these abilities does not benefit society as a whole but mostly the manufacturing sector. These skills are essential in healthcare management/delivery systems. Society 5.0 intends to connect all these aspects through the integration of CPS, AI, and fog-cloud computing. This will also create global competitiveness and facilitate socioeconomic balance

clinicians to remotely examine the patient, make a diagnosis, and provide patient prescription (Reshma 2019). Remote health monitoring systems can be redesigned from the already available hospital equipment using advanced technology (Reshma 2019).

2.1 Fog- and Cloud-Based CPS for Diagnosis and Disease Management

The next generation of digital systems should have new methodologies which incorporate modular design approaches, highly configurable systems, and secure hardware and software components. Federated cloud is a collaboration of cloud providers who deliver services, which could include healthcare services to the cloud

broker to the consumer's request and satisfaction. Here the middleware infrastructure and service layers are replaced with a cloud broker (manages cloud services and establishes relationships between cloud providers and consumers). A classic service enabler, which is a messaging platform that allows efficient and consistent exchange of information, notifications, or communication between the applications and enablers, is incorporated into private cloud infrastructures (Andriopoulou and Lymberopoulos 2012). Federated healthcare cloud broker architecture is proposed for accessing and sharing information at different sites. Policy-based, service-level agreement (SLA) verification and reputation-based approaches are computed trust-enhancing instruments to ensure the security and privacy of the users. The development of a software with multi-tier cloud applications is also suggested for distribution among more than one layer thus providing efficient management and high security (Gao et al. 2017).

Early detection of the disease is crucial in determining the treatment strategies which could lead to the reversal or cure of the disease. Fog-cloud-assisted CPS can assist with screening and early detection of the disease even in remote areas. The physical space includes healthcare providers and data (medical, personal, and environmental datasets) collected which is integrated into cyberspace where analysis of real-time data (diagnosis, evaluation of adverse effects, and sending out alerts) occurs. The fog layer of the cyberspace serves as a bridge between the physical space and the cloud layer. The connection between the fog and cloud layers allows for the classification of the disease and storing of medical information. To achieve this, the fog layer–based naïve Bayes classifier was used to classify ulcerative colitis user into critical or non-critical events. Cloud layer–based IoT sensors are embedded in the user's body for monitoring purposes. The principal component analysis was used for predictive accuracy and ensuring the reduction of redundancy and background noise. Thereafter, deep neural network (DNN) was used to assess the current stage of ulcerative colitis. The multilayer perceptron (MLP) was used to classify ulcerative colitis into different stages. This novel IoT-fog-cloud-assisted CPS was predicted to accurately diagnose and classify ulcerative colitis. The benefit of the system is that patient information is stored on a cloud where it is accessible anytime it is needed remotely and at the point of care. Patients can constantly be monitored, and an alarm will be set off to alert healthcare providers should the patient be in need of emergency assistance (Verma et al. 2020). Medical cybernetics (MC) includes monitoring devices that use mathematical processes and measurement models embedded within a wearable sensor system. Zsolt suggests that current monitoring systems such as exercise heart rate monitors can be improved by the integration of CPS tools such as cloud computing to assist in the prevention or early diagnosis of cardiometabolic conditions. Their goal is to develop devices that can support fitness goals by building resilience and improved physiological reserve capacity. These new-generation devices will measure parameters such as insulin resistance and maximal oxygen uptake (VO2max) for risk assessment of cardiovascular disease (CVD) (Zsolt 2020).

The risk of developing coronary heart disease (CHD) can also be assessed with the assistance of a cloud-based cyber-physical localization system. High-risk

patients can be tracked and located with global positioning system (GPS)-enabled monitors for prompt emergency responses and facilitation of home-based healthcare management services. The physical systems such as wearable devices will collect data from the user which will be stored in a cloud. The data will be accessible to both the user and healthcare professionals for a long period of time. Should the patient develop CHD over time, diagnostic alerts due to an abnormal electrocardiogram (ECG) reading will be sent to the user, caregivers, and the treating doctor (Sood and Mahajan 2018). The incorporation of AI systems in the early detection of non-communicable diseases (NCDs) could be one of the cornerstones of the efforts toward a cancer-free and metabolic disease-free Society 5.0. Machine learning (ML) algorithms can be integrated with CPS to identify risk factors, predict and classify the disease, and facilitate the monitoring of several NCDs (Ferdousi et al. 2021).

3 Nanotechnology

The concept of a supersmart society (5.0) contributes to the realization of United Nations (UN) sustainable development goals (SDGs). Nanotechnology/nanoscience is already contributing immensely to accelerating SDG 3 vision. Pokrajac and co-authors discuss how nanotechnology can be aligned with SDGs to accelerate the progress toward the 2030 vision. The authors are developing a multisectoral approach by inviting leading nanocenters to contribute to the realization of this vision. This includes the development of messenger ribonucleic acid (mRNA) for the development of COVID-19 vaccines. Monitoring of patients with the use of microchips and nursing robots for preventative and therapeutic purposes will ensure extended healthy life expectancy. As a result, the global cost of medical care will be minimized (Pokrajac et al. 2021).

The NoC systems can be developed for the detection of dysregulations in genomic and/or proteomic processes that lead to diseases. Cellular signaling and response can be modeled using biochemical reaction networks such as stochastic networks. Explicit models which identify bound or unbound molecules or particle-based models which identify ways in which molecules interact with each other causing either activation or inhibition of the other can be implemented. Following this, techniques such as the Gillespie-based, particle-based rule evaluation, or spatial particle-based can be utilized to get information on how cellular interactions enable normal function or disease development (Bogdan et al. 2015).

Automated CPSs (ACPSs) play an important role in the implementation of early and reliable diagnostics. The efficiency of next-generation microprocessors will depend on the use of multicore accelerators for high performance of multiple tasks and energy efficiency. The ACPS multicore accelerator uses NoC to facilitate personalized healthcare. However, limited computational speed can affect the effectiveness of the processing components of the NoC. Thus, Hou et al. bridged this gap by developing a novel 3-D optical NoC (ONoC) topology structure for the ACPS

that could quickly identify disease biomarkers as in the case of aberrations in a protein structure that could lead to a particular disease. Data from the chip was captured using the proteomic and genomic sensing technology, and this was achieved by the inclusion of the intralayer on-chip optical router onto the 3-D torus topology structure followed by the incorporation of the vertical on-chip optical router. The signal-to-noise ratio (SNR) – aware routing-on-chip algorithm guarantees favorable and improved reliability of data transmission intended for human–machine interaction. In terms of the area of the chip, the topology structure corresponded to a smaller chip area. The advancement of the ratio was directly proportional to that of the topology scale thus allowing the system to provide automated diagnosis and personalized healthcare. A novel grooming-on-chip mechanism improved computation speed for assessing biomarkers. Therefore, the ONoC-based ACPS accelerator operated at a faster speed for rapid analysis of the biomarkers. Photonic sensing was used for the detection of biomarkers thus ascertaining the accuracy and reliability of the results. The size of the chip and automation (no need for technical expertise) made it convenient for use in personalized healthcare (Hou et al. 2019).

Li et al. designed a NoC-based multicore architecture as a solution for large-scale nonlinear model predictive control (NMPC) problems. Management of big data sets in healthcare management and service delivery systems is crucial. Thus, computational platforms should be able to analyze big data sets and determine control decisions from information collected from physical and cyber processes. For this to be possible, the NoC-based multicore systems could be used in cases where a virus such as human immunodeficiency virus (HIV) manages to escape immunosurveillance and spreads. The CPS technology utilizes sensed data to detect the pathogen and a model predictive control (MPC) approach to administer an engineered compound or trigger protein to detect and control the infection. For this model to work, a large-scale system of cognitive hierarchical architecture which can collect data from the sensed physical and cyber layers developing dynamical models that can provide accurate real-time decisions was considered. To solve problems usually associated with MPCs, a CPS with multiple computational units with NoC-enabled parallelized multicore chips was developed. The specific CPS was intended for HIV gene therapy simulation where the MPC can regulate the administration of protected T cells to reduce the viral load. The MPC algorithm developed was aimed at achieving dynamic optimization through performing system estimates and determining the possible outcome before decision-making can take place. Computational platforms embedded into network-of-networks architecture for real-time control decisions surpass their predecessors with limitations in memory bandwidth and energy consumption. The approach taken by the authors was a parallelized formulation of a nonlinear MPC (NMPC). Its computational and communication workload characteristics were analyzed for designing an effective NoC-based multicores. The increased prediction horizon facilitated the performance of the NoC and attained considerable improvements in network latency and energy consumption compared to the mesh NoC-based counterparts (Li et al. 2016).

The inclusion of very-large-scale integration (VLSI) systems in NoC provides the ability to be efficient and fault tolerant. However, challenges in mapping real-time

application tasks to multicores accelerator limit the advantage of improved network latency and energy consumption which contribute to the output. To leverage the maximum potential of the chip, efficient mapping of the cores is required. To achieve this, a clustering-based technique is incorporated in order to leverage the main algorithm. Thereafter, an Andean condor algorithm (ACA) is applied as a mapping technique on the microprocessor cores of the NoC. This algorithm provides the highest performance when compared to other state-of-the-art algorithms (Mehmood et al. 2022). Nanorobots are another breakthrough nanotechnology that will be discussed in the following section.

4 Robotics

4.1 Surgery

Robotic surgical technology is minimally invasive with limited hospital stay and fast recovery. This technology provides evidence-based, state-of-the-art standard of care with better surgical outcomes. This technology is already introduced in more advanced countries and so, to facilitate the alignment of Society 5.0 with SDGs, the establishment of robotic-assisted collaboration programs between local surgeons and international robotic experts will improve skills training models. Robotic surgical skills come with the benefit of reduced exhaustion experienced by surgeons particularly in public hospitals with a long waiting elective theatre list, resulting in better decision-making and reduced conversion. The rate of conversion is unlikely with robotic surgery with the benefit of reduced technical error (Randell et al. 2015; Bateman 2015). Training will improve the effectiveness of theatre staff, coordination, and operative duration. Ergonomic training will improve the technical skills of the operating surgeon (Kanji et al. 2021). Advancement of robotic surgical systems in Society 5.0 will come with the development of autonomous systems that makes it easier to maneuver the ergonomics of the robotic console thus reducing strain experienced by the operating surgeon. The idea of having robots assist in surgical treatment was first entertained in 1967, although it took three decades for the first surgical robot to be developed. In the 1980s, the orthopedic image-guided system used in prosthetic replacement was developed. Thereafter, the United States (US) Food and Drug Administration (FDA) approved the da Vinci surgical system by Intuitive Surgical which is now widely used in countries that can afford it around the world (George et al. 2018).

According to literature, patents for the da Vinci surgical system expired in 2019, and this was followed by several robotic systems that were in development. The robots are categorized according to their control consoles with some using arrangement of robotic arms, laparoscopic handles, eye tracking, microscope-like oculars, and so on (Rassweiler et al. 2017). The new laparoscopy surgical robots, Senhance surgical robotic system and the REVO-I Robot platform, were introduced. The differences between da Vinci and Senhance surgical robotic systems are the independent arms rather than a “cluster” of arms and the unique eye tracking system that

makes it easier to manipulate and operate the latter. The position of the monitor is placed in such a way that surgical trainees can see and follow the surgical procedure. Recurring costs are less because of the reusable laparoscopic instruments. The REVO-I Robot platform has a four-armed robotic operation cart like the da Vinci and the advantage of reusable endoscopic instruments, making it more cost-effective (Rao 2018). Nakadate et al. suggested that the next-generation robotic surgery should be accessible and have extended dexterity for port surgery. The authors suggest the integration of sensor technology and data storage (Nakadate et al. 2015) of which in this case fog and cloud computing might be advisable.

4.2 Other Healthcare Robots

The use of robots in state hospital pharmacies which usually have a high number of patients has proven effective in facilitating service delivery and reducing waiting time for discharged/outpatients who need their prescription medicine before heading home. The surge of COVID-19 has also facilitated the use of robots for effective and regular sanitation of certain areas of the hospital without the need of exposing healthcare workers to infectious diseases. Turnaround time for diagnostic laboratories has also been improved by the use of automated laboratory equipment capable of processing several samples at the same time. Medical robots acting as caregivers can be used to monitor and take care of the elderly remotely. These robots could provide medication and regularly monitor health status. In case of an abnormal reading or an emergency, the robot can alert the healthcare providers who will then make a diagnosis and provide prescriptions (Owen-Hill 2022; Holland et al. 2021). Other interesting future healthcare robots to embrace the concept of Society 5.0 are nanorobots. A micro-ingestible origami robot comes in a form of a capsule that can be ingested. When it reaches the stomach, the robot unfolds, allowing it to detect a swallowed button battery which if left long enough damages the lining of the stomach. The robot can also patch the burned stomach lining and deliver the drugs to the affected area for enhanced recovery. The robot is designed in such a way that the structure that removes the battery from the stomach is folded in an anelliptic cylinder package and frozen so that it can dissolve when reaching the stomach. The diametrically oriented cubic neodymium magnet embedded into the robot will attract and pull the battery toward the robot. This magnetic attraction is also used to guide the robot to the battery's location. Once the battery is removed through the gastrointestinal tract, another origami robot is sent to patch the inflamed area burned by the battery. This robot has a similar design with the difference being that, once it reaches its destination, it degrades in order to release the delivered drug (Hardesty 2016; Miyashita et al. 2016). Nanorobots can also be used in targeted cancer therapies. A DNA robotic system has a DNA aptamer which specifically identifies nucleolin expressed by tumors and thrombin with the tumors. Coagulation gets activated within the tumor and deprives the tumor of blood supply (Li et al. 2016). Future robotic systems and their application in health will improve healthcare management

Table 1 Future healthcare robotic systems

Robot	Key roles	References
Nanorobots	Precision oncology (target and kill cancer cells) Patch wounds Remove foreign objects Deliver drugs to a precise location	Li et al. (2016), Hardesty (2016)
Tele-nursing	A nurse can control the robot remotely and perform normal patient care tasks for patients.	Hauser and Shaw (2020)
AI doctors and coaches	Artificial intelligence algorithm is developed to assist clinicians effectively and diagnose and treat patients according to their specific diseases.	Banks (2022)
Exoskeletons	These robots are used in physical rehabilitation to assist patients to recover from injuries. The robot trains the body how to move again.	Banks (2022)
Clinical training robots	These robots allow trainee doctors to practice skills including surgical skills until they are ready to treat patients. Trainees can go back to training modules saved on the robots to access their progress.	Alexander (2020)
Blood sampling robots	Blood can be drawn with precision from the patient's arm and be tested instantaneously thus providing fast results and healthcare service. They could also administer intravenous fluid as first-line patient treatment.	Leipheimer et al. (2019)
CPS-based homecare robotic systems (HRS)	Based on the concept of autonomous cyber-physical systems rather than closed-loop human–machine systems. These robots are capable of decision-making without human intervention unless something out of the ordinary happens. They are social companions expected to serve as first-aid robots in case of emergency. They are to be involved in assisted living, interventional rehabilitation, and disease prevention programs.	Yang et al. (2020)

by delivering accurate, timeous, and reliable diagnostic, decision-making, and treatment tools (Table 1).

5 Metaverse Platforms in Healthcare Industry

Metaverse is a three-dimensional (3D) cyberspace that is a replica of the physical/biological world integrated into digital reality. Metaverse is facilitated using virtual reality (VR), augmented reality (AR), mixed reality (MR), extended reality (XR), and high-speed internet (5G/6G). Users of VR can have a real physical world experience in a virtual realm through digital technologies. With AR technology, the physical or biological object is integrated into virtual space and gets projected as a 3D object. The XR technology on the other hand integrates the physical/biological

and virtual (VR, AR, and MR) worlds in virtual space. The XR technology is expected to be more in demand in the future and strategical plans for its implementation in Society 5.0 healthcare industry must be in place. These strategies can include education and training of medical professionals on the use of metaverse services to solve healthcare challenges (Lee 2022), especially in low- and middle-income countries (LMICs) where healthcare service delivery is poor due to a lack of human resources and infrastructure. Strategies should also have a means of securing global competitiveness in the healthcare industry (Lee 2022). These strategies should then align well with the SDGs and the 2030 agenda. The SDGs 3, 9, and 10 aim to reduce premature mortality by ensuring good health and promoting well-being (Chotchoungchatchai et al. 2020).

Human rights to good health and well-being must not be discriminatory and should accommodate everyone despite their age, race, and gender. To protect human rights or remedy the right to health, Nampewo et al. suggest that there be people responsible for ensuring that human rights to health are enforced in healthcare management services. Enshrining legal laws and delegating human rights laws to health to specific duty bearers will ensure that all patients are treated fairly and with respect (Nampewo et al. 2022). Access to healthcare services which includes infrastructure (SDG 9) is enshrined in the Bill of Rights in the Constitution of the Republic of South Africa, 1996, but the realization and practicality of it in the existing healthcare status in South Africa is not yet possible (Kirby 2010). This is the reality that is faced by many LMICs. Efforts to improve the quality of healthcare delivery systems in the country are not enough (Maphumulo and Bhengu 2019) more so if there is a lack of infrastructure. These issues should be addressed during the implementation of smart hospitals in LMICs to ensure that quality healthcare services are provided to all (SDG 10) (Ngoc Dinh et al. 2020). Thus, future development of smart industrial innovation and infrastructure should be cognizant of these issues and facilitate the implementation of virtual realities which will reduce the use of invasive health management protocols. The development and availability of infrastructure should reduce global inequalities and insure global healthcare competitiveness (Fig. 2). In metaverse, a patient's real-world health data can be used to generate the patient's digital twin which could be used for diagnostic purposes and decision-making or predict clinical outcomes.

The development of new digital systems should be able to address global development goals. In particular, SDGs 3 (good health and well-being), 9 (industry, innovation, and infrastructure), and 10 (reduced inequality) are centered around the achievement of improved disease-free life expectancy. These goals can be reached through the development of AI-integrated smart hospitals/infrastructure that can be readily available even in LMICs to minimize global inequalities. Metaverse will transform the world of medicine by allowing for the diagnosis and treatment of patients to be performed remotely without the need for invasive therapeutic interventions, improving patient survival and reducing medicolegal concerns. For medical metaverse systems to be of great success, high internet frequencies (5G/6G) will be required to provide increased capacity, very high speed, and reduced latency.

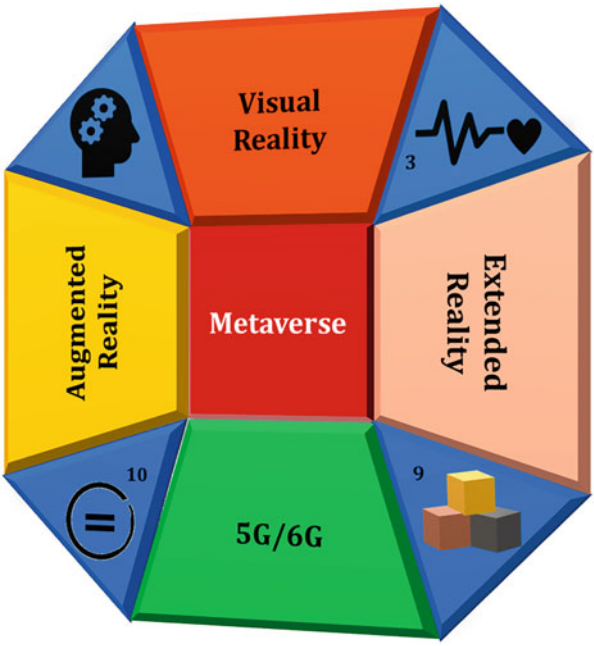

Fig. 2 Implementation of metaverse systems in health 5.0 with the integration of AI applications

Hologram technology is a system that allows 3D polarized projection of images (Fig. 3). It can be utilized in treatment planning of invasive procedures such as surgical interventions. Clinicians can use the projected 3D organ structure in a holographic image for decision-making. The image will be an exact replica of the organ studied and thus provide detailed information of the patient's organ during the procedure. Moreover, an injury or fractures of soft or hard tissue can be picked up with ease on the patient's hologram. Patient data can be stored on digital platforms (vide supra), allowing clinicians to track the patient's progress through readily available medical records. Radiological holograms could be applied in cardiovascular, chest, genitourinary, musculoskeletal, neuroradiology, pediatric, and head and neck radiology (Haleem et al. 2020). A metaverse of medical technology and AI (MeTAI) can facilitate medical imaging-guided diagnosis and therapy. For instance, a patient presenting with a cardiovascular disease can be taken for a CT scan which will then provide information on the potential pathologies. This data will then be projected on the patient's avatar and scanned using virtual CT scanner. Three-dimensional printing of physical avatars could mimic real scans and improve not only decision-making but also patient education about their condition (Wang et al. 2022).

Invasive surgical procedures such as biopsies will not be necessary for diagnosis and decision-making. Clinicians will be able to examine the exact replica of the 3D human organ projection before proceeding with therapeutic interventions

The future of surgical training will include the simulation of surgical procedures using VR. The concept dates back to the mid-1990s when Ota et al. suggested that

Fig. 3 An example of Society 5.0 medical hologram system

surgical trainees could be taught new surgical procedures and their level of competence assessed before they could operate on patients. Information stored during training can be revisited to allow trainees continual practice to perfect their skills. The VR simulation could be used to mimic laparoscopic surgical techniques thus improving training without the cost of expensive animal training models (Ota et al. 1995). A virtual reality simulator for laparoscopic surgery (MIST VR) which simulates movement needed to perform minimally invasive surgical procedures minimizes the need to practice on patients. The model could provide all the elements that mimic laparoscopic surgery and could accurately separate a novice surgeon from a trainee. Measurement of psychomotor skills gave feedback on the effectiveness of training and junior trainees could be separated into those that require more training and the group that is ready to operate on patients (Taffinder et al. 1998).

Initially, VR and AR were used in anatomical education before implementation as tools for surgical training. However, AR is applied to enhance neuroimaging data. HoloLens, the AR device by Microsoft Inc., is a headset computer hologram that allows the user to observe, listen, and interact with the projected physical world/object. The LCD screen is displayed in front of the user's eyes, and the spatial sound technology and gestural interaction promote a distinct interactive holographic environment. The data needed to project computational objects is stored in the HoloLens thus eliminating the need for computer storage systems. Karmonik and colleagues developed an algorithm that could be used to create AR objects from MRI data. The algorithm was created using readily available cost-free software. High-resolution

MRI images of the brain were imported into FreeSurfer. The left and the right brain hemispheres were obtained in the stereolithographic (STL) format. Both hemispheres were combined on a 3D visual platform using ParaView and stored in the X3D format. The task-based fMRI images were analyzed, and the white matter tracts were reconstructed using different systems before functional connectivity (FC) was determined. The created algorithm for converting the image data into 3D objects could successfully provide a virtual display of the brain through the AR device (Karmonik et al. 2018). A 3D printed and AR kidney model was created for a better understanding of the anatomy of the kidney. The model could be utilized in planning therapeutic intervention and decision-making during robotic partial nephrectomy. As in the previous study, radiological imaging was used to collect data. Image segmentation was performed using other algorithm platforms followed by 3D printing before the kidney could be virtually displayed using an AR device (Wake et al. 2018).

6 Challenges of CPS Healthcare Systems

The need for the development of novel architectures for cellular and molecular modeling has long been recognized although their development comes with several challenges. The heterogenicity, structural variability, and complex functionality of biological systems pose these challenges. Biological interactions are multiscale and relevant simulation approaches can be a challenge even with the use of specialized hardware. Analysis of biological proteins generates a large amount of data which could range from gigabytes to terabytes depending on the time scale of the simulation software used. This could lead to tedious analysis and interpretation of results (Bogdan et al. 2015). The exchange of information between the patient and the healthcare providers is important for the early detection of the disease and decision-making. The complexity of the anatomical and physiological parameters in relation with the patients' demographics, for example, newborn versus the elderly and female versus male, require the development of computational intelligence that can accommodate all these issues (Lee et al. 2012).

The ability to tailor-make healthcare management systems according to specific diseases/personalized treatment comes with its pros and cons. Medical CPSs are vulnerable to cyberattacks making cybersecurity a big concern. These attacks could be due to terrorism or organized crime. The safety of these technologies must be assured by the development of high-confidence, authenticated software that can guarantee the security of medical CPSs. Software systems that not only handle big data but guarantee the confidentiality and safekeeping of these data while providing easy access to the user are critical. If these data fall into the wrong hands, it could compromise the patient's health making them vulnerable to discrimination, possible bodily harm, and abuse. The performance of real-time applications requires low fault latency to prevent delays that could disturb the operational cycle of medical CPSs. This could lead to poor data sharing and consequently affect timeous patient diagnosis and treatment (Lee et al. 2012).

Confidentiality is important in the security layer. The proposed framework for Society 5.0 shall include sharing of personal information using different security methods, such as the OAuth 2.0, user-managed access (UMA), and self-sovereign identity (SSI). The OAuth is the standard protocol utilized for authorization thus allowing an application to access information from the other for the end user with an access token. The UMA is layered on top of the OAuth 2.0 allowing the user to have options in terms of accessibility to personal data, the period and conditions of access. The users can manage and monitor sharing preferences from a central control. The SSI is a sovereign and portable identity. It can be utilized for personal purposes or as companies giving the user verified credentials related to their identity for access to all relevant digital services and ensuring confidentiality at the same time. For instance, these protocols could assist in cases where healthcare providers need access to patient data such as medical history or reports using OAuth and UMA. Patient consultation fees could be paid using payment applications that require both the healthcare practitioner and the patient to have access to payment-related data for the application using OAuth and UMA (Patil et al. 2022; Yildiz et al. 2022).

Lastly, safety for the use of medical CPSs should be assured by issuing operational certificates. The process of approving and validating these devices should be cost-effective thus ensuring that these get distributed to provide much-required services (Lee et al. 2012). Currently, the cost-effectiveness of medical CPS devices such as robotic systems is not certain as it is difficult to prove that the benefits of robotic surgery outweigh that of traditional open and laparoscopic surgery (Chiu et al. 2019).

With regards to these future novel wearable, ingestible, implantable, and other similar direct human contact technologies, safety and the impact on the biology and behavior of human beings is not clearly defined. For example, technology-related addiction from smartphones, the internet, and video games is a well-known risk associated with obesity which leads to metabolic diseases such as diabetes and CVDs. This is a critical problem that currently has detrimental impacts on the lives of adults and most children (Kracht et al. 2020; Haghjoo et al. 2022; Porter and Goolkasian 2019). The other concern includes the increasing psychological impact seen with interactions through virtual platforms. A high percentage of individuals engaging in these activities are reported to develop mental health issues leading to depression and suicide (Twenge et al. 2018). These are concerns that cannot be ignored when developing innovative CPSs for future health management services so that the adverse effects do not outweigh the intended benefits of these technologies. On the contrary, there are games that have solely been developed to assist people to cope with stress (Ajmal et al. 2022). Metaverse has been reported to induce intense negative emotions which are also associated with violent behavior compared to the use of computers (Lavoie et al. 2021; Drummond et al. 2021). However, it is worth noting that metaverse can also be used to encourage and promote healthy living (Plante et al. 2003). The ONoC-based chip are also not always reliable as the data generated have the potential to mislead the medical practitioner, causing false interpretations as a result of the imprecise understanding of the biomarkers (Hou et al. 2019). The safety of other medical CPSs such as

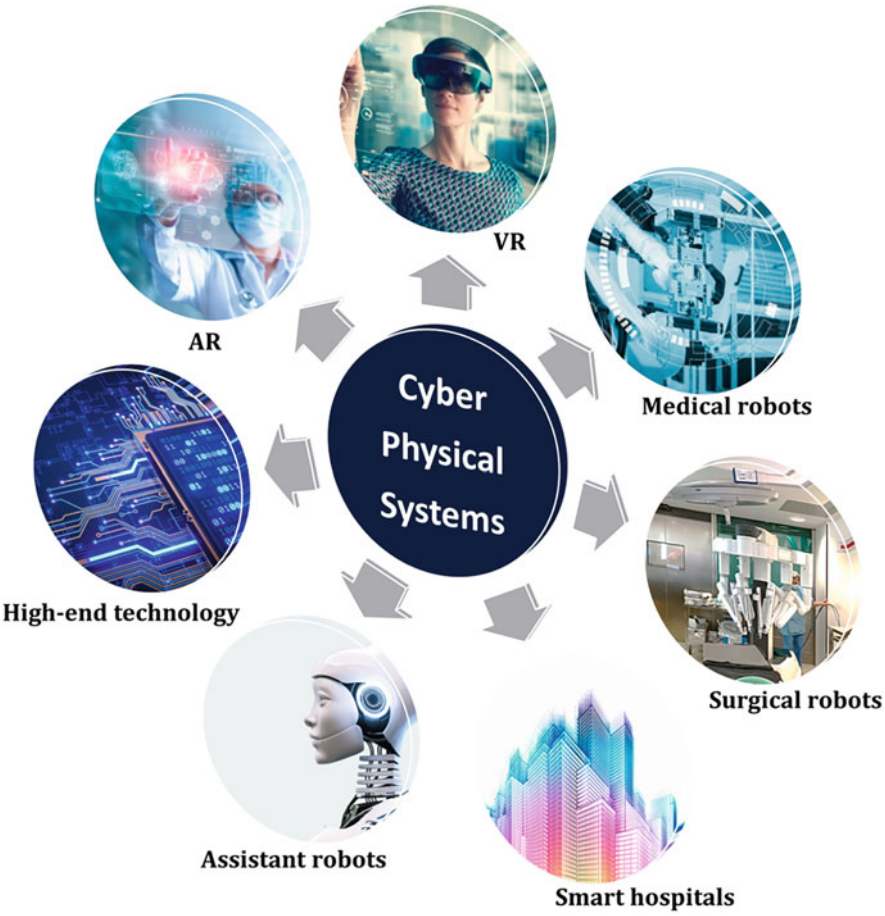

Fig. 4 Summary of the contributions of healthcare CPSs in Society 5.0. Development of high-end technology for monitoring systems. Medical robots clean and sanitize certain areas in the hospital. Assistant robots assist patients with adherence and monitoring of general health status. High-end technology is used to develop systems such as remote monitors. Metaverse (AR/VR) allows the user to see, hear, and interact with the projected organ in cyberspace. Augmented reality–AR; Visual reality–VR

miniature robots including origami is yet to be investigated as these types of innovations are still under laboratory experimental stages. Whether the biodegradability of the robot will take long enough to develop certain adverse effects is not yet known. The method for removal and discharge of foreign materials from the gastrointestinal tract by the robots is also not yet well defined (Miyashita et al. 2016). We can therefore not omit or gloss over these very important issues. Safety measures have to be in place when developing these technologies. This includes high security measures and ensuring that there are limited or no adverse effects associated with these technologies (Fig. 4).

7 Conclusion

Integration of embedded software that regulate monitoring devices, fogging, automated physical systems, and AI algorithms in healthcare management is about to change the way medicine is practiced in Society 5.0. Medical CPS applications permit remote patient monitoring through sensor technology, digitalization of data storing/mining/sharing, and alerts sent to care providers. Integration of AI and cloud/fog computing enables the processing and storage of big data. Digitally assisted patient management ensures timeous, less invasive, and effective methods of treating patients. The security of CPSs can be assured by the development of reliable autonomous security patches that detect any form of a security hole and eradicate the threat before it can cause any harm. Should there be any disruptions, these should be dealt with in a timeous manner to prevent any delays in patient care and management.

Apart from the cybersecurity concerns, which can be dealt with by continuous research and reprogramming of security systems, some of the biggest concerns in LMICs are the potential loss of jobs which most of these countries have worked hard to acquire, scarce skills, and lack of medical personnel. This stems from the automation of hospital services which in some instances could potentially replace human labor. Yes, machines will occasionally require human intervention, but the question would be, how many people will be needed to check if the machine is operating well and optimally? How many times will the machines need to be serviced by humans and how many people will be required to provide these services? Will the era of automation lead to self-services as well? Although machines cannot completely replace humans, these are real societal concerns especially in countries like South Africa where job creation is a challenge. Plans to ascertain global socioeconomic balance still sound further off as the poor might still not be able to afford these advanced technologies. Although overall survival is bound to improve over time, the disparities between hospitals might still exist. Private hospitals are only afforded by a certain class of individuals who will certainly have access to the best healthcare management services facilitated by high-end technologies. The less fortunate might have access to average healthcare technological advancements, and this would be a violation of human rights to good and efficacious health service delivery. For these reasons and others mentioned in the text, the concept of Society 5.0 promises to align with UN SDGs to ensure equality and a long healthy life span for all.

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Transformation of the Healthcare Ecosystem in the Era of Society 5.0

Meshack N. Bida, Sylvia Motlalepule Mosito, Thabiso Victor Miya, Demetra Demetriou, Kim R. M. Blenman, and Zodwa Dlamini

Abstract The term "healthcare ecosystem" refers to a system in which patients, healthcare providers, healthcare policy makers, and administrators participate in health outputs. The COVID-19 pandemic has given us new lessons and changed the definition of norm worldwide. Some lessons may be temporary, but, groundwork changes in our approach to healthcare ecosystem design will be necessary to assist in handling the challenges of future catastrophes. The healthcare ecosystem is mainly comprised of value creation formula, customer value proposition (CVP), as well as partner network. These elements are driven by four business model pillars which are: management, information, financing, and human resources. The use of artificial intelligence (AI) in healthcare promises to revolutionize healthcare ecosystem structural reforms in terms of robustness, agility, and accuracy. Digitization of the healthcare system is occurring on several fronts such as cloud-based technology, blockchain technology, and medical Internet of Things (IoT). Many of these health

M. N. Bida (✉)
Department of Anatomical Pathology, Faculty of Health Sciences, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: meshack.bida@nhls.ac.za

S. M. Mosito
Department Otorhinolaryngology, Faculty of Health Sciences, Steve Biko Academic Hospital, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: Sylvia.mosito@up.ac.za

T. V. Miya · D. Demetriou · Z. Dlamini
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Hatfield, South Africa
e-mail: thabiso.miya@up.ac.za; dd.demetriou@up.ac.za; zodwa.dlamini@up.ac.za

K. R. M. Blenman
Department of Computer Science, School of Engineering and Applied Science, Yale University, New Haven, CT, USA

Department of Internal Medicine, Section of Medical Oncology, School of Medicine, Yale Cancer Center, Yale University, New Haven, CT, USA
e-mail: kim.blenman@yale.edu

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technologies offer a hope to improve access to healthcare to under-resourced communities as well as provide quick often real-time access to patient health data for quick real-time clinical decisions, but they are not without limitations. Whereas some of these limitations are purely technical, others are related to compromised patient privacy. These healthcare technologies further improve the wave of precision medicine in the long run, by improving the turn-around time for diagnosis and treatment. The privacy, safety, and security of patient health records can be set at the highest level using healthcare technologies through several oversight mechanisms available. However, legitimacy of implementation remains subject to the legal framework of human rights policies, the ability to avoid potential environmental health hazards, as well as the economy of scale.

Keywords Healthcare ecosystem design · Artificial intelligence · Digitization · Precision medicine · Oversight · Privacy and security · Human rights

1 The Main Objectives of Healthcare Ecosystem Design

The main objectives of healthcare ecosystem in oncological settings are to work toward increasing access to screening, early diagnosis, and improving accessibility of high-quality medicinal treatment. It could also assist to improve the community and patient's knowledge of cancer across a broad range of other topics—including lifestyle modifications, quality of life benefits, and diet. The improved healthcare ecosystem will be used to ensure that the patients focus on the cure rather than the disease itself. Therefore, every individual in the cancer care ecosystem has a role to play in reforming and providing support to every patient with cancer (Singh 2020).

By weighing the costs of services with the benefits to the consumer, effective utilization of resources, prevention of over-servicing, reduction of fruitless expenditure, as well as coordinating care for maximum effectiveness can be achieved. The value creation formula can be described as the value of care which comprises of quality service, end results, and well-being divided by the total cost of patient care over a period. This translates into the actual measurement of improvement in patient's health outcomes for the given cost of attaining that improvement. The purpose of value-based care revision is to enable the healthcare system to generate more worth for patients. The ideal model of the ecosystem of healthcare should include a range of levels of healthcare, from community-based, secondary healthcare centers to tertiary healthcare centers (Viswanadham 2021).

The efficiency ideas in healthcare should always involve the patient's contribution in creation of value. The providers should aim at matching the value creation standard process to the customer (patient) (Nordgren 2009). Soon, healthcare should embrace collaboration, cooperation or partnerships, and affiliations in all sectors of the biological and life science in the ecosystem.

2 The Trends of the Healthcare Ecosystem

The terrain of the healthcare ecosystem is rapidly changing with five main trends becoming apparent:

- Hybrid care models combining virtual services
- Digitalization of healthcare specialties
- Increased AI adoption
- Migration of health systems to the cloud
- Advanced precision medicine

3 Hybrid Care Models Combining Physical and Virtual Services

Hybrid healthcare comprises of physical (in-person) and telemedicine consultations (Fig. 1). It is also driven by telecommunication tools such as Zoom meetings, video conferencing, etc. Several aspects of clinical care such as patient monitoring, appointment scheduling, and follow-up can also be done in a virtual platform. The patient's individual circumstances determine if remote management or face-to-face management will be ideal (Rongey et al. 2011).

The COVID-19 pandemic has significantly accelerated telehealth adoption and is rapidly changing the patient and practitioner experience. Several specialist practices such as dermatology have benefited from telemedicine during the COVID-19 pandemic and have managed to operate even during the height of total lockdown. However, some patients were not yet comfortable with telemedicine and still prefer physical consultations. Nonetheless, video conferencing consultations have been welcomed by most patients. For some patients with minor medical conditions, such

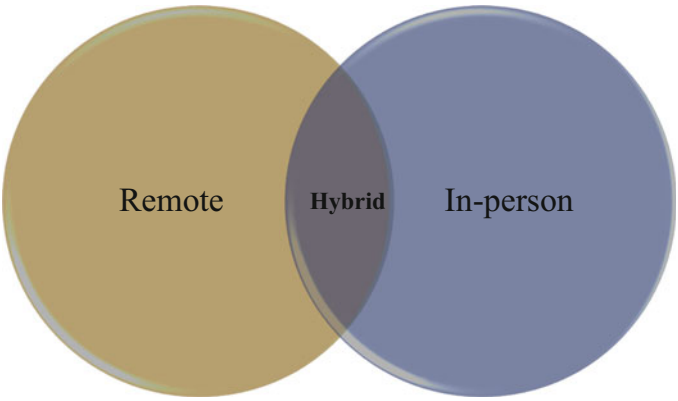

Fig. 1 A hybrid model of the healthcare system

as psoriasis or acne, telemedicine consultations remain a preferable option. But for patients who may need surgery or biopsies, telehealth consultations are not an option.

A general workplace model mixes physical contact and remote consultation and gives room and support to employees. Employees have better work-life balance and autonomy in a hybrid;/ workplace and tend to be more applied to their work. This makes the workplace productive. A genera workplace which prioritizes the health of employees may be of value to some of the HR technologies. Some of the benefits include:

- **Increased employee productivity:** Several factors contribute to improving employee productivity: fewer interruptions at home compared to the office, increased autonomy to choose location and work hours, repurpose commuting time, and the opportunity to go to the office at times when in-person collaboration is ideal.
- **Reduced overhead costs:** Institutions or companies now take into consideration the real estate opportunities and strategies to reduce office space or locate their offices to smaller cities which can reduce the cost of production and office expenses such as electricity bills and rental. Genera employees often become more engaged, leading to reduced costs and less turnover.
- **Staff experience and work-life balance:** Autonomy and improved flexibility increase job satisfaction and happiness. In turn, this increases performance at work and overall employee well-being. An integrated focus on work-life balance can lead to a prosperous hybrid workplace.
- **Additional protection through social distancing:** With COVID-19 variants still posing a threat to physical contact, the genera workplace model enables the office space to be designed in a way that emphasizes safety and sanitization. Mixing and matching who is in the office, and when, enables social distancing and increased cleaning. In turn, this makes it easier if there is a need to perform contact tracing (Durai 2022).

3.1 Digitization of Healthcare Specialties

The health ecosystem digital era requires innovations that advance diagnosis and treatment, especially in hospital-based patient care that results in a reduction of error (Fig. 2) (India 2017). Furthermore, numerous innovations, such as video consultations or virtual meetings, are also required to ensure continuous care through the facilitation of off-site patient management. This can be achieved through telemedicine by reducing wastage, such as time and labor in the delivery system (India 2017). By partnering with individuals to support self-management, digital innovation will positively impact on the socioeconomic determinants of health, such as transportation costs and lesser consultation fees using remote technologies (Serbanati et al. 2011).

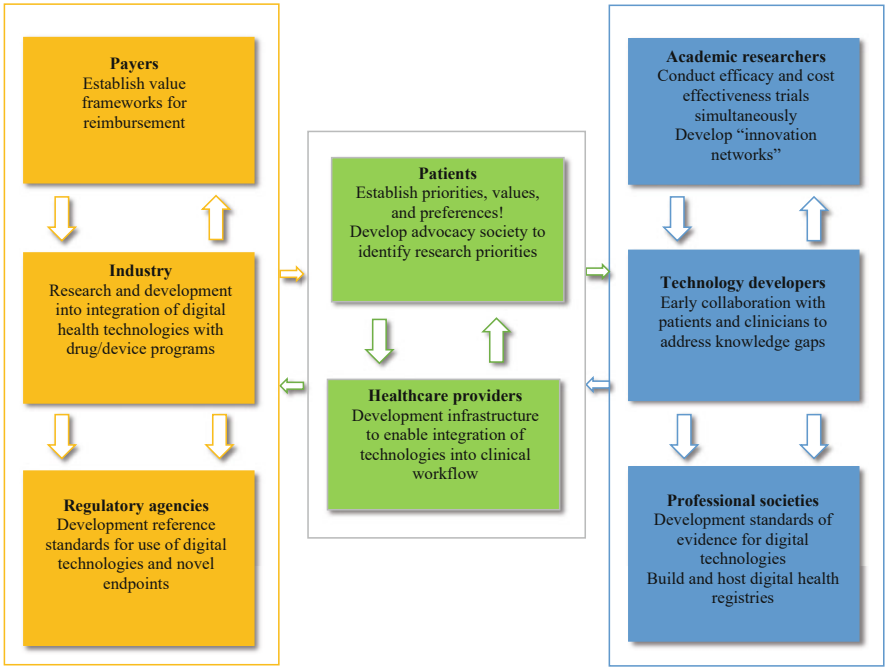

Fig. 2 Utilizing digital health technology to create evidence and deliver evidence-based healthcare (Adapted from Sharma et al. 2018)

Digital technologies provide advantages that are associated with the possibility of remote access to many medical services, and in the last decade have led to the rapid spread of digital medicine. Furthermore, there are several negative factors that have emerged through the diverse use of digital technologies in medicine. These technologies may cause serious harm to the life and health of people, and induce significant damage to the society, especially where the diagnosis is incorrect which results in mismanagement of patients (Mirskikh et al. 2021).

The information age of healthcare provides opportunities to optimize clinical research and clinical care delivery using telecommunication. Regarding telecommunications in patient care and research, although of high quality, there are major concerns about patients' protection and privacy, especially due to the absence of legislation that guarantees ownership on the part of the healthcare provider in cases of mismanagement. This requires new regulatory policy innovations before full-scale implementation (Sharma et al. 2018). The types of innovations that are likely to be adopted in a healthcare organization should address the quality improvements in health outcomes.

4 Digital Transformation of the Healthcare Ecosystem Through Blockchain Health Technology

The COVID-19 pandemic has negatively impacted even the world's best healthcare systems because of the state of operating on disconnected and centralized networks with inefficient data-sharing capability. Decentralization, with effective patient metadata sharing using blockchain technology, provides an opportunity to preserve and accurately utilize patient data. Deploying this blockchain technology in the healthcare ecosystem enables the regulatory authorities and healthcare providers to process large volumes of data, make timely decisions, and develop better health policies to intervene. Blockchain is a technology that keeps a record of healthcare information or data in a secure and immutable manner**.** Blockchain was introduced via Bitcoin, and research is ongoing to explore its suitability and application to non-financial markets. Research in the application of blockchain technology in the healthcare sector is still new and will have a major impact, especially in the access and management of a large volume of data (Agbo et al. 2019). Instead of using a central database, the blockchain record is distributed across networks, with optimal information security. The authorized users can upload or download data but cannot delete or alter the data. The system preserves and exchanges patient data through healthcare centers and individuals. Blockchain technology also reduces error in a significant way, by allowing several participants to play an oversight role and thus gives ideal operational efficiency in the healthcare system (Burniske et al. 2016).

The features of blockchain include immutability, transparency, efficiency, better security, and decentralization (see Fig. 3):

– Features of blockchain:

  Decentralization: Blockchain uses a decentralized and distributed ledger to deliver the optimal processing capabilities of all participating users in the network. This decreases latency and eliminates errors that may occur from any point of the user.

  Immutability: It is the ability to ensure the stability of entries by creating immutable ledgers. In blockchain technology, the blocks are permanently saved and never changed if the participating user continues to maintain the network.

  Transparency: A high level of transparency by sharing entry details among all users involved in the network.

  Better security: Blockchain offers better security, especially public types of blockchain where a public key infrastructure is in place, to protect against adverse actions to change data. This security feature in the blockchain network protects the integrity of information.

  Efficiency: Blockchain distributes all data entries to make it more transparent, thus allowing data verification at multiple points of usage (El Bassam 2021).

Healthcare institutions and healthcare providers often work in silos in the healthcare ecosystem without the benefit of momentary updates in patient information. This insufficient interoperability allows a high level of information gap and is

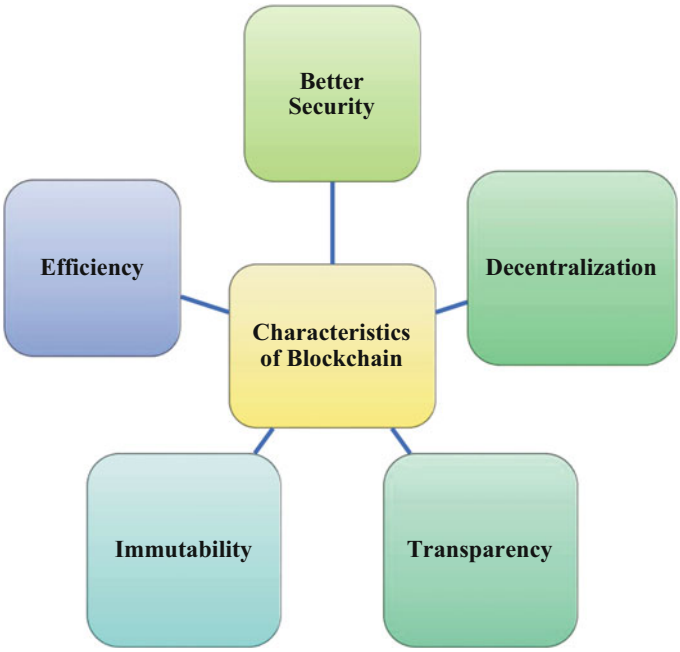

Fig. 3 A blockchain is a decentralized architecture with built-in security to increase the trust and integrity of transactions (Adapted from El Bassam 2021)

error-prone in decision-making during patient management. For example, some of the patient data in the use of medicines may be relevant to the pathologists in terms of diagnosis and if such information is shared among all healthcare providers timeously, it may be helpful for the healthcare practitioners to make a timeous diagnosis. Large volumes of healthcare metadata are shared across the healthcare system and in so doing errors, fraud, and duplications can be avoided (Engelhardt 2017).

Thus, blockchain development for healthcare addresses the following key lapses:

- Patients can avoid medical services that are irrelevant to their current care.
- Physicians have full access to the medical history of a patient, thus minimizing the risk of inaccurate decision-making in emergency cases.
- Ability to trace first and last mile delivery verticals in pharmaceutical stores as well as to identify the specific medicines based on the active ingredients (Panwar and Bhatnagar 2020).

- Limitations of blockchain application in healthcare:

In many ways, the potential of blockchain technology in the healthcare industry is sometimes overstated. It has up to date remained as theoretical frameworks, layouts, or models, seldom with a prototype or pilot implementation especially in the most under-resourced areas, where the impact is likely to be most observable to learn

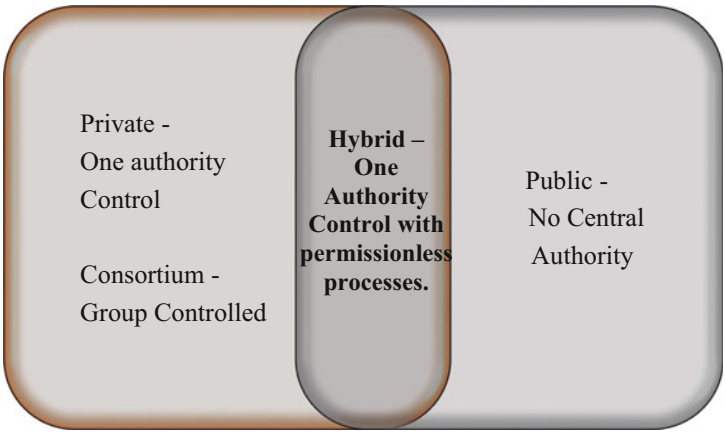

Fig. 4 Types of blockchain: Public, private, or something in between (Adapted from Wegrzyn and Wang 2021)

from. Thus, large-scale deployment of blockchain technology in the healthcare industry is rare in practice.

In addition, blockchain is not well suited as a storage facility due to the capacity constraints of computational needs in every network participant (often called "node"). Storing large records on this blockchain technology, including full electronic medical records or genomic data records, would be costly or inefficient if such computational needs are not in place. In this regard, government institutions rather than private healthcare organizations are best suited for this task. It is also difficult to use blockchain technology as an analytic tool for such data, thus providing limited clinical decision support and statistical analysis, especially for research use.

On the Protection of Personal Information Act (POPI Act) in South Africa, storing personal health data "on chain" (i.e., in blockchain) will make such information visible to other network participants, which is data privacy infringement (South African Government 2013). Then there are patient rights under the EU General Data Protection Regulation, particularly the right to erasure, which are incompatible with the immutability of blocks in a chain (Europe 2022) (Fig. 4).

All types of blockchains can be regarded as permissionless, permissioned, or both. Permissionless blockchains allow any user to pseudo-anonymously join the blockchain network (i.e., to become "nodes" of the network) with minimal or no restriction to the rights of the nodes on the blockchain network. Permissioned blockchains have built-in restrictions to data access on the network to certain nodes and often restrict the rights of the nodes on the particular network. However, the identities of the users of a permissioned blockchain are known to the other users in the network (Wegrzyn and Wang 2021). Hybrid blockchains are centrally controlled by a single organization, but with a level of oversight performed by the public blockchain. In this regard, data security in the case of healthcare blockchains can be customized accordingly to comply with the protection of patient information policy

in South Africa, for example, by regulating access to information using codes or password protection (Wegrzyn and Wang 2021).

4.1 Digitalization Through the Internet of Things

In the last ten years or so, there has been an increase in the development of health devices and instruments that can be operated using the internet. These devices are referred to as the Internet of Things (IoT) devices. These IoT devices have a wide range of industry application which includes process systems, manufacturing, and law enforcement but are now increasingly being implemented in the field of healthcare systems (Pradhan et al. 2021a, b).

Medical IoT can also be used to collect patient's information, for diagnosis of diseases, for monitoring of patient's health condition, and to provide alerts in case of a medical emergency (see Fig. 5).

The use of IoT devices in the healthcare sector is referred to as medical IoT and has now become a large field of study, which is transforming the healthcare systems' operations, by enabling remote patient consultation, accessing of patients' vital records by physicians, and even doing minor surgical procedures remotely, such as incision and drainage of superficial skin abscess and self-sampling for specimen procurement for HPV testing (Akkaş et al. 2020). Some of these devices have been

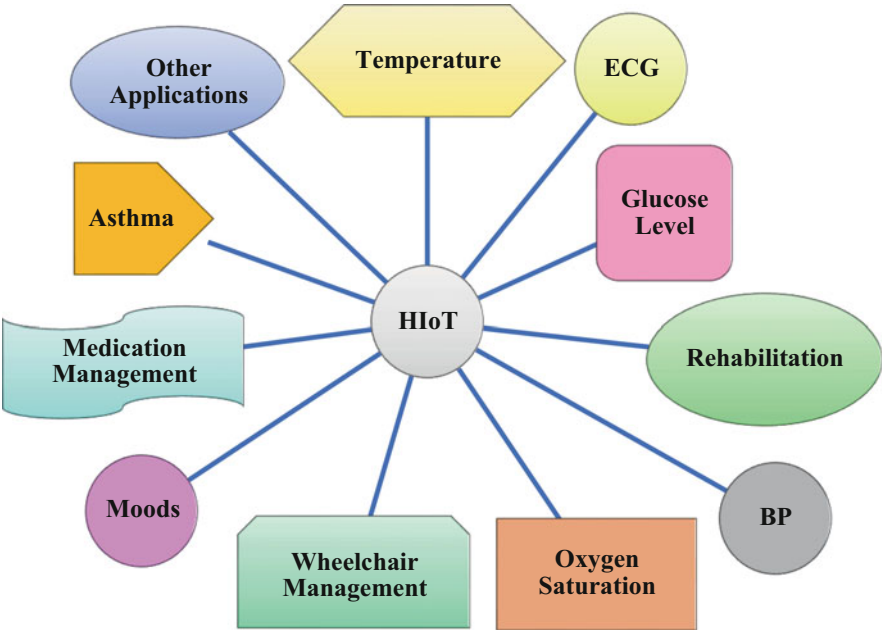

Fig. 5 Categories of IoT application (Adapted from Pradhan et al. 2021a)

applied as IoT-enabled biosensors, IoT in medical implant manufacturing, IoT in rehabilitation devices, IoT-enabled medical robotics, IoT in genomics, as well as IoT devices in pharmaceutical industries (Akkaş et al. 2020). A complete IoT system consists of four separate components that operate together to ensure the required output (Pradhan et al. 2021b).

- **Sensors/Devices:**
  The sensors are connected to special devices and collect minute data from the surrounding environment. Some of these data include geographical location or vital data of a patient, such as temperature, pulse, or blood pressure. Sensors can be attached to a device such as a mobile phone which already has built-in sensors such as GPS, camera, and accelerometer.
- **Connectivity:**
  The data is sent to a cloud infrastructure or an IoT platform with the help of either wireless or wired networking technologies, such as Bluetooth, Wi-Fi, cellular networks, ethernet, etc.
- **Data Processing:**
  The data is stored in a cloud infrastructure, analyzed, and processed by a Big Data Analytics Engine, for clinical decision-making. This analysis could range from checking if the temperature, heart rate, blood pressure or blood glucose readings are within an acceptable range (Jagadeeswari et al. 2018). The processed data is then used to act accordingly or provide a medical opinion.
- **User Interface:**
  The end user is notified often by an email, text, notification, or alert sound triggered on their IoT application.

4.2 Benefits of IoT

The benefits of the application of IoT in other industries provide a positive spin-off in the healthcare ecosystem, which includes:

- **Access to High-Quality Data:**
  One of the most frustrating things in practicing healthcare is accessing patient data in good quality. Clinical history, laboratory results, medical treatment, and even surgical procedures for an individual patient are often hand scribbled with illegible handwriting or poor electronic records data quality. IoT promises to magnificently improve data quality especially with verification and timeous access (Pradhan et al. 2021b).
- **Better Tracking and Management:**
  Over time, health records become difficult to store and access at the point of need. IoT has the potential to trace back any such medical history as may be relevant at the point of care, irrespective of where and when such data was accumulated.

- **Efficient Resource Utilization:**
  One of the challenges in managing patients is the wastage of resources through duplication of tests, for example. Because of the transparency that is offered by IoT technology, such wastage could be reduced.
- **Automation and Control:**
  Automation drives laboratory medicine, and this links well with IoT to allow remote access to essential laboratory information within the network.
- **Comfort and Convenience:**
  The interconnectivity of devices and aggregation of data provide the patient with full control over the monitoring of their health condition with accessible remote monitoring by the clinical care team. Several visits to the healthcare center for monitoring becomes unnecessary in some cases of chronic care, such as diabetes and hypertension, especially if hand-held devices are used to monitor patients in this regard.
- **Saves Time and Money:**
  The cost of healthcare delivery is markedly reduced by cutting overheads such as travel and several face-to-face consultations, especially in some follow-up consultations which allow remote monitoring. Specialist physician consultations take place quicker on the network with delay.

Some real-world applications of IoT presently in use are:

- **Smart Home:**
  Smart home systems such as connected inhalers**,** smart thermometers, ECG monitors, and blood pressure monitor devices offer security and convenience and save time.
- **Wearables:**
  Devices such as Smart Watches and Fitness Tracking Bands that can be worn can, with the help of installed software, track and monitor heart rate, blood pressure, sleeping and eating habits, caloric intake, etc. The measurements made by these devices, can be relayed to a healthcare service provider.
- **Smart Cities:**
  Smart cities provide their citizens with a preventative aspect of community-based healthcare and allow public health data to be easily collected from citizens. Smart cities assist to minimize environmental pollution and provide optimal waste management (Menon et al. 2022).

4.3 Examples of Internet of Things

Several examples of IoT are out there in public but the one that is often spoken about in the healthcare industry is *Hero Health*. It is a medication dispenser that is used for home treatment and elderly care. This smart appliance also sends alerts to your smartphone if they miss a dose, thus assisting the physician in monitoring the patient (Mathew et al. 2018). Other examples such as Blossom, Philips Hue, Nest Learning

Thermostat, and Amazon Go have not found a niche yet in the healthcare sector so far and are mainly used in manufacturing, especially with regards to equipment monitoring (Fig. 6).

4.3.1 Limitations of Internet of Things–Based Systems

Several challenges are encountered in the application of medical IoT:

- **Servicing and Cost:**
  Like any other computational system, IoT requires continuous upgrading regularly. Every IoT-based system involves many connected medical devices and sensors which require high cost of maintenance, servicing, and upgradation costs.
- **Power Consumption:**
  Most IoT devices consume large quantities of voltage requiring a high-power battery. Integration of the IoT system with renewable energy systems may help to address this challenge.
- **Standardization:**
  Standardization of medical IoT devices, although without its faults, is based on the communication protocols from data aggregated. The validation and standardization of electronic medical records (EMRs) recorded by IoT devices should be done on a wide scale. This can be achieved if various organizations and standardization bodies form working groups for the standardization of the devices.

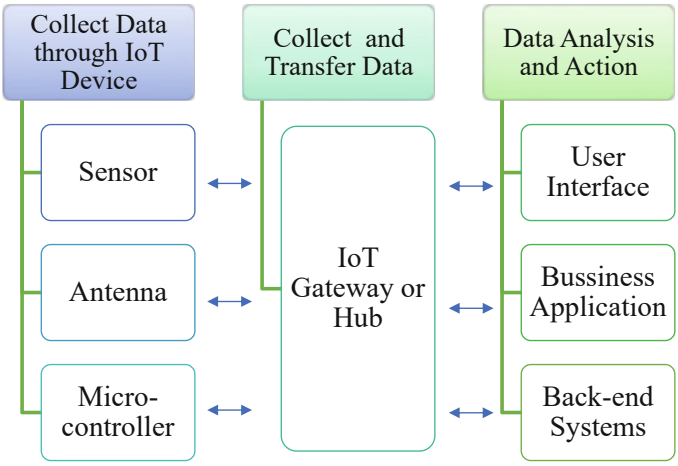

Fig. 6 An example of how an IoT system works from collecting data to taking action (Adapted from Pradhan et al. 2021b)

- **Data Privacy and Security:**
  Internet of Things–aided applications in healthcare networks are susceptible to cyberattacks. This may result in mismanagement of patients' valuable information as well as negatively affecting patient treatment.
- **Scalability:**
  Most medical IoT-aided devices are not liable to scalability as new information on emerging diseases is gathered due to a lack of uniformity among the connected devices.
- **Identification:**
  Patients often have multiple diseases and are seen by multiple healthcare specialists which may compromise the identity of the patient, caregiver, and doctors among each other in a single treatment process, due to large volumes of specific data that needs to be correctly captured (Gatouillat et al. 2018).

4.3.2 Digitalization Using Robotic Services

The IoT-aided robotic system is a wireless network that offers robotic services by interconnecting multiple robots with the smart environment, using information and communication technologies to share large volumes of data. The IoT-aided robotic system is integrated with various sensors directed toward particular healthcare goals such as disease monitoring, diagnosing, and doing simple tasks, depending on the level of integration. The higher levels of integration systems may perform complex operations (Alotaibi and Yamin 2019). In other words, the IoT-aided robotic system is simply a complex form of IoT that also has the functional advantage of robotic technology. The layout of an IoT-aided robotic system consists of three layers: the physical layer, the network control layer, and the application layer.

The Internet of Things and robotics are closely linked. The Internet of Robotics Things (IoRT) is also viewed as the integration of robotics technologies in IoT scenarios (Afanasyev et al. 2019). The sensors are used to collect vital health data of the patient's body such as blood pressure, pulse, and temperature. The sensors may also be upgraded to include switches, actuators, and other drives that can be used to perform simple tasks. Robots can connect either with other robots with sensors or actuators, to create a multi-robot network of routers, and controllers through communication network protocols. The application layer solely depends on the objective of the integrated system. The healthcare applications of an IoT-aided robotic system depend on the nature of tasks and objectives which are drafted in the communication protocol as a set of functionalities which can meet the demands. Some of these functionalities may involve the quaternary care of patients as in the rehabilitation of patients and remote management of chronic diseases and disabilities, such as remote management of paraplegics, diabetes, or psychotherapy.

Once machine learning techniques have been applied to these robots, the robots are able to develop recognition ability and the ability to perform complex tasks and are able to function in various scenarios in which they are deployed. The robots can access sensor data that are recorded in real time such as speech, image, and video.

These data are time sensitive and must be processed in real time to allow prompt intervention and treatment where necessary (Hadidi et al. 2018).

4.3.3 Increased Artificial Intelligence Adoption

"AI is a capability of a computer program to perform tests or reasoning processes that we usually associate with intelligence in a human being."

Medical science has improved and continues to do so immensely, increasing the life expectancy of individuals worldwide. As life expectancy rises, the healthcare systems face an increase in the need for healthcare services. The high life expectancy means that the cost of healthcare delivery increases. The workforce is increasingly facing increasing demands and struggling to accommodate the needs of its patients. The demand increases due to the aging population, lifestyle changes, and changing patient demands. Treating such patients is costly and requires systems that are dynamic and suited for long-term continuity of care.

In the context of the healthcare ecosystem, AI has the potential to improve accuracy, that is, diagnostic precision, thus yielding better outcomes as well as reducing the time of production. This is seen largely in laboratory diagnosis, clinical diagnosis, imaging analysis, research studies, financial administration, documentation, workflow simplification, and other duties in the healthcare system.

Currently, medical management spending is exorbitant and without major structural changes, the healthcare system will struggle to remain effective. The adoption of AI has the potential to positively alter the medical management system and assist in the challenges set out above (Dhamnani et al. 2019). AI in healthcare has relevance in the processing of claims, clinical documentation, revenue cycle, and medical records management. AI technology can assist healthcare professionals to diagnose patients by analyzing symptoms, suggesting personalized treatments, predicting risks, and detecting abnormal results (Table 1). Outweighing the benefits and risks of AI, concerns have been raised regarding the impacts, benefits, and risks of AI on patients, healthcare professionals, and healthcare systems. There are also debates on how AI and the data that supports it should be used.

A complete adoption of AI into the healthcare system is still in its early stages. In low socioeconomic settings, AI adoption is significantly affected by social power which can either be knowledge-based or non-knowledge-based. The knowledge-based power structures are social powers related to knowledge and skills, such as expertise in AI. They can also include informational, expert, and referent powers. This knowledge-based power is therefore more applicable in areas of large-scale high socioeconomic development, which are capacitated in terms of human resources. The non-knowledge-based power structures comprise of coercive, reward, and legitimate powers. They are not related to personal knowledge and individuals' skills (Sun 2021). Additional benefits of AI in medical sciences include patient diagnosis, end-to-end drug discovery and development, as well as improvement of communication between healthcare providers and patients (Ekins 2016; Dilsizian and Siegel 2014). In the recent past, computer algorithms have virtually

Table 1 Major healthcare companies using AI in medical sciences around the world (Adapted from Basu et al. 2020)

Company name	Main purpose	Website
AiCure (New York City), patient-oriented	Utilizes audio, video, and behavioral information to better understand the link between patients, disease, and treatment.	https://www.aicure.com
Aidence (Amsterdam, the Netherlands), clinician-oriented	AI for radiologists that improves diagnostics for lung cancer treatment.	https://www.aidence.com
Aiva Health (Los Angeles), administrative and operational-oriented	The first voice-powered medical care assistant: Connects patients with the correct healthcare providers for communication.	https://aivahealth.com
Babylon Health (London), administrative and operational-oriented	Uses NLP and AI to generate an internationally accessible and affordable healthcare system.	https://www.babylonhealth.com
Bot MD (Singapore), clinician-oriented	Bot assistant: Answers clinical questions, transcribes case notes, and organizes images and files automatically.	https://www.botmd.io/en/
Suki (San Francisco), clinician-oriented	Voice-controlled digital health assistant for physicians.	https://www.suki.ai
Insitro (San Francisco), patient-oriented	Utilizes advanced machine learning together with computational genomics to decrease time and cost related to drug discovery for patients.	

eliminated errors in the health system, often very attractive and intimidating to humans (Basu et al. 2020).

Artificial intelligence applications in healthcare can be clinician-orientated, patient-oriented, or administrative and operational-oriented AI (Davenport and Kalakota 2019).

4.3.4 Migration of Health Systems to the Cloud

Cloud computing augments healthcare technologies such as electronic medical records, mobile applications, patient portals, and big data analytics (Fig. 7). It is scalable and flexible, can be customized to most healthcare ecosystems, and ultimately improves the decision-making process. By leveraging cloud-based computing solutions, healthcare systems can reduce costs, enhance privacy, and improve patient care quality through collaboration and interoperability. Examples of healthcare cloud computing include Amazon Web Services (AWS), which has been rated as a leader in the healthcare cloud computing market.

Cloud-based healthcare can be described as the integration of cloud computing technology to create and manage cloud-based healthcare services. Since the generated data can be securely stored off-site, it is regarded as a critical benefit for provider organizations regardless of the volume of data stored. This cloud-based healthcare system tackles the following essential requirements of the healthcare industry:

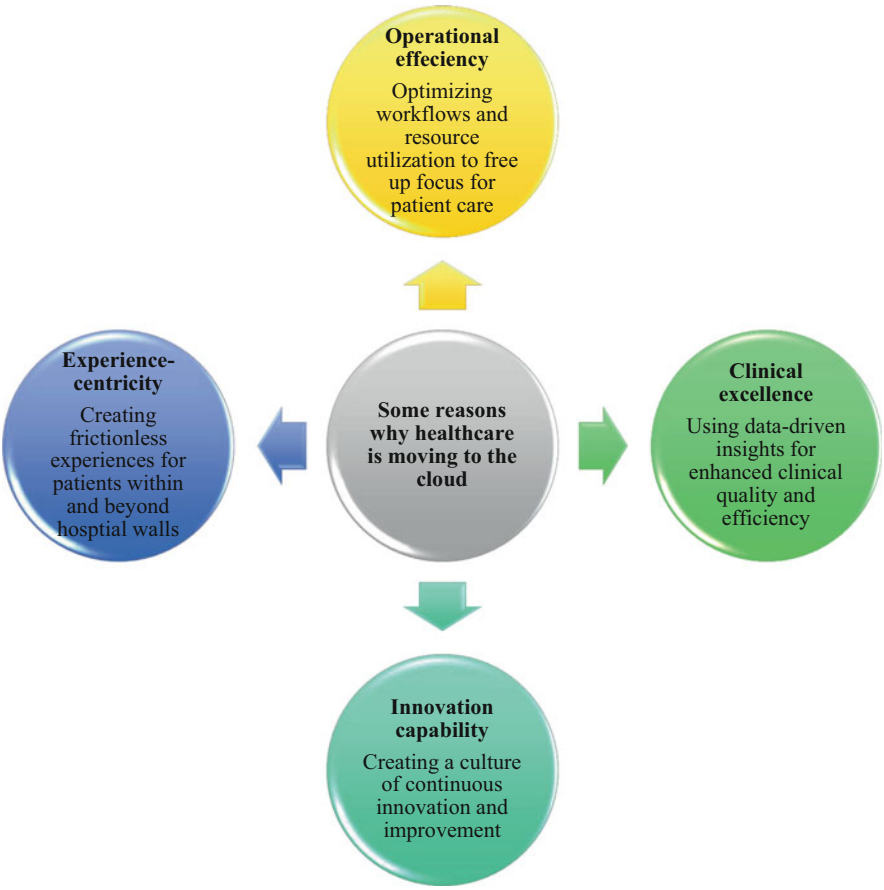

Fig. 7 Some reasons why healthcare is moving to the cloud (Adapted from ScienceDirect)

1. On-demand access to computing with large volume storage resources, which will otherwise not be possible in old healthcare systems
2. Support enormous datasets for electronic health records (EHR), genomic data, and radiology images offloading
3. Ability to share EHR among authorized physicians and healthcare facilities in different geographic locations, with timely access to life-saving information and reducing the need for double testing
4. Improvement in monitoring and analysis of diagnosis, treatment, performance, and cost data

Healthcare's digital transformation has encouraged patients to seek out more in the way of operational efficiency, clinical excellence, innovation capability.

4.3.5 Advanced Precision Medicine

The world is in a period of enormous progress in the fight against cancer. We now have immunotherapy and cancer early diagnostic tests which we never had before. Despite having these tools, we still have persistent inconsistencies in cancer end results. Precision medicine (also referred to as personalized medicine) is a technologically advanced approach to mass population screening, disease diagnosis, treatment, and prevention based on the individual's uniqueness in terms of genetic makeup, unique environment, and lifestyle. The emerging field of precision medicine is an area of enormous potential and is rapidly catching the public eye. The future of precision medicine rests on the different technologies that are integrated to complement the knowledge and skills of healthcare professionals in the milieu of clinical practice. This requires ongoing research to understand the knowledge gap as well as weighing the benefits it provides in patient management.

According to Prosperi et al. precision medicine is the "approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person" (Adams and Petersen 2016; Prosperi et al. 2018). The current treatment for cancer may be a combination of surgery, chemotherapy, radiation, and immunotherapy, depending on the histologic type of cancer and its staging. Looking at the gene level, precision medicine can help decide on individualized treatment with certain medicines demonstrating to be more efficacious for specific genes (World Economic Forum 2020). It needs a balanced healthcare ecosystem to attain personalized prevention and treatment. This can be achieved by incorporating risk assessment into the primary healthcare setting and ensuring that the healthcare providers in the primary care are provided with the right equipment to make precision prevention possible (Ayodele 2022).

From targeting late-stage cancers to curing rare inherited diseases, precision medicine is assured to impact millions of people within the next decade. The biggest challenge in the field of precision medicine is patient confidentiality. The protection of privacy, confidentiality of personal and medical information, of the participants is critical, especially with the POPI Act's policy innovation. During research, participants need to be briefed about the risks and advantages of partaking. In essence, researchers must have a rigorous informed consent process. Lastly, cost is also a critical issue in precision medicine and needs to be addressed. Precision medicine partially depends on data collection and analysis. The data collection, storage, and sharing, which are crucial to implementing precision medicine, make security, privacy, and integrity a serious concern to patients, healthcare providers, and society as a whole (Rasch 2018, 2021).

5 Technology and Innovation in Biomarker Discovery Through Genomics and Multi-omics Data Processing

Omics technologies are critical in advancing precision medicine through the discovery of new biomarkers. To date these technologies have not been fully exploited given that only a few omics-derived biomarkers have been incorporated into clinical practice. A careful selection of potential biomarkers requires a high level of sensitivity and specificity to be clinically relevant. The ideal omics-driven biomarker should have features with high predictive power in accuracy, be less robust in analytic terms, as well as be cost-effective in production (Fortino et al. 2020).

6 Funding Mechanisms in Propelling Health Innovation

Access to quality healthcare is a major problem worldwide. Together with poverty, these two factors are the twin devils causing poor livelihood for many across the globe. However, innovative finance through partnerships can assist to make access to healthcare a possibility. These partnerships can redirect resources and address market inefficiencies and other systemic deficiencies that are preventing people in lower socioeconomic regions to access healthcare. Healthcare companies can potentially play a major role as investors, innovators, and advisors to generate financial returns and develop new markets, and eventually improve health outcomes. In this way, new opportunities are identified through finance partnerships, thus breaking down access barriers at each stage of the healthcare value chain.

6.1 Innovative Finance Can Be Applied in Four Key Areas of the Healthcare Ecosystem

- **Research and Development (R&D):** The main focus of financing is product development partnerships as well as investment funds through research. These goals can be achieved using incentives and collaboration often between the under- and over-resourced partnerships. It is a sure way of ensuring skills transfer as well as capacity building.
- **Core Operations:** Optimizing core operational platforms can be facilitated by volume guarantees, payment plans, and investment agreements. In this way, new business models are usually conceived which ensures a wider distribution network that increases access to healthcare. A good example of volume guarantee arrangement is the use of contraception devices by the majority of women in low socioeconomic settings through a group of funders in Africa (Tsui et al. 2017).
- **Health Systems:** Through financing small business enterprises, the health systems can be strengthened and expanded. These financial ventures may take the

form of credit trade finance and social bonds which can strengthen the capacity to deliver medicines, patient education, and health services to remote areas previously untapped.
- **Patients and Customers:** There are opportunities for healthcare companies to start micro-economic ventures in savings, credit, and insurance. This has the potential to stimulate demand and improve access to health services and products (Nordic Precision Medicine Forum 2022).

7 Alignment with Sustainable Development Goals

One of the Sustainable Development Goals (SDGs), as adopted by the United Nations in 2015, is Goal 3 for "GOOD HEALTH AND WELL-BEING." The evolution of the healthcare ecosystem should be aligned with this goal by working toward removing barriers of access to healthcare using technology. An effective healthcare ecosystem will allow increased access to screening, early diagnosis, and improved accessibility to high-quality medicinal treatment. This will implement SDG Goal 3 by assisting good health and well-being. It can also assist to improve the community and patient's knowledge of cancer, lifestyle modifications, quality of life benefits, and diet. The improved healthcare ecosystem, as previously mentioned, can be used to give hope to the patients for better options in disease monitoring and management. In the same breath, access without affordability will be meaningless and, in this way, cost-effective funding strategies should also be pursued through collaborative partnerships especially targeting low-income communities. Good health should not be a prized commodity but a basic human right for us to realize the 2030 Agenda of sustainable development. Multiple fronts of the pursuit of the 2030 Agenda of sustainable development should include addressing the health of our communities as part of dealing with socioeconomic inequalities.

8 Overall Impact of Technology on the Ecosystem

The impact of technology on the healthcare ecosystem is closely interlinked with other determinants such as affordability, eagerness to the adoption of new technologies, status of health of population, and skills level of healthcare professionals to utilize these technologies. Due to the lack of widespread usage in a greater population scale, modeling quality improvements, such as its impact on life expectancy, aging populations, productivity, and gross domestic product (GDP), is a challenging task (Marino and Lorenzoni 2019). Given the low-level adoption of digital technology, especially in low-income countries, an autoregressive distributed lag (ARDL) model approach has been used in some studies in countries such as BRICS (Brazil, Russia, India, China, and South Africa), which demonstrated increasing life expectancy between 1993 and 2019, except in Brazil (Jiang et al. 2022).

The impact of technology on the healthcare work force has been variable in most studies, reflecting the complex nature of technology integration in the healthcare ecosystem. Several determinants come into the picture such as eagerness to adopt technology, especially due to physicians' attitudes and skills. There is a lot of variation in the impact, with many healthcare organizations seeing no benefits (Acemoglu and Autor 2011).

9 Human Rights

Several of the transformative technologies which have impacted the healthcare ecosystem are by nature global and operate based on a set of rules and principles that have a law-like nature—the Lex Cryptographia. This law-like nature of these technologies makes some of the utilization by international organizations difficult due to questionable compliance with the local laws and foreign policy perspective, thus questioning the legitimacy of use in some countries. Lex Cryptographia is defined as a set of rules that are managed through smart contracts in a setting of decentralized organizations. These complex systems of smart contracts are required for technologies such as blockchain for purposes of code-dependent self-executable rules among the individuals participating in a blockchain network (Dimitropoulos 2022). Blockchain technology is so global that the United Nations and the World Bank have adopted it. The World Health Organization (WHO) has partnered with major blockchain and technology companies to launch a distributed ledger technology (DLT)-based platform for sharing data concerning the coronavirus pandemic to facilitate "fully private information sharing between individuals, state authorities and health institutions."

10 Privacy

In terms of privacy, blockchain technology maintains long-term storage and confidentiality of patient data and records. Such data or records can also be stored as immutable data or records depending on the situation. The types of data and records that can be stored include medical history, treatment-related data, and laboratory information all of which could be historic or current. Access to data can be regulated to allow only certain individuals to have access or modify or add additional data. For example, some participants may only have read the data, whilst others are able to load additional data. This serves well for maintaining and controlling patient privacy, especially where data access by unauthorized participants may have undesirable consequences, for example, HIV status not readily accessed by the nursing staff, etc. (Haleem et al. 2021).

11 Safety

Blockchain technology in the healthcare ecosystem can preserve and exchange health data and records of patients, as well as accurately identify serious errors in the workup and management of patients. This can range from the appropriateness of pharmaceutical prescriptions, doses, to the frequency of medicinal treatment. Some patients may be allergic to certain medical drugs and information on any allergies can be obtained from the clinical history of the patient. This will be flagged by this technology to ensure the safety of patients. In clinical trials, decision-making with regards to the continuation of the trials when adverse reactions are experienced by patients, can be safely done in the early phase of the trial (Haleem et al. 2021).

12 Security

Storage and management of patient health data and records must be stored with versatility, accountability, and authentication for data access. As the health records and data are accessed and used for different purposes, safekeeping, decentralized protection, and confidentiality are paramount to avoid threats of unauthorized access. Thus, there is a great potential for blockchain technology to improve data efficiency for healthcare, as well as assist to avoid the fear of data manipulation and ensure a unique data storage pattern at any desired level of security. Through a distributed ledger network that adds and never deletes or modifies records without a common consensus, security is guaranteed. The high level of data security is provided by a cryptographic hash that connects newly added information, but at the same time blocks records with a data block. The distributed blockchain ledger architecture ensures that data is not processed in any particular centralized hub or venue and is accessible and accountable to all network users (Haleem et al. 2021).

13 Oversight

Using common consensus mechanisms, adequate oversight can be achieved throughout the blockchain network of interconnectivity. Two common consensus mechanisms have been described which includes:

- Proof of Work (PoW) is one of the most common consensus mechanisms. The blockchain users or miners (a blockchain user/node who participates in a competition with others to solve complex cryptographic problems, to validate a particular block) have that block added to the blockchain and receive a reward for doing so.
- Proof-of-Stake (PoS) is the second most common consensus mechanism alternative to PoW. This uses low energy, less processing time, low cost, and low

computational power than PoW. The PoS consensus mechanism uses a randomized method to select the participants who get to create the next new block in the chain. Instead of miners, the validators are present in PoS. The users can stake their tokens to become a validator which means they lock their money for a certain period of time to create a new block. The user who has the biggest stake has the highest chance to become a validator and a chance to create a new block. This process also depends on that one user, considering how long the coins have been staked. By using this consensus mechanism in the network, we can save the energy of other validators because only selected validators can create a block.

Several other consensus mechanisms have been adopted in other industries and include Delegated Proof of Stake, Proof of Authority, and Proof of History.

Several important blockchain concepts and definitions are:

- Ledger—A record of transactions over time while still allowing for tracking and analysis. It documents the transfer of ownership and is ultimately a means for proving ownership.
- Block—A block is a unit of data (or record) that holds a collection of transactions which, together with many other blocks arranged in a specific order, form a blockchain.
- Hash—Digital equivalent of a fingerprint; unique and useful for detecting changes in a file. This is one component that makes the blockchain secure.
- Consensus mechanism—A fault-tolerant process to achieve agreement about a set of data among many users or nodes. Proof of Work is one of the most common consensus mechanisms.
- Miner—A blockchain user/node who participates in a competition with others to solve complex cryptographic problems, to validate a particular block, have that block added to the blockchain, and receive a reward for doing so.
- Blockchain can refer to: (1) a data structure which represents a series of immutable transaction records; (2) an algorithm or a collection of technologies; (3) a distributed, peer-to-peer network of systems; and (4) a system of recording information in a way that makes it difficult or impossible to change, hack, or cheat the system (HHS 2021).

14 Energy Crisis

Blockchain technology presents with it the potential side effects due to the increasing needs in electricity for validation of all blockchain-based transactions or records, which could eventually generate some crypto-damages and give rise to several health issues. The implementation of blockchain technology should be done with caution to ensure a real sustainable, ethical, and consistent healthcare system. The potential environmental and eventually health impact cannot be underestimated with the increasing use of blockchain within the healthcare ecosystem. This lack of consideration becomes somewhat of a paradox as technological solutions are

meant to improve healthcare and must therefore be implemented in a way that does not harm the environment nor human health (Schinckus 2022).

15 Resource Crisis

Although blockchain technologies are useful in improving efficiencies in the healthcare ecosystem, the technology infrastructure comes with a high demand of, amongst others, human capital in terms of technological skills, high tech computer infrastructure as well as bandwidth connectivity. These resources are, in most low-income countries, simply not affordable. Thus, the uptake of this technology is likely to lag in the developing economies as the implementation of these technologies is likely to create a resource crisis in many ways. Careful consideration of several factors is necessary to avoid disruption of these developing economies. A phased-out approach is perhaps the best way to avoid creating a resource crisis, by selectively identifying urbanized areas before a complete rollout is undertaken. One of the strategies of implementation is to consider public health intervention especially disease-specific screening, as this is likely to reduce the global burden of diseases, mortality, morbidity, and economic costs (Bhattacharya et al. 2019).

16 Conclusion

Advancements in the healthcare system such as electronic consultations and videoconferencing assist in real-time diagnosis as well as accessing digital therapeutics. These strategies have become vital as part of the fourth industrial innovation, through advancement in medical science and dependence on digital platforms. The efficient extraction of high-volume information analytics through internetworked machines has grown to a great extent. Society 5.0 involves a human-centered community which seeks to strike a balance between high economic demands and societal liabilities by combining the cyber and physical space. AI seems to be on the high rise and intimidating to healthcare providers. However, it remains a viable option in achieving equity in the provision of high-quality healthcare to society. Most healthcare technologies are already in the domain of genomic analysis, clinical data storage, big data, and analytics to drive precision medicine. However, full-scale extension in the implementation of these strategies in clinical platforms is still lagging, especially in the low socioeconomic setting. Digital technology innovation is gradually impacting the healthcare sector using several technologies, such as blockchain technology, IoT, and IoT-aided robotics. Blockchain is a relatively new technology that can be used to manage large volumes of patient data in a transparent and accountable manner. It operates as a ledger of transactions where all ledger entries are visible to all participants within a communication network.

A large body of knowledge about the layout of medical IoT systems, their components, and the network of communication among the different components exist, albeit with minimal practical implementation experience, more so in the under-resourced communities mainly due to cost barriers. These technologies should be expanded to the low socioeconomic populations as pilot projects with carefully planned financing strategies. They will certainly be tested in their robustness especially when it comes to remote diagnosis and patient monitoring. There is a guarantee of privacy, safety, and security of patient health records through several oversight mechanisms available. However, several countries may need to relook at their healthcare policy and legal framework to bolster the legitimacy of implementation and address the potential environmental health hazards to avoid potential litigations.

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Healthcare Transformation Using Blockchain Technology in the Era of Society 5.0

Thabiso Victor Miya, Benny Mosoane, Georgios Lolas, and Zodwa Dlamini

Abstract Prior to the advancement of technology as we know it today, many hospitals stored maintenance and patient medical records using paper-based record systems. However, this is changing as the digital era is tremendously advancing. The shortcomings of paper-based record systems include data loss, manipulation, and access constraints. In some healthcare facilities, patient medical records are kept only for a certain period of time. Thus, patients are unable to retrieve their medical records after a certain period of time. Although many facilities store patients' medical records in electronic computer systems, these data can still be accessed and manipulated without the knowledge of the patient. However, this downside can be solved by the use of Blockchain technology. Blockchain can be described as a structure that stores records of transactions into blocks in cyberspace. This technology prevents records from being manipulated or corrupted without a common consensus. In essence, Blockchain is a "digital ledger" whereby every transaction is monitored and permitted by the owner using a digital signature, thus making this technology secure and reliable. With regard to data management and maintenance, the introduction of Blockchain technology will make a significant difference to the healthcare ecosystem in Society 5.0. Blockchain technology, although it is not a panacea, provides fertile ground for investment and experimentation as well as

T. V. Miya (✉) · Z. Dlamini
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: thabiso.miya@up.ac.za; zodwa.dlamini@up.ac.za

B. Mosoane
Department of Anatomical Pathology, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: benny.mosoane@NHLS.ac.za

G. Lolas
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa

Department of Medicine, National and Kapodistrian University of Athens, Athens, Greece
e-mail: glolas@med.uoa.gr

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proof-of-concept testing. Blockchain is still in developmental stages and as such, it faces several challenges such as latency, security, privacy, and usability. Thus, legal and technological experts need to collectively revise feasible solutions that are in line with human rights so that this technology can thrive and succeed.

Keywords Blockchain technology · Society 5.0 · Healthcare · Patients · Medical records · Human rights

1 Introduction

1.1 Health Data Challenges in the Healthcare Industry

Proper management and safe retrieval of large personal health data generated during the provision of services and conducting business remain as important challenges for the healthcare industry (Attaran 2022). This generated health data is mostly non-standardized across systems, inaccessible, and difficult to comprehend, utilize, and share. Furthermore, this data is pulled from diverse sources and stored in centralized information technology (IT) systems, thus making it difficult to manage and share (Attaran 2022). Requesting, compiling, sending, and receiving patient data requires many resources and is also time-consuming (Clim et al. 2019). Secure retrieval and efficient management of this data allow healthcare systems to generate a holistic view of patients, enhance communication, improve health results, while also improving care quality and treatments (Bresnick 2016). Other significant challenges facing the healthcare industry are the lack of comprehensive and secure population health data, interoperability, and inaccessibility of medical records. Lastly, the security of the generated healthcare data is also an important issue in this industry. For instance, numerous healthcare organizations store critical health data in a centralized IT infrastructure which is vulnerable to hacking, ransomware, and other cyberattacks (Bresnick 2016).

There has recently been a move towards patient-driven interoperability, whereby the exchange and use of healthcare data are patient-driven (Kamble et al. 2018). However, the development of infrastructure, computer programs, and tactical methods that can bring data reliably and securely is still in its infancy stage (Gordon and Catalini 2018). Healthcare data systems that are currently in use have numerous challenges which include data accuracy, integrity, quality, and patients' privacy. Thus, innovative technology that can help resolve these problems is urgently needed. Blockchain technology is emerging as one of the promising solutions to the current challenges facing the healthcare industry (Pirtle and Ehrenfeld 2018).

2 Blockchain Technology in 5.0 Society

2.1 What Is Blockchain Technology?

Blockchain technology was first introduced in 2008 through the Bitcoin cryptocurrency technology endoskeleton by Satoshi Nakamoto. This technology is based on technologies and concepts from 1991 by Stuart Haber and W. Scott Stornetta (1990). Post inception, Blockchain has been applied in numerous industries including healthcare, finance, and business (Kassab et al. 2019). Blockchain technology can be described as a decentralized public digital ledger that records transactions across different computers (Haleem et al. 2021), essentially a living list of linked digital records. Blockchain is verified and linked to the previous "block," thus forming a long chain as shown in Fig. 1. This means that the data involved cannot be retrospectively changed without changing the following blocks (Haleem et al. 2021). In Blockchain, transactions are registered and checked publicly, thus providing a certain level of accountability to the participants (Kumar et al. 2018). Furthermore, Blockchain data is maintained on networks instead of a central

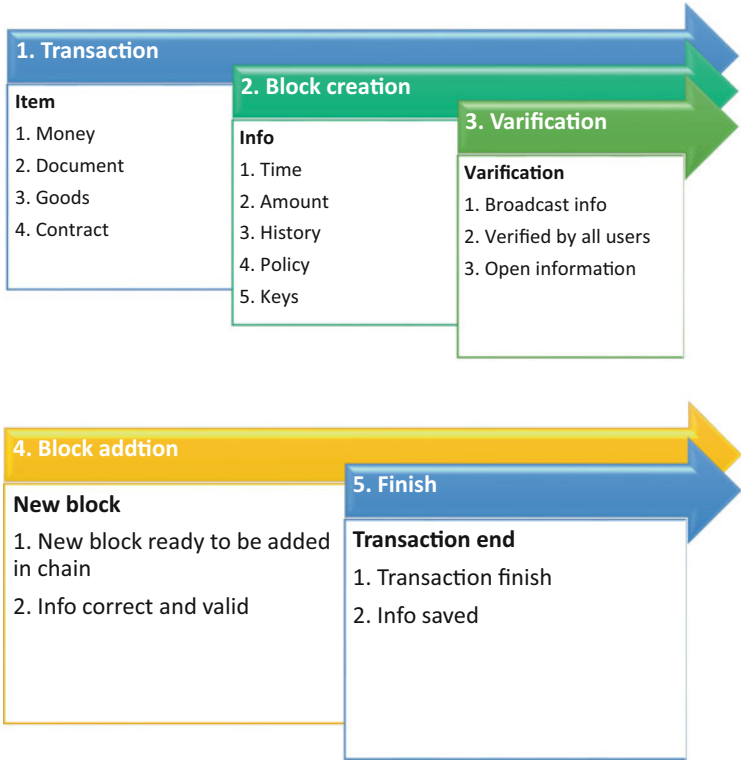

Fig. 1 Basic steps on how transactions are initiated, verified, and executed using Blockchain technology. Adapted from Onik et al. (2019)

database. This is important because it improves stability and prevents the data from being hacked (Moona et al. 2019).

3 Blockchain Structure

A block in Blockchain technology comprises information, a hash of the current block, a hash of the previous block, and a timestamp (Monrat et al. 2019; Shahnaz et al. 2019) as shown in Fig. 2. A hash in Blockchain can be described as an arbitrary number that miners usually alter to receive a certain hash value. The received value is then used to significantly decrease the exertion required to check transactions in a block (Iansiti and Lakhani 2017). Transactions in Blockchain can be described as small units of tasks stored in public blocks. These transactions are verified by the system participants and are, thus, tamperproof. Furthermore, participants in this system are able to replicate, host, and maintain the Blockchain. This enables the Blockchain to be protected from unauthorized access and hackers (Iansiti and Lakhani 2017).

4 Blockchain Categories

There are currently four Blockchain categories, namely private, public, consortium, and hybrid Blockchains (Ray et al. 2020). Private Blockchains are for single enterprise solutions, and they are used for tracking data exchange between

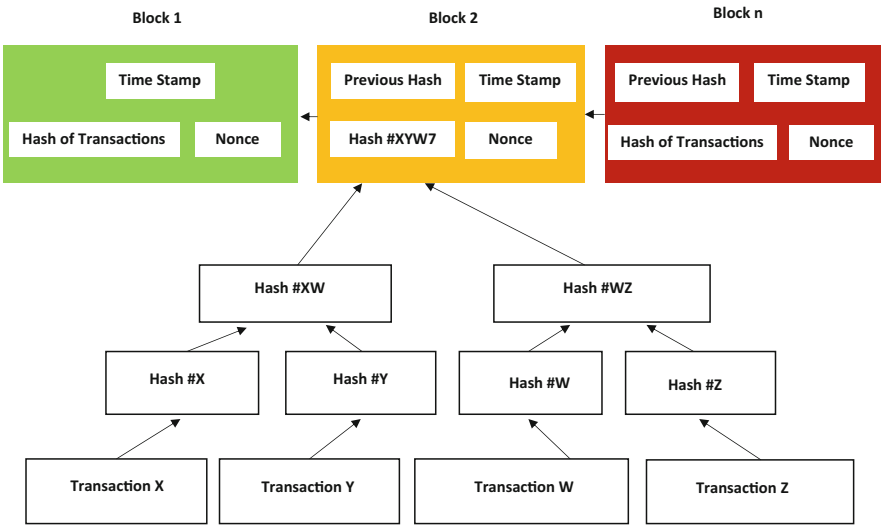

Fig. 2 Components of Blockchain technology. Adapted from Monrat et al. (2019)

individuals or various departments. Furthermore, each participant in private Blockchain needs consent to join in and to be considered as a known member. Conversely, public Blockchain is a decentralized network where each member has access to the Blockchain data and could also participate in the consensus process (Wood 2014). Examples of public Blockchain include Ethereum and Bitcoin (Wood 2014). Consortium Blockchain on the other hand is a permissioned network that is accessible to a certain privileged group. This type of Blockchain is utilized as a synchronized distributed database that tracks data exchange between participants and is both auditable and dependable (Wood 2014). Lastly, hybrid Blockchains are a combination of public and private Blockchain benefits. In this case, the public Blockchain is used to make a completely accessible ledger, while the private Blockchain runs in the background to control changes to the ledger (Wood 2014).

5 Applications of Blockchain in Society 5.0 Healthcare

5.1 Healthcare Record-Keeping Using Blockchain

Blockchain technology can be used as a record-keeping solution in healthcare (Attaran 2022). In particular, Blockchain is a useful mechanism for recording steady and continuous growth of transactions (Cheng et al. 2018). Therefore, this technology can be used to secure personal information, healthcare records, important medical information, as well as DNA data. Blockchain can be used in healthcare to securely store patients' medical records whereby doctors and patients can remotely access those records (Finasko 2017). Furthermore, Blockchain allows for a heterogenous protection system and movability across different phases. Therefore, this enables healthcare providers to make an integrated health records system that is centered around the patients. Thus, patients have full control of their data (Bresnick 2016). This Blockchain-driven integrated health system can help to curb fraud and also allows for reconciliation of records and activities. Furthermore, this integrated health system enables patients to remotely access, manage, and securely share their medical information with healthcare professionals anywhere around the world. It also enables patients to track their medical backgrounds like vaccines, chronic diseases, and allergies (Bresnick 2016). Li et al. proposed a medical data Blockchain-powered preservation system that enables a reliable storage solution to ensure the verifiability and primitiveness of medical data and simultaneously ensure users' privacy (Li et al. 2018). The proposed system also enables users to permanently preserve critical data. Moreover, if tampering of the data is suspected, the originality of the preserved data can be verified (Li et al. 2018). In another study, Zhang and Lin proposed a Blockchain-powered personal health information system which is secure and ensures the privacy of the users (Zhang and Lin 2018). This system is mainly for diagnosis improvements in the e-Health systems (Zhang and Lin 2018). Since Blockchain technology is immutable, it can help to improve the

accuracy of diagnosis. Privacy and security assurance are important issues in the proposed system (Zhang and Lin 2018).

5.2 Healthcare Data Sharing Using Blockchain

Inadequate interoperability of data leads to the complexity of identifying patients (Attaran 2022). It also leads to information blockage whereby healthcare providers constrain the exchange of electronic health information or patient data (Attaran 2022). Blockchain can make it easier to share healthcare data across system users and also end the problem of interoperability in the Society 5.0 healthcare system (Paranjape et al. 2019). Patients are identified using a unique identifier called hash ID in the permissioned healthcare Blockchain (Paranjape et al. 2019). This hash ID ensures the security and privacy of the system user and, thus, puts the patient at the helm of the ecosystem. Furthermore, patients oversee the sharing of the decryption key associated with their own blocks of data with their healthcare provider. Therefore, Blockchain will enable patients and healthcare providers to receive or access accurate and updated comprehensive medical information (Paranjape et al. 2019).

5.3 Healthcare Data Security and Identity Management Using Blockchain

Medical data security and patient privacy are pivotal issues in the healthcare industry (Attaran 2022). Therefore, there is a need for innovative solutions that can effectively resolve these issues. As previously mentioned, healthcare providers often store medical information in old IT infrastructures that are susceptible to hacking (Bresnick 2016). Loss of this medical information often leads to the loss of a lot of money (Bresnick 2016). Thus, healthcare providers have begun investing in novel technologies such as advanced data encryption and artificial intelligence (AI) to prevent cyberattacks on medical data (Duffy 2018). Blockchain technology can provide identity management and health data security solutions to the healthcare industry (Bouras et al. 2020). This technology can protect medical data and curb cyberattacks. Blockchain protects confidential data through encryption, thus rendering it immutable and indecipherable. As previously mentioned, Blockchain uses hash ID which is a unique number that is only known by the user. Thus, healthcare providers can access patient medical information only with clear access to the Blockchain record (Yaeger et al. 2019). Therefore, this puts the patients at the center of the Blockchain network. Interoperation of medical data between healthcare providers increases diagnostic accuracy and probability of successful treatments. It also reduces the healthcare cost, which is beneficial to the patients (Leon 2018). Lastly, Blockchain allows patients to keep their medical data secure while also allowing

them to share it with their preferred healthcare providers. Thus, it provides complete ownership of the medical data and guarantees authenticity against potential cyberattacks (Leon 2018).

5.4 Monitoring of Patients Remotely

Blockchain technology plays a key role in storing, sharing, and recovering medical data, remotely (Ben Fekih and Lahami 2020). Thus, Blockchain can potentially be used to monitor patients remotely. To do this, medical data are collected using tools such as mobile devices, the Internet of Things (IoT), as well as body area sensors (Ben Fekih and Lahami 2020). For example, Ichikawa et al. applied Blockchain to their mobile health app which facilitates cognitive behavioral therapy for insomnia (CBTi) through smartphones (Ichikawa et al. 2017). CBTi is the most effective method for treating insomnia (Jacobs et al. 2004). However, it is expensive, labor-intensive, and it is based in medical facilities (Ichikawa et al. 2017). Due to its high cost and lack of trained clinicians to perform this treatment, many patients do not have access to the CBTi method (Ichikawa et al. 2017). To overcome this problem, Blockchain technology has enabled developers to deliver CBTi through the internet. This is done by collecting patients' medical data from their smartphones. The data then gets stored in the network server where feedback on the stored data can also be transferred back to the patients (Ichikawa et al. 2017). Griggs et al. also created a system that utilizes Blockchain smart contracts feature to analyze patients' medical data collected by Wireless Body Area Networks (WBANs) (Griggs et al. 2018). These WBANs are created through different implanted or wearable patient medical devices that measure and record vital indicators, in real time (Griggs et al. 2018). These vital indicators include glucose levels and heart rates. Other medical devices are actuators that can automatically provide treatments, based on measurements recorded by the sensors (Griggs et al. 2018). In 2016, it was reported that approximately 7.1 million patients worldwide use remote monitoring to manage their health (Mack 2017).

5.5 Healthcare Financial Records Management Using Blockchain

Fraud and billing errors are critical issues in healthcare billing (Attaran 2022). Thus, modern innovative technologies are required to solve these problems. Blockchain can solve these issues by decentralizing billing records which can process payments while also preventing fraudulent transactions (Giancaspro 2017). Blockchain has a feature called smart contracts. These smart contracts are self-activating and their terms of agreement between the buyer and the seller are written directly into lines of code. Furthermore, these contracts are distributed across a decentralized network of

Blockchain (Giancaspro 2017). Smart contracts are located in a specific area in the Blockchain network and have a specialized address. These contracts are invoked by depositing cryptocurrency to a unique address. This is followed by a verification process in the consensus protocol (Luu et al. 2016). Importantly, these smart contracts do not require a third party or updated security and traceability (Li et al. 2018). Smart contracts can help eliminate mistrust between the payers and healthcare providers by permitting a more capable healthcare payment model. In addition, penalties and reimbursements can be executed through unique health parameters within the medical record in the Blockchain network. This in turn helps eliminate human errors from applying value-based payments (Yaeger et al. 2019). Smart contracts Blockchain can alert patients' insurance companies about billing and claim settlements. This in turn increases fraud detection effectiveness while also decreasing administrative costs and pricing (Lorenz 2016). Blockchain can help insurance companies improve claims processing by acquiring inputs from various sources without compromising the information (Lorenz 2016). Lastly, Blockchain technology can provide reliable medical insurance data storage solutions. These solutions can ensure the verifiability and primitiveness of the data while also ensuring high credibility to network users (Zhou et al. 2018).

6 Application of Blockchain in Society 5.0 Pharmaceuticals

6.1 Drug Tracing Using Blockchain

Counterfeit drugs are a major issue faced by the healthcare industry (Attaran 2022). In developing countries, over 15% of drugs sold are counterfeit (Singh 2019). It is reported that pharmaceutical companies lose approximately $200 billion each year due to counterfeit drugs (Singh 2019). The problem of counterfeit drugs can be solved using Blockchain technology through the provision of drug traceability, security, and visibility. Blockchain utilizes features such as point-by-point and authenticity tracking to prevent drug counterfeiting while also ensuring the genuineness of the drugs produced by specific pharmaceuticals. Furthermore, this technology allows users to authenticate the drugs before they purchase them (Haq and Esuka 2018). Besides tracking the drugs from the manufacturer to the patient, Blockchain can also record drug effectivity on the patient after use (Haq and Esuka 2018). This data is subsequently stored for future statistical purposes (Haq and Esuka 2018).

6.2 Clinical Trials Using Blockchain

Clinical trials commonly generate a lot of data and are expensive to conduct as they take years to complete and often involve fraud (Attaran 2022). Therefore, it is

important to develop a transparent solution that can ensure that anyone can review clinical reports. The solution also needs to secure and protect the authenticity of the trial results to prevent mutability (Attaran 2022). Blockchain technology can be used to facilitate clinical trials through the provision of document verification and data integrity (Singh 2019). Lastly, this technology ensures that the generated data does not get modified without the consent access (Singh 2019).

6.3 Public Health Management Using Blockchain

The recent COVID-19 outbreak has shone a light on the importance of population health data (Nash 2015). This data is a critical tool used to promote good health practices and also to treat various health problems (Nash 2015). It is difficult to carry out analytical solutions needed to map COVID-19 behavior and impact without a comprehensive population health data system (Postelnicu 2020). Blockchain can provide instant information regarding potential outbreaks to relevant health institutions (Postelnicu 2020). Blockchain facilitates the collaboration of various healthcare providers involved in healthcare initiatives using distributed ledger technology. This is important because it allows healthcare providers to gain insights into critical healthcare trends (Postelnicu 2020). Overdosing on medical compounds such as opioids is another critical issue facing the healthcare industry (IBM 2018). Blockchain can be used to provide the sole source of comprehensive information regarding the purchase of any controlled substance in all dispensers. The seller can use this information to determine the appropriate number of opioids a dispenser can order, for example. Lastly, this information can also be used to raise awareness about alcohol and drug abuse (IBM 2018).

6.4 Healthcare Supply Chain Using Blockchain

Blockchain technology is used by pharmaceutical companies to track raw materials, components, or compounds in the supply chain (Singh 2019). Pharmaceutical researchers can also use Blockchain to obtain health- and medical-related supply chain data. The authenticity and origin of medical supplies can be identified using Blockchain, thus improving the security of the supply chain (Bocek et al. 2017; Shanley 2017; Vecchione 2017). Lastly, Blockchain technology can be applied across different sectors in the healthcare industry, including vaccine transportation, perishable foods, medical supplies, and clinical trials (Rijmenam 2018).

7 The United Nations Sustainable Development Goals Versus Blockchain Technology

In 2015, the United Nations (UN) Member States created 17 Sustainable Development Goals (SDGs) (United Nations 2015). These UN SDGs are aimed at ending poverty and other major challenges facing humanity and the planet in alignment with strategies to improve education and health (Hughes et al. 2019). Furthermore, the goals are also aimed at reducing inequality, stimulating economic growth, preserving oceans and forests, while also tackling climate change (Hughes et al. 2019). Thus, if these goals can be systematically addressed, the world will be a better place to live in (de Villiers et al. 2021). Digitalization has been widely accepted as an important part of attaining these UN SDGs. In fact, digital technologies are seen as both enablers and obstacles to sustainability, equality, as well as social inclusion (Zheng and Walsham 2008). For the purposes of this chapter in relation to healthcare in Society 5.0, Table 1 discusses how the UN's "Good health and well-being" SDG (United Nations 2015) can be integrated into Blockchain technology.

The integration of Blockchain into the UN SDGs emphasizes the many benefits that can be achieved by the widespread adoption of this innovative technology (Hughes et al. 2019). However, this requires international partnership and substantial investment to effect security, standards, and governance (Thiruchelvam et al. 2018). Lastly, migration toward Blockchain technology should be spearheaded by developing economies as this will reduce adoption barriers (Thiruchelvam et al. 2018).

8 Blockchain Challenges and Limitations

Different researchers have identified a number of challenges and limitations associated with Blockchain technology. According to Khan et al. (2020), Blockchain technology is error-prone and possesses some architectural issues. Below is a summary of the seven main technical issues associated with Blockchain technology identified by Swan (2015).

Table 1 The "Good health and well-being" UN SDG vs. Blockchain technology. Adapted from Hughes et al. (2019)

UN SDG	Blockchain technology
Good health and well-being	Blockchain technology could facilitate change in relation to sustainability that can impact health, medication, and humanitarian aid supply and distribution. Developing countries still face challenges in relation to the integrity of basic food products and medical supplies. Furthermore, logistical management and enforcement across geographical diversity and linguistic barriers are also major challenges in developing counties. Blockchain technology can help solve these challenges by enabling parties to ship and monitor the lifecycle of health products by using its transactional integrity and immutability features. This will in turn improve the health and well-being of the citizens.

8.1 Low Throughput

Throughput is one of the seven issues associated with Blockchain as identified by Swan (2015). For example, a Blockchain-powered Bitcoin network can process 3 to 20 transactions per second (Xu 2016). According to Khan et al. (2020), the maximum number of transactions in the Bitcoin network does not exceed five. Conversely, Cong and He (2019) reported 47,000 transactions per minute in the visa.com network after conducting several network stress tests. Therefore, if e-commerce companies process transactions using Blockchain, then they will fail (Khan et al. 2020). This is due to transactional delays and will subsequently increase network communication costs (Khan et al. 2020). Min et al. (2016) proposed a permission Blockchain network to increase protocol performance. This is achieved by partitioning the main network and computing power into sub-committees, also known as chunks (Min et al. 2016). The purpose of this method was to increase throughput and lower latency while retaining the Bitcoin network security (Min et al. 2016).

8.2 High Latency

High latency is an important issue in the Blockchain-powered Bitcoin network (Khan et al. 2020). Bitcoin network requires 10 minutes to process one transaction and requires even more time to prevent double-spending issues (Khan et al. 2020). Although Bitcoin has security measures in place to reject double-spending, it eventually exacerbates latency further. Eyal et al. (2016) proposed a novel Bitcoin-NG protocol aimed at enhancing throughput while also lowering the latency. The authors claim that latency will only be limited to the propagation delay of the network. They managed to achieve this by decoupling the Bitcoin network into two planes and transaction serialization. Eyal et al. (2016) reported a lower latency in Bitcoin-NG compared to the original Bitcoin. Croman et al. (2016) also proposed a suggestion to increase throughput while lowering the latency. The suggestion is that the block size should not go beyond 4 megabytes (MB), and that the block interval should not be less than 12 seconds. This will increase throughput to about 27 transactions per second (Croman et al. 2016).

8.3 Security and Privacy Issues

Blockchain technology is best known for its innovative security features. Bitcoin cryptocurrency is a notable innovation by Blockchain, and it is said to be more valuable than real gold (Khan et al. 2020). Therefore, this makes Bitcoin a valuable target for hackers. The first security risk in the Bitcoin network is identity theft

(Xu 2016). Identity on this network is a combination of private and public keys. However, private keys determine the overall security in the network. Furthermore, storage of these private keys requires wallets. Various wallets are available in the market, for example, paper, web, desktop, hardware, and mobile wallets (Khan et al. 2020). Paper and hardware wallets are said to be more secure, but they are not enough to prevent private key theft (Khan et al. 2020). Ethereum cryptocurrency is another popular Blockchain implementation (Wood 2014). In the case of Ethereum, private keys are secured by a wallet provider company. The company provides password protection solutions for private keys. Thus, if the keys get stolen, the funds cannot be accessed and stolen (Sohaib et al. 2019). Two-factor security is another solution that can be used to prevent the theft of private keys (Goldfeder et al. 2014). In this instance, private keys can be shared between two devices such as a mobile phone and a computer. A confirmation is forwarded to the owner's mobile phone whenever a transaction is executed from a different phone or computer. A transaction will be signed and ready for successful execution, only after the owner's confirmation from the phone (Goldfeder et al. 2014). Eclipse attacks are other examples identified by Heilman et al. (2015). Eclipse attacks involve the exploitation of numerous IP addresses to monopolize connections through a node of the victim. Hackers can then attack consensus systems, selfish mining, or double-spending (Heilman et al. 2015). This can be prevented by choosing specific outgoing connections or by disabling incoming connections (Heilman et al. 2015).

With regard to privacy, some aspects of Blockchain are pseudonymous. This means that user identity is hidden behind a public key while other aspects of transcriptions are shared publicly (Sweeney 2000). This is particularly problematic with regard to health data. This is because people can be identified using basic demographic information (Sweeney 2000). Therefore, if an individual's identity is matched to their public key, all the transactions associated with that particular key are then known to be associated with an individual (The European Parliament and the Council of the European Union 2016). This problem is not only limited to public Blockchain, but it is also catastrophic to the private Blockchain. This is because an individual may not want all users to gain access to the same data or they may want to revoke data authorization sometime later (The European Parliament and the Council of the European Union 2016). However, both of these options are not possible if their identity has been linked to their public key. Thus, Blockchain innovations that provide selective disclosure of private data will be needed in the healthcare sector (The European Parliament and the Council of the European Union 2016).

8.4 Fork Issues

In Blockchain, forking happens when alterations need to be made (Khan et al. 2020). Two types of forks exist in Blockchain, and those are hard and soft forks. Nodes adopt any change that occurs within the network. When nodes are upgraded, they continue to validate blocks. Soft fork is when non-upgraded nodes continue to

validate blocks. Conversely, with hard forks non-upgraded nodes do not continue to validate blocks. In hard fork, Blockchain network is permanently separated into two chains. Additionally, non-upgraded nodes remain on the existing Blockchain while upgraded nodes transition toward a novel Blockchain. In contrast, a soft fork remains temporary until the software upgrade is complete. After the upgrade, nodes continue to work on a common chain and the Blockchain does not split (Khan et al. 2020).

8.5 Wasting of Resources and Energy

Proof of work (PoW) is crucial in the Bitcoin network because it provides security against cyberattacks. However, a bundle of computing resources gets wasted, including electricity bills and hardware costs (Khan et al. 2020). Approximately 15 million dollars' worth of energy is wasted every day (Koteska et al. 2017; Yli-Huumo et al. 2016; Reynolds et al. 2017). This energy wastage does not align with UN SDG number seven which is "affordable and clean energy." Thus, innovative solutions need to be implemented to address this issue.

8.6 Usability

According to Swan (2015), the Bitcoin application programming interface (API) is way less user-friendly compared to the current standards of other new user-friendly APIs such as the commonly used REST API. A lack of expertise may impede the incorporation and utilization of Blockchain technology in the healthcare industry (Haleem et al. 2021). Thus, innovative solutions need to be implemented to address these issues.

8.7 Size and Bandwidth Limitation

The constantly increasing size of the Blockchain in the Bitcoin network is an important issue. In February 2016, the Bitcoin database size was recorded at 500000 MB (Yli-Huumo et al. 2016; Koteska et al. 2017). According to Visa, the size will approximately reach 214 PB each year if the network continues to grow (Khan et al. 2020). According to Kim et al. (2017), the size will grow each year due to the addition of new blocks of data to existing data. As the number of nodes increases, data will also increase. Furthermore, this data is broadcast to all nodes in the network, subsequently leading to increased costs. Thus, the easiest way of managing the data size is to erase old blocks that are not currently needed (Kim et al. 2017).

8.8 Human Rights Issues

Blockchain technology is a gift and a threat when it comes to the issue of human rights (Naves et al. 2019). The right to privacy, to remedy, and not to be discriminated against are particularly at risk. To ensure that the positive impact of this technology outweighs the negative, human rights must be considered at an early stage of Blockchain development. The right to privacy is particularly vulnerable in this instance because data cannot be altered or deleted once it has been submitted to a Blockchain platform. This means that errors made with regard to personal data cannot be reversed (Naves et al. 2019). Although the right to privacy needs informed consent from the participants for the usage of their personal information, there is a risk that Blockchain platforms are technically complex, and so participants will find it difficult to understand. Permissioned or regulated permissionless Blockchains operate by certain rules, therefore they can be easily regulated and forced to comply with current legal systems. Thus, legal and technological experts need to come together and devise solutions that are both technically feasible and prioritize human rights (Naves et al. 2019).

9 Conclusion

Despite being in its early developmental stages, Blockchain technology has numerous innovative applications in the healthcare industry. Due to its inherent data encryption and decentralization capabilities, Blockchain can enhance the security of medical records, cost reduction, supply chain, improve access control, improve interoperability, improve data integrity, strengthen trust in clinical trials, and also prevent counterfeit medical supplies (Fig. 3). Other beneficial applications of Blockchain technology include medicines tracing (drug discovery, development, and distribution process), smart contracts, and healthcare insurance mediation.

Blockchain applications in healthcare will continue to broaden in the future. However, Blockchain challenges such as throughput, latency, security, privacy, usability, size, and bandwidth problems still need to be addressed. Various organizations and individual researchers have already proposed innovative solutions to address the challenges and limitations of this technology. Nevertheless, this technology will be of great benefit to Society 5.0 once it is completely adopted into the healthcare system in the near future.

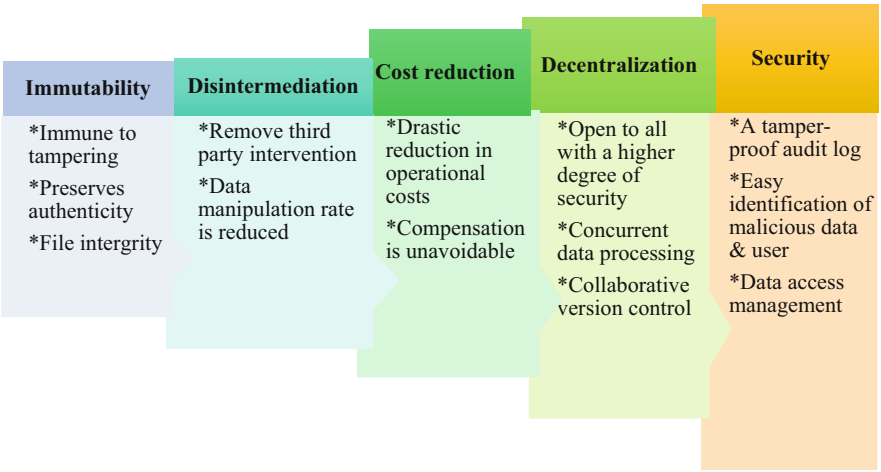

Fig. 3 Overview of Blockchain advantages on healthcare. Adapted from Onik et al. (2019)

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Society 5.0 Healthcare: Ethics, Legal Rights, Human Rights, Safety and Security

Kim R. M. Blenman, Rodney Hull, Charles Maimela, Thulo Molefi, Richard Khanyile, and Zodwa Dlamini

Abstract The smart digital technologies required to make Society 5.0 and healthcare possible in our current society are new and in many cases operate in ethical gray areas as they can be misused or used incorrectly, violating human rights and values in many countries and especially in those with low resources. Some of the issues include violation of privacy, ignoring patient autonomy, bias, targeting vulnerable groups of people, cost, availability, accuracy, transparency, trust, employment, and safety-related issues. The gathering of patient data is one of the major concerns surrounding these technologies. This is due to the invasion of privacy associated with the collection of this data and the ability of this data to be used without the individual's permission in some countries. The gathering of information not relevant to healthcare may constitute an invasion of privacy. The

K. R. M. Blenman (✉)
Department of Computer Science, School of Engineering and Applied Science, Yale University, New Haven, CT, USA

Department of Internal Medicine, Section of Medical Oncology, School of Medicine, Yale Cancer Center, Yale University, New Haven, CT, USA
e-mail: kim.blenman@yale.edu

R. Hull · Z. Dlamini
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: rodney.hull@up.ac.za; zodwa.dlamini@up.ac.za

C. Maimela
Faculty of Law, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: charles.maimela@up.ac.za

T. Molefi · R. Khanyile
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa

Department of Medical Oncology, Faculty of Health Sciences, Steve Biko Academic Hospital, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: thulo.molefi@up.ac.za; richard.khanyile@up.ac.za

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ease of analysis with which artificial intelligence (AI) can identify patterns within patient data may lead to overdiagnosis and overtreatment. There are fears that as these technologies advance there may be a loss of autonomy due to a lack of transparency of exactly how a specific AI works, what it is actually producing, how that product is confirmed, and how that product is being interpreted to make a healthcare decision. As such regulations are currently being put in place in many countries to ensure that a human being plays a vital role in the decision-making process. Biased data and outdated datasets could lead to AI adopting age, gender, ancestry/ethnicity, cultural, socioeconomic, or other biases against specific groups, usually those who were historically disadvantaged or suppressed. The diverse means by which this information is gathered is also a cause for concern. Many of the wearable, mobile devices currently offered are not pure medical devices but are entertainment or fashion devices with the built-in ability to record an individual's biometrics and vital signs. As such, the reliability of these devices is unclear. Even pure medical devices require maintenance, calibration, and upgrades, all of which could influence the quality of data collection. Despite these challenges, the promise held by these technologies for advancing healthcare is too great to ignore, and as such there are a variety of solutions to these problems which are being put in place or have been proposed. These technologies require the creation of new laws and a reassessment of legal rights surrounding privacy and liability and the creation of legal frameworks to ensure the safety of these technologies as well as reexamining the laws surrounding consent and intellectual property. This chapter, although not intended to be exhaustive, will discuss some problems and ethical issues surrounding these new technologies and some potential solutions. We hope that this will start the continued discussion on how to incorporate these new technologies legally, ethically, safely, and securely in keeping with the highest standards of human rights.

Keywords Privacy · Transparency · Liability · Bias · Data collection · Accuracy

1 Introduction

New technologies are the cornerstone of the new smart society proposed by Society 5.0. The adoption of these new technologies holds much promise in optimizing and improving healthcare, leading to a healthier population. However, many challenges, both ethical and practical, face the adoption and application of these new technologies. The ethical concerns, in particular, are wide and varied and are present in clinical, research, public health, and personalized medicine applications. These new technologies present many ethical problems around data usage, data access, trust in the new technologies, the technologies negatively influencing patient–doctor communication, the efficiency of health services delivered by these technologies, safety, and liability issues. Apart from these issues, there is a problem surrounding the cost of these new technologies and whether poorer countries will have access to or be able to implement these technologies safely and ethically.

A PubMed (United States National Institute of Health National Library of Medicine) search revealed that there are very limited publications on ethics and the promising technologies for the Society 5.0-based healthcare system in the MEDLINE database of references from life science and biomedical topics. Most publications are concerned with ethics and artificial intelligence, big data, bioinformatics, and the digitization of healthcare (Fig. 1a). Apart from peaks in papers, especially those concerning ethics and bioinformatics, the trend is a modest increasing number of papers that have remained flat from 2017 to 2022. It is hoped that these papers will drastically increase especially as these topics become more important as a concerted effort is made to move to a Society 5.0-based healthcare system. The newer technologies represented in Fig. 1b have significantly fewer publications. It is apparent that before Society 5.0 can truly be implemented, ethical and other human-centric (e.g., legal rights, human rights, safety, and security) questions surrounding the use of the technologies required for its implementation need to be addressed.

2 Human Values and Ethics

All new medical technologies or devices must be built around a core of human values. Alongside this, there must be accountability for the use of these technologies. The aim of Society 5.0 and healthcare in this society is human-centered. As such, the implementation of these new technologies requires not only input from medical science but also from the social sciences and humanities as well as from lawmakers and economists just to name a few (Dignum 2019). When designing a device or software to be used in healthcare 5.0 the following tenets should be remembered:

1. Ethics in design—Involves considering various ethical issues during the design of the device or software. For example, this includes avoiding age, gender, ancestry/ethnicity, cultural, socioeconomic, or other bias in the implementation of the technology.
2. Ethics in application—This highlights the ethical behavior of those individuals involved in the design and use of these tools and devices. For artificial intelligence (AI), this would also cover the curation of the AI learning and giving it data sets representative of the population it will be working with.
3. Ethics for diverse stakeholders—This involves making sure that these tools and devices are regulated by rules and laws that protect all stakeholders. This will also ensure that the technology can be effectively and safely applied to healthcare systems (Dignum 2019).

One of the most important factors in the development of Society 5.0 is that this smart society will aid in the world achieving the sustainable development goals (SDGs) put forth by the United Nations (UN). The official purpose of the UN is to "maintain international peace and security, develop friendly relations among nations, achieve international cooperation, and be a center for harmonizing the

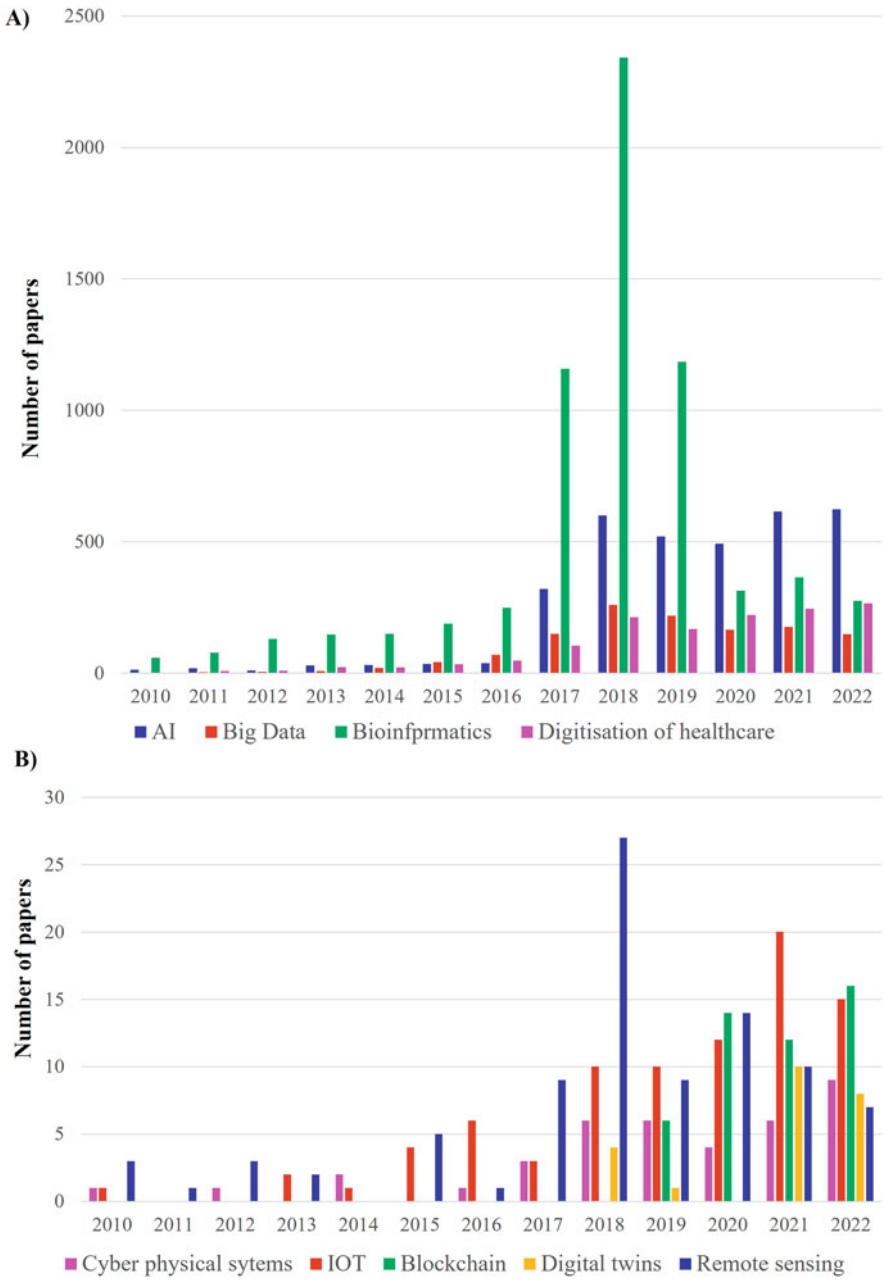

Fig. 1 Papers with ethics and various digital technologies in their titles or abstracts from PubMed. (**a**) The results with the highest number of papers included ethics and artificial intelligence, ethics and big data, ethics and bioinformatics, and ethics and the digitization of healthcare. (**b**) The search terms with a smaller number of papers included ethics and cyber-physical systems, ethics and the Internet of Things, ethics and blockchain, ethics and digital twins, and ethics and remote sensing

actions of nations." Since it was founded in 1945 it has been involved in the worldwide promotion and protection of health (Brown et al. 2006). However, the new digital technologies required for this smart society have also led the UN to develop ethical frameworks and regulations regarding the use of these new technologies. In terms of artificial intelligence, one of the most important and prevalent of these new technologies, the United Nations spent two years preparing a report outlining the ethical use of AI. The purpose of this report was to help ensure that the report and the six principles it covers can help serve as a foundation for the ethical implementation of this technology. The six principles outlined in the report are:

Protecting autonomy—The first UN guideline states that the final say on all health decisions should be made by a human being. Ideally, that human being should be the patient in consultation with their doctor or health professional. Doctors must be able to, if they feel it is necessary, reject the conclusion and decision of an AI system. Additionally, patient data should be protected and not be accessed without patient permission (WHO Guidance 2021).

Promoting human safety and well-being—AI and any health-related technology should be constantly monitored to make sure they are working correctly (WHO Guidance 2021).

Ensuring transparency—Information regarding the design of AI systems must be freely available and their operation must be transparent enough so that they avoid becoming black boxes (WHO Guidance 2021).

Fostering accountability—There must be a mechanism to hold someone accountable if a technology leads to patient harm, through incorrect use, AI making a mistake through errors in learning (poor data or algorithm development), or a failure in the technology itself. This means there must be a method for determining who is at fault and how they should be penalized (WHO Guidance 2021).

Ensuring equity—Making AI and other medical technologies easily accessible to the whole world (low-, middle-, and high-resource countries). This can be achieved by making sure it is available in multiple languages and is trained using diverse sets of data to avoid overfitting. Finally, it must be ensured that no ancestry/ethnicity or other (age, gender, cultural, socioeconomic, etc.,) biases are present in any data analysis or collection technologies (WHO Guidance 2021).

Promoting tools that are responsive and sustainable—The maintenance and updating of devices and software should not be so expensive or difficult that it cannot be done in healthcare systems with limited resources. There must be mechanisms in place to remove ineffective devices or software, and regular updates must be available (WHO Guidance 2021) (Fig. 2).

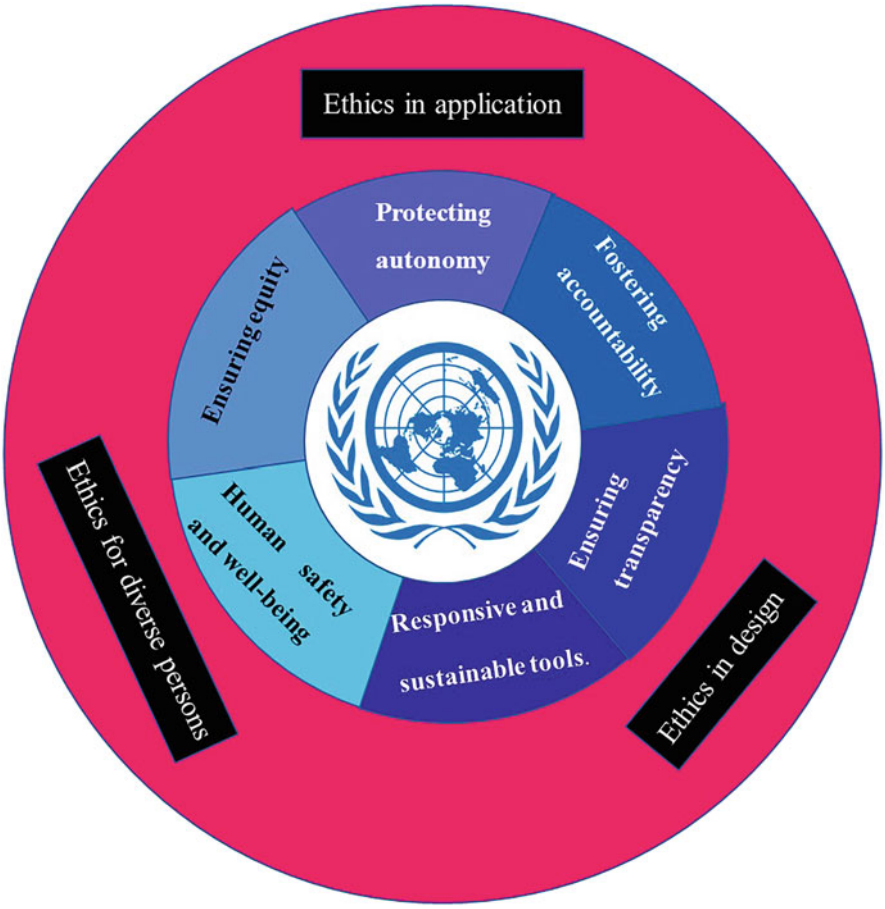

Fig. 2 Principles guiding the ethical application of digital technologies and their relationship with the UN guidelines on AI. The general guidelines when it comes to creating an ethical piece of technology for healthcare include maintaining ethical considerations during the application and design of the technology, as well as ensuring that it benefits or does no harm to any of the stakeholders

3 Specific Ethical Problems Surrounding Healthcare Technologies in Healthcare 5.0

3.1 Sociodemographic Biases and Protecting Vulnerable Populations

Ethical issues around sociodemographic biases include concerns over discrimination based on ethnicity, age, gender, socioeconomic status, disabilities, mental health, and even culture. Artificial intelligence systems can either consciously or

unconsciously reflect the biases of those who created it or those that taught it leading it to discriminate against vulnerable groups or individuals. For instance, in cultural bias there may be issues such as the technologies or the implementation of the technologies ignoring cultural differences and applying a one solution fits all approach. An example of this is facial recognition software, which is less able to consistently recognize African faces compared to European faces, most likely because it was trained on Asian and European faces. This can also serve as an example of problems with data or training data quality (Kaur et al. 2020). Two types of bias exist, data bias and societal bias. Data bias occurs when a dataset is used in machine learning that is biased toward certain individuals. This can happen easily with the use of artificial intelligence and machine learning (ML) by using inappropriate or incomplete datasets as training datasets. The choice of the dataset must take ethical issues into consideration. It must also evaluate human dignity. Older datasets may include terms or classifications now known to be meaningless or even immoral, such as data with racist or sexist classifications or terms. This becomes especially dangerous if this is applied to new data collected in a biased way. This threat becomes even greater if it is the intention of the user to purposefully stigmatize a group of individuals based on certain traits and use the AI to justify their actions or plan/implement these actions (Ghassemi and Mohamed 2022; Chang and Obermeyer 2020). Societal bias involves societal norms leading to us thinking in very set ways ignoring individuals that fall outside of these societal norms. This will result in any AI trained with data edited by a data scientist with these societal biases to also try and force decisions regarding these vulnerable individuals to conform to societal norms. These societal biases include gender, sexuality, and disabilities (Mozafari et al. 2022). Biases can also occur if, for instance, a device or AI is designed and developed in a resource-rich setting and then used in a low-resource setting. These two settings will differ in the treatments that can be safely and fairly performed (Price et al. 2019).

One of the greatest fears when it comes to AI targeting groups due to demographics, racial, ancestry/ethnicity, or genetic differences is the targeting of a specific group for special treatment, which in the most extreme case could result in genocide. This is easy to see with respect to the application of AI to autonomous weapon systems. This may result in a situation such as that imagined in fictional works such as the motion picture *The Terminator* (Poghosyan 2020). It is not difficult to see how medical information can be used by AI, big data, digital twinning, and cloud computing to instigate, plan, or justify genocide, segregation, or stigmatization based on historical examples of the use of medical science in these situations. The genocide of the Herero and Nama people which took place in Namibia in the early twentieth century involved medical sterilization, and medical science was used to justify these actions by "confirming" the superiority of certain populations over others (Semmens 2019). Another example is that of the Tuskegee syphilis studies which took place from 1932 to 1972. During these studies, African Americans were purposefully left untreated in order to observe the progress of the disease (Brandt 1978). Yet, another example is the Havasupai Native American Tribe (study 1989, Arizona, USA) in which their genetic material was taken and not used for the

purpose that it was originally intended but was also used for other purposes without the patient's consent (Sterling 2011). The ability of AI to learn from and adopt racist attitudes from those individuals it interacts with has been shown to occult easily and without intention. In 2016 Microsoft launched an AI called Tay. Tay was designed to be an AI chatbot that would interact with individuals on social media to develop conversational understanding by learning from other individuals on social media. Over a period of just 24 hours, the AI developed racist and sexist attitudes and began using racist and sexist language, resulting in the AI being shut down (Schwartz 2019).

The Singapore framework group released a framework detailing how AI should be used to ensure that it conforms to ethical standards and has a means of ensuring responsibility. One of the central tenets of this framework is that AI should be able to conform to the different societal contexts of the communities the AI intends to serve. In order to do this, the AI must be designed to recognize different societal norms and values (Makridakis 2017).

3.2 Protection of the Individual

3.2.1 Employment and Job Market

Major concerns of healthcare 5.0 are how the adoption of new technologies will affect jobs related to healthcare as well as budget and resource allocations in healthcare institutions. For instance, it is important to note that the introduction of AI into the workplace will result in changes in the types and needs for certain jobs due to it causing a shift in the demand for required skills. It will also affect the size of the workforce as AI, and many of the other smart technologies, will allow an increase in efficiency and many jobs will be able to be done, debatably, with less staff. Currently, AI is having a greater effect on middle-skilled jobs, while robotics is affecting lower-skilled jobs (Kristin 2017). Job losses in certain sectors may be offset as new jobs are created, especially around the new digital technologies which will be introduced and become more common in the smart Society 5.0 (Cooke and Zubcsek 2017). However, as a society, we must be intentional in ensuring the diverse representation of individuals who will be in these new fields.

3.2.2 Informed Consent

There is an active debate globally concerning whether a patient is required to give informed consent for their data to be used by these smart technologies or even collected and stored in the first place. It is possible that the collection of information will become fully automatic, instantaneous, and ubiquitous just like the constant collection of location-tracking information from individuals who have smartphones. This could happen to the extent that it will be impossible for anyone to avoid.

However, the storage and use of this data is another question. This is especially a concern if the patient does not want certain types of information to be used or accessed (Win 2005). If these technologies become the standard for patient care, the clinical care team must not only request the use of these digital technologies but also educate the patient on what these technologies will do, how they will help, and the risks involved. In addition, if the technology such as AI is operating in a way the clinical care team does not fully understand, that is, if the AI is a black box, must the clinicians disclose that they do not fully understand how the diagnosis was reached or why the treatment regime decided on was chosen based on the AI assessment (Win 2005)? If the patient has a right to have the treatment explained to them and the clinical care team cannot do so, it could be said that the patient's rights are being violated if the technology and treatment were used without the patient's consent (Win 2005).

3.2.3 Safety

The IBM Watson AI for Oncology treatment is meant to select the best treatment for patients based on their medical records. However, it became apparent that some of its recommendations were unsafe and incorrect (Strickland 2019; Brown 2018). These errors were due to the AI being trained using a small number of hypothetical cases rather than actual patient data (Strickland 2019). This highlights the concerns regarding the safety and effectiveness of AI. The safety of AI's recommendations, diagnoses, and prognoses can only be ensured by using valid datasets for training as well as having a human user or technician understand how the AI works. This is true of any of the digital technologies used in this new era of smart healthcare.

3.3 Excess Data Collection, Data Quality, and Over- and Under-Diagnosis

The danger of hyper-collection of data occurs when data not useful to patient care or relevant in healthcare is collected and stored (Institute of Medicine (US) The National Roundtable on Health Care Quality 2010). This excess data could be used for purposes, nefarious or benign, without the consent of the patient. This excess data can, for example, be sold to or acquired by private companies for marketing purposes. An example is the contact-tracing application developed by the Singapore government to help in the fight against the COVID-19 pandemic, which was found to be collecting data that could be used in criminal investigations (Wong et al. 2022). This repurposing of healthcare data is known as "function creep," and is greatly helped and facilitated through the collection of excess data. The inclusion and analysis of unnecessary data in any analysis performed by an AI may result in incorrect or false predictions due to data that is unrelated to the task at

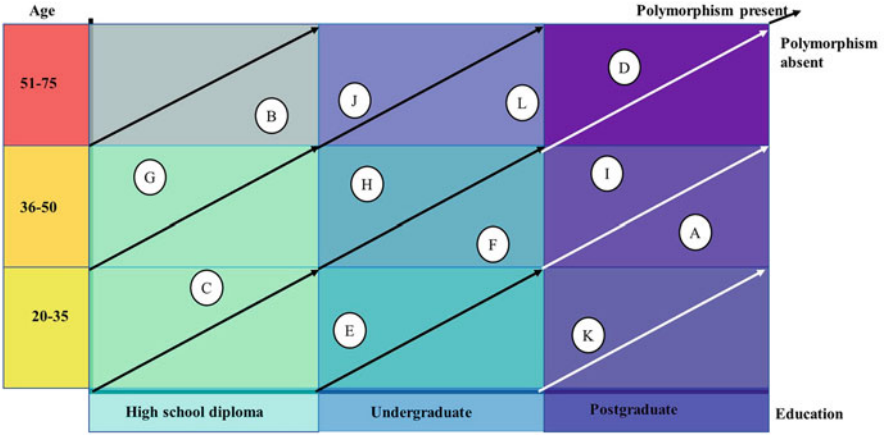

Fig. 3 The processes of deductive disclosure and sampling bias. A collection of data describing individuals' data on their age, education level, and whether they have a genetic polymorphism can be used to identify an individual or a group of individuals. For instance, even if the data has been anonymized, by looking at all three parameters (dimensions) we can deduce that if the data shows the individual is between 36 and 50, has a postgraduate level of education, and does not have the polymorphism, this is individual A. This figure also demonstrates sampling bias. These samples were most likely collected at a university campus as most of the subjects have a tertiary level of education, which is not true of the general population

hand, clouding the decision-making process of the AI by overcomplicating the process (Bagaria et al. 2020). The problems caused by using poor-quality data can clearly be seen in the failure of many of the applications designed to help during the COVID-19 pandemic. For instance, the AI COVID-19 detection software that used chest scans to make their diagnosis. This data was poor in quality and resulted in a very low success rate in the prediction of a positive COVID-19 infection (Mohamadou et al. 2020).

Historically, health research has been prone to the collection of biased data and the stigmatization of certain groups of people. Many of the datasets used to teach AI can be biased since they predominantly consist of data from individuals who according to sociopolitical race are considered white men of European descent (Mahmood et al. 2014). This data can also be influenced by societal biases (Mahmood et al. 2014). An AI using this data or a digital twin being created using this data may result in patients of different ethnicities and socioeconomic statuses being over- or under-treated (Vyas et al. 2020). Figure 3 gives a simple example of sampling bias. The samples collected here show a larger percentage of individuals having higher education qualifications than is true of the general population. A simple explanation is that these samples were collected from a university with staff and students having higher education levels than most of the population.

Overdiagnosis is the process whereby actions are carried out unnecessarily due to the presence of indicators that a problem may arise. An example of this is the presence of a genetic marker which may predispose an individual to a disease,

which requires surveillance but no further actions or treatment. It can also apply if a condition that can cause no harm or symptoms is diagnosed and treated rather than being merely noted and observed (Kale and Korenstein 2018; Mandl and Manrai 2019; Bunnik et al. 2015; Walker and Rogers 2017). The ease of testing, including self-testing, diagnosis, and remote diagnosis, has led to a period of new digital screening tests which are being developed faster than they can be tested for their accuracy and effectiveness (Capurro et al. 2022). This may lead to many false diagnoses as well as under- and overdiagnosis.

3.4 Privacy and Protection of Information

As information technologies advance, the collection and availability of data grows. This raises valid concerns about who can access this data and what it can be used for (Mai 2016). One of the risks surrounding data collection and storage arises from the fact that disclosed information could potentially be used to identify an individual (Bader et al. 2016). Associated with this are risks surrounding the dimensionality of data. Even if data is anonymized, it is possible to re-identify an individual through association with multidimensional data. That is, with only one parameter most individuals cannot be eliminated, but with each additional parameter the number of individuals in each dataset diminishes until an identification can be assigned (Fig. 3). This process is known as deductive disclosure (Rothstein 2010). Some of the new technologies that will be used to drive healthcare in Society 5.0 pose a threat to privacy by their very nature. This includes remote sensor technology, the Internet of Things, GPS in smartphones, social media, and large omics databases (Bader et al. 2016). Accidental disclosures of health-related data are more likely as the volume of data increases (Lundberg and Lee 2016). This may happen due to malicious data hacking or through inadvertent data mismanagement (Myers et al. 2008).

With the rampant use of technologies such as social media, the IoT, cloud computing, and AI using big data, it has been suggested that what people consider a normal level of privacy will change (Xafis 2015). Even before the current big data era, it became obvious that privacy can no longer be considered as the ownership of data since the generation of much of this data involves many people. Even in clinical tests, the results are generated by lab workers and are known by the clinical care team who commissioned the tests. Even if the results should not be publicly disclosed, the information is still known by multiple people and could be obtained from one of these individuals in some countries (Mai 2016).

Currently, data relating to an individual's health is protected by the law in most nations. Since healthcare technologies in Society 5.0 revolve around the collection of large amounts of data from many sources, the number of people involved in the collection of this data is vast and that number grows when the people involved in data curation are taken into account. The intensive collection of data from individuals may itself pose an ethical risk as it can infringe on the rights of an individual who may not want their data collected but are not given the choice due to the

automated collection of data that occurs with the IoT. It may also increase the risk of an individual's data being stolen through data mining inference attacks (Krumm 2007).

Another question is that of the ownership of data. The practice of selling patient data is on the rise with both companies and governments having sold patient data for profit (Lords 2018). The trading of data by public companies for commercial, insurance, or marketing purposes is known as data brokerage. The data obtained from a variety of sources that makes smart healthcare possible would also be valuable to companies. This healthcare data may be used to sell specific products based on an individual's health or be used to alter the risk-based contributions for medical or life insurance as well as to pharmaceutical companies (Prainsack 2017; Gerke et al. 2019). This function creep is another violation of data privacy, and the data sold or exchanged through data brokerage violates the doctor–patient relationship. This is further complicated by the excess collection of data discussed in Sect. 3.4. where unrelated data is gathered under the guise of health data in some countries. Patients need to be protected from such practices. Another issue which must be resolved is whether a patient has the right to change or remove information. This data is meant to reflect the patient and, therefore, there must be a good reason to edit it. The removal of data would decrease the ability of any smart technology such as AI or digital twinning to recommend treatments or diagnose illness, but are there circumstances where it would be within the patients' right to remove data? Also many technologies analyze data in real time, so if a patient wants this data deleted then it is likely that the results of the analysis would also need to be deleted (Gerke et al. 2019).

Currently, health data is protected by law and legally informed consent is required from the patient to share this information. However, the networking of devices and databases in the smart society could potentially render this legal protection obsolete. The maintenance and use of data also pose a problem since software and hardware are frequently upgraded. This could potentially result in digital obsolescence where data may not be transferrable to newer systems if standard backward compatibility approaches are not included in the technology designs. This may result in the loss of data. Another problem is data interoperability. This becomes a problem if data is collected by devices from different manufacturers using different analysis or operating software. This may lead to data being unable to be used or being entered into the analysis or AI software incorrectly (Sandborn and Packaging Technologies 2007).

4 Inherent Flaws in the New Technologies

The implementation of these advanced technologies that are required to implement smart healthcare in Society 5.0 may be too expensive for many low- and middle-income countries (LMICs). The costs associated with these technologies are varied. In terms of gathering data, the internet in many LMICs may not be fast enough to

support many of the remote technologies. Additionally, the construction of smart sensors is complicated by the need for sensors, actuators, and connectivity functions. This complexity leads to increased costs.

The information technologies used to gather information that is to be used to drive digital healthcare and smart individual-centered healthcare have demonstrated that they can have problems with accuracy. Even if data is accurately captured, stored, and curated, this may change over time as stored data is sensitive to changes or upgrades in software and hardware. Currently, the most popular operating systems are Android, Windows, and iOS. The transfer of data between these operating systems as well as the accessibility of data using browsers and different software is not always directly possible without conversion software. Even with conversion software some data may be lost. This problem is known as data transferability. This is especially true when it comes to the software on different smart devices not being directly transferable to the OS or software of the storage system or analysis software. The end result of this is unusable or corrupted data (Sandborn and Packaging Technologies 2007). For remote sensors, such as worn devices or smart devices that connect through the IoT, to be accurate, these devices need to be calibrated. Generally, this calibration cannot be done remotely and requires the input from an external processor. This may be even more problematic in LMICs where there may be a lack of technicians, or the technician or calibrating device may only be available in urban centers (Majumder et al. 2017). There are questions surrounding the accuracy of many of the devices that are used to gather information for the digitization of healthcare. This is especially true of the remote sensors or devices that record data and submit it via the IoT. These include smartphones, wearable devices, appliances, motor vehicles, and even social media and internet search histories. For example, the Apple Watch can collect data on an individual's heart rate and energy expenditure. However, when assessing the use of the Apple Watch for monitoring the heart rate and energy expenditure of a cardiac patient, it was found that the device overestimated energy expenditure (Falter et al. 2019).

Technologies such as AI (including ML) and many of the remote data-gathering procedures create a sense of mistrust due to a lack of transparency. This is most prevalent in regard to AI. This is because it is not always clear how the AI has come to its final decision. This is especially true of ML or deep learning algorithms as they can adapt and change in ways that the original creator did not foresee or intend. This is known as the black box problem (Poon and Sung 2021). This lack of transparency can lead to mistrust and doubts about the result given by the AI (Sorell et al. 2022). This has resulted in reluctance in the adoption of these technologies for diagnosis and treatment recommendations in some countries. There is also a lower tolerance for machine errors than there is for human errors, which is enhanced when a user is unable to understand what could have led to the technology failing.

5 Applications to Medical Research

The incorporation of these technologies into medical research is a point of concern as the reliability and accuracy of the results generated through these technologies are uncertain. One of the problems the use of these technologies can lead to is overfitting. In this case, the data used by an AI tool or recorded by a remote sensor is specific to a group of individuals and not the population as a whole. The use of this data to formulate a treatment or construct the digital twin of a population will lead to errors when used on patients outside of the small group used to obtain the data. An example of this is research data concerning heart attacks, which is mainly obtained from men. Using this data to create models for the prediction and prognosis of heart attacks will not be accurate when applied to women (Sallstrom et al. 2019). The collection and maintenance of research data are also complicated by the large amounts of data that are now possible to collect using technologies such as remote sensing, the IoT, cloud computing, and AI tools. As more data is collected and analyzed it becomes far more likely that disclosure of study participants' private information will occur. In another example of deductive disclosure, genome-wide association studies that report allele frequencies could be used to identify individuals in that study if someone had access to this person's genotype (Braun et al. 2009).

6 Legal Rights and Issues

6.1 Regulation

In the United States, some laws have been recently put in place that include the regulation of these new digital technologies. The 21st Century Cures Act includes mechanisms that support the adoption of electronic health records, nationwide interoperability, and information blocking. In response, the FDA has a created a Digital Health Center of Excellence which includes documents and guidance on digital health content, digital health policy, digital health reports, medical device interoperability, augmented reality and virtual reality in medical devices, software as a medical device (SaMD), device software functions including mobile medical application, wireless medical devices, and the digital health software precertification pilot program (https://www.fda.gov/medical-devices/digital-health-center-excellence). It is anticipated that the regulations and guidance will grow as more technologies are created specifically for the diagnosis, prevention, or treatment of disease in the new era of Society 5.0 healthcare.

In other countries, discussions are still ongoing as to the regulatory fate of this technology. Global bodies such as the United Nations have deliberated on minimal requirements in their guidelines for the ethical use of AI. In LMICs, such as Africa, the Organization for Economic Co-operation and Development ("OECD") reported that 700 AI policy initiatives have been implemented by 60 countries since 2017,

and 42 countries adopted the OECD's intergovernmental AI policy guidelines. However, only five African countries contribute to the OECD's 60-country membership (ALT Advisory 2022). The status of regulation of AI, in particular, is given in Table 1, where it can be seen just how much work needs to be done on the continent.

In 2020, Cyril Ramaphosa, the president of South Africa, called for a unified regional approach to AI involving the creation of a blueprint for African nations on which to base the development of their own AI policies. South Africa, in collaboration with other African nations as well as Smart Africa Alliance and multidisciplinary stakeholders, is attempting to create an Artificial Intelligence Blueprint aimed at outlining opportunities and challenges as well as to make recommendations on policy. The African Union (AU) has established an AU working in 2019. The mandate of the Working Group is threefold. Firstly, to facilitate the creation of an Africa-wide stance on AI. Secondly, to develop an Africa-wide capacity-building framework. Finally it aims to create a think tank to carry out these functions in order to realise both the AU's Agenda 2063 and the UN SDGs (ALT Advisory 2022).

6.2 Data Privacy and Protection

Various laws in various countries exist to protect an individual's privacy. However, these may not be sufficient in the big data era with smart healthcare being driven by technologies that are reliant on big data. In the United States of America, the Health Insurance Portability and Accountability Act (HIPAA) protects privacy, but it only covers specific health information and only relates to specific "covered entities" which includes clinical organizations, health-related companies, and their associates (Cohen and Mello 2018). In a smart healthcare system, information is going to be gathered by many organizations and systems not covered by this act or is data collected by the individual through wearable devices (Price and Cohen 2019). This act does not protect de-identified health information, which is allowed to be shared and used freely. However, we have already discussed the challenges with de-identified data in many dimensions (Fig. 3). In LMICs like Africa, the Malabo Convention is a set of laws adopted by the AU. The stated aim of this convention is that it is "aimed at strengthening fundamental rights and public freedoms, particularly the protection of physical data, and punish any violation of privacy without prejudice to the principle of the free flow of information." Some of the laws and regulations that the convention contains include the necessity for each state to establish a national data protection authority ("DPA") and limited provisions for the regulation of AI. These limited regulations apply to the automated processing of personal information and for people not to be subject to decisions based solely on the automated processing of data (ALT Advisory 2022).

Cybersecurity of the IoT, where the smart healthcare system of Society 5.0 will operate, is a concern as the IoT is vulnerable to deliberate attacks, both cyber and

Table 1 The state of AI regulation on the African continent (ALT Advisory 2022)

Country	Data protection legislation addresses automated decision-making	Has a national AI strategy	Has draft policy on AI	Expert body on AI	National Development Plan priority
Algeria					
Angola					
Benin					
Botswana					
Burkina Faso					
B Burundi					
Cabo Verde					
Cameroon					
Central African Republic					
Chad					
Comoros					
Congo (Rep. of)					
Cote d'Ivoire					
Democratic Republic of Congo					
Djibouti					
Egypt					
Equatorial Guinea					
Eritrea					
Eswatini					
Ethiopia					
Gabon					
The Gambia					
Ghana					
Guinea					
Guinea-Bissau					
Kenya					
Lesotho					
Liberia					
Libya					
Madagascar					
Malawi					

(continued)

Table 1 (continued)

Mali					
Mauritania					
Mauritius					
Morocco					
Mozambique					
Namibia					
Niger					
Nigeria					
Rwanda					
Sao Tome & Principe					
Senegal					
Seychelles					
Sierra Leone					
Somalia					
South Africa					
South Sudan					
Sudan					
Tanzania					
Togolese Republic					
Tunisia					
Uganda					
Sahrawi Arab Republic					
Zambia					
Zimbabwe					

The various laws and regulations that a country should have in place to ethically and responsibly institute AI. The green boxes denote that the country has the rules, regulations, or advisory bodies in place while the red box denotes that the country has no such regulation in place. The table clearly shows that much work is still needed for the ethical use of AI to be implemented in Africa Table columns must be alliged with each other

physical attacks (Perakslis 2014). There are multiple targets for cyberattacks which include wearable devices, company or hospital servers, medical devices, and patient data storage clouds (Masons 2017). These attacks can risk patient data, either resulting in data leaks or the loss of data, which can threaten a patient's privacy or healthcare. These attacks could even interfere with the functioning of the AI or bioinformatic tools resulting in poor analysis of data and incorrect recommendations (Perakslis 2014). It is necessary to create and enforce an international law that details cybersecurity, its implementation, and the strengthening of underlying systems and infrastructure to make these systems more resilient and responsive to attack. The greatest difficulty is that this must be done across borders, regardless of the wealth of a country or region (Perakslis 2014; Gerke et al. 2019).

Privacy in the European Union is protected by the General Data Protection Regulation. This is a newer law and contains specific definitions on what health-related data is specific for an individual and is related to their physical or mental health. The act also accepts a broader definition of what an entity is that gathers or uses data and what the provision of health services means (Irish National Teachers'

Organisation 2018). The act prohibits the processing of genetic data, biometric data, and data concerning health, but does also include a list of exceptions. These exceptions include cases where explicit consent is given or if the analysis of and use of the information is required for public health or if it is needed for archiving purposes to advance the public interest. Research purposes are another exception, both scientific and historical (Irish National Teachers' Organisation 2018). Under this act, patients and individuals whose data is collected must be informed and made aware of the existence of technologies which can automatically analyze and interpret this data to make decisions regarding the profiling of the population and themselves. They must also be informed about the consequences of these analyses (Irish National Teachers' Organisation 2018). The individuals must be able to access the data used in these analyses and to insist on the right not to be subject to a decision made by the automated analysis of their data (Irish National Teachers' Organisation 2018).

6.3 Liability and Responsibility

Another important question is who is responsible or liable when these technologies fail, cause harm, or even death. This is especially a concern for the use of automated machines for surgery or AI-based treatment selection. There are multiple individuals or companies that could bear responsibility. These include the software developers or engineers, the company that builds the smart device or robotic system, individuals or regulatory bodies that approved the device or software for medical use, and/or the healthcare professionals who were the endpoint users of the technology. Additionally, what should be done if something an AI tool has learned, through poor data or incorrect analysis, leads to harm? Should governments or regulatory bodies decide who is at fault or should it be decided on a case-by-case basis? It is impossible to hold the technologies themselves accountable but if manufacturers or designers could be shown not to have tested or constantly monitored for quality assessment and quality assurance, the software, robot, or device extensively then they may be held responsible. It is for this reason that it has been suggested that a list of stakeholders should be generated showing who is responsible at what stage of use or implementation of the technology (Dignum 2019). This is further complicated when humans follow the recommendations of a given AI tool, for example, for treatment. What are the legal repercussions if a doctor follows these recommendations only for it to be incorrect and lead to harming the patient? Additionally, could a doctor be held responsible for choosing not to follow the recommendations given by the AI tool? Even if this leads to harm, there is no way of knowing if the recommendation given by an AI tool would have had a better outcome (Dignum 2019).

Currently, in the United States, AI- and healthcare-related software are defined as a tool under the control of the health professional and they are responsible for any errors that occur, resulting in them being sued for *medical malpractice* if anything happens that lead to these technologies causing harm (Esmaeilzadeh 2020; Price et al. 2019). However, if the details of the technology is hidden from the clinician or

if the AI/ML- based algorithm comes to a decision in which the clinician has no insight (i.e., black box), should the clinician be responsible? This is a future consideration since neither AI tools nor any other digital technology are used as a standard of care and are currently only used in supportive roles and the clinician is not without options, such as ignoring the recommendations made by an AI tool that has analyzed data collected from various sources (Price et al. 2019). The fact that these technologies play a supporting role also means that legal claims against the manufacturers may fail in some countries (Price and Nicholson 2017). Corporate liability and vicarious liability laws may also be used to assign blame against the hospitals or medical institutes that purchase software or devices to assist in patient treatment in some countries. Negligent credentialing laws may also apply here for some countries. These laws state that a hospital is responsible for verifying the credentials of their medical staff and in the same way, they would be responsible for verifying the accuracy and reliability of the software or devices they use to treat patients (Gerke et al. 2020).

The European Parliament published the Civil Law Rules on Robotics: European Parliament resolution in 2017. This resolution stated that the current liability laws will not suffice for the regulation of these new technologies in healthcare and new laws need to be developed and put in place. This was followed by the creation of the EU's New Technologies Formation (NTF) group in 2019. This group released a report on these new emerging technologies. Some of these recommendations were that AI robotic systems that operate in a public space must be held responsible for any damage they cause and those using technologies that can be considered as autonomous are still accountable for any harm caused (Nagamarpalli 2021). In 2020, the European Commission published a report on AI, the IoT, and robotics concerning their safety and implications for the liability which concluded that while existing laws can cope, they need to be adjusted. Adjustments also need to be made to national regulatory frameworks concerning product liability (Cohen et al. 2020) (Fig. 4).

6.4 Intellectual Property

The cost of developing these new technologies as well as gathering the data that they require is high, and companies and individuals require the promise of financial rewards to incentivize them to develop these technologies. However, information technologies have long been plagued by piracy and theft, and the rights of the companies to the information they collect and the software they develop for these new technologies must be corrected. This must be balanced against the desire for open-source software, freedom of information in science, and equal access of all, regardless of economic and developmental limitations, to databases and these devices and software (Lemley and Shafir 2011). These technologies and the information they require are currently protected by a variety of laws, including long contracts, copyright, trade secrets/the law of confidence, database rights, competition

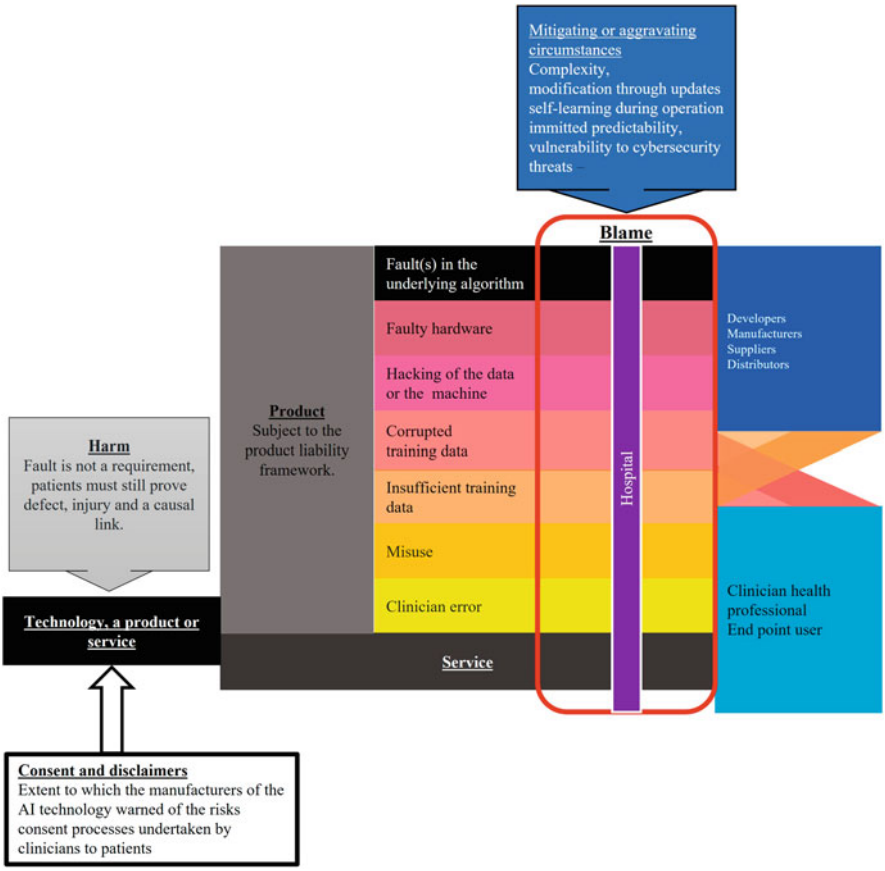

Fig. 4 The assigning of liability when new digital "smart" technologies cause harm. The first step in establishing responsibility is examining consent and disclaimer information. What did the patient give assent to and were they warned of the risks? The patient must then be able to prove that harm was done to them through the use of technology. The liability framework to be followed once harm has been established depends on whether the technology is classed as a service or a product. If the technology is classed as a service, the blame would almost always fall on the endpoint user. However, if the technology is a product, then blame can fall on a variety of individuals or companies. In almost every case, blame can be assigned to the hospital of the healthcare facility that approved the use of the technology in the facility

law, and personal data integrity rights (Minssen and Pierce 2018). However, these laws are sometimes not compatible with large databases made up of unstructured nonrelational data (Gervais 2019). Also, these laws may hinder the transformation of technologies such as AI tools into transparent entities as trade secret laws and contracts can protect the disclosure of algorithms and hide software functions and datasets (Gervais 2019). Public-private partnerships need to be encouraged as do incentives to share data (Richter and Slowinski 2019).

7 Solutions to Some of These Issues

Many of the issues surrounding the ethical and moral implementation of these digital technologies would be solved through the implementation and adoption of a means of assigning responsibility for the design of these technologies and the accountability for their failures. These regulations should help to protect human rights and ensure the well-being of patients and conform to ethical principles and societal values (Bhattacharya et al. 2020). This would require the formulation of new laws and regulatory bodies or government departments to efficiently control the application of these new technologies. These bodies would help to establish a chain of responsibility (Dignum 2019). Regulatory bodies must also ensure that autonomous AI tools are specifically designed with a clear aim, and this aim must be beneficial to the Society 5.0 framework as well as constantly monitored for deviations from its aim and programming (Anderson et al. 2018). To correctly perform these functions, the members of these regulatory bodies and the lawmakers overseeing the implementation of new laws must have a clear understanding of the capacity and limitations of all these technologies. These laws and regulations may be difficult to formulate and enforce as they must deal with issues around accountability, responsibility, and transparency, but with diligent oversight, this process can succeed (Dignum 2019).

Biases in datasets may be resolved as the amount of collected data increases. With the prevalence of data collection sources such as the IoT any skewness in the data should eventually be corrected and the databases should come to resemble the actual population. This can be additionally improved if attempts are made to collect data from underrepresented groups. It should also be noted that different algorithms for analysis or machine learning should be used for different population groups, or the AI or bioinformatic software should be able to narrow its functionality based on different population groups only in circumstances where this is the only option or it is warranted by a scientific rationale such as biology (e.g., cancer patients with BRCA mutations).

When it comes to improving the transparency of AI technologies, it has been proposed to use a stepwise approach, where the AI functions in a small stepwise fashion allowing clinicians and healthcare professionals to clearly understand each of the small steps the AI makes to get to the final decision. Another option would be to create an AI that generates a log of all its activities and actions (Kwong et al. 2022). The excessive collection of information and the trading of information without an individual's consent is another issue that would require the action of lawmakers and regulatory bodies. The misuse of information or the use of poor or historically biased datasets is more difficult to solve and would require careful auditing of these datasets as well as teaching the AI when to exclude data. In addition to this, the learning and development of the AI can be audited at every stage. This can be done by carefully analyzing the results generated by the analysis of the data performed by the AI and checking the results for accuracy and meaningfulness. These results can be used to fine-tune the performance of the AI (Hripcsak et al. 2016). The regulation of devices that can be used to record medical data as well as

laws controlling how long a device can function without an upgrade or service would vastly improve the reliability and accuracy of collected data.

The autonomy of these different technologies, such as automatic data collection and transmission, the real-time creation of digital twins, and automated decisions made by AI and implemented by robotics, is a cause for concern as it may violate human values and rights and could lead to discrimination and immoral unethical actions. These aims should not be, for instance, the creation of an AI or medical device that can be used to replace health workers, but rather to improve the lives of patients, health workers, and not replace the final decision of the patient in consultation with their doctor and clinical care team. Regardless of the role the technology is expected to play, it must always consider the individual rather than groups of individuals or treat all populations as if they are identical regardless of socioeconomic status or culture (Dignum 2019).

8 Conclusion

The digitization of healthcare and biological information is proceeding rapidly and is required for the implementation of a smart society and the healthcare system to match, that is, Society 5.0 Healthcare. Despite these technologies posing significant ethical challenges, they offer too many promises of truly personalized healthcare to be ignored, and it is basically the responsibility of governments, regulatory bodies, and international cooperation in the form of organizations like the UN to implement means to effectively regulate these technologies so that they do no harm. The UN has already formulated guidelines for the use of AI, and other regulatory bodies already exist for digital twins and medical devices. This is similar to the situation in the early twentieth century regarding the sale of medicines and drugs, which initially was unregulated and led to a great deal of harm and in many instances death. New laws and regulatory bodies were created to control and enforce laws surrounding the testing, manufacture, and sale of drug therapies. The same process will have to be performed for these new technologies. These ethical issues can be solved as long as these technologies are implemented cautiously with extensive testing and auditing and as long as the healthcare system these technologies promise to improve remains human-centered.

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Way Forward for Society 5.0 and Next-Generation Healthcare

Zodwa Dlamini, Rodney Hull, Ravi Mehrotra, Richard Khanyile, and Thulo Molefi

Abstract We envisage living in a society where scientific and technological innovations lead to reforms in human health by merging cyber and physical spaces. The concept of Society 5.0 was first proposed in Japan. Society 5.0 is a smart, knowledge-based society, which uses digital information-based technologies such as artificial intelligence (AI), cloud computing, and the Internet of Things (IoT) to gather and analyse large amounts of data. Elements of Society 5.0 are human-centric and promote the integration of the physical world and cyberspace in its economic development and innovation framework. The promotion of a smart, knowledge-based, human-centric society is designed with the hopes of leading to a better life for all human nations, regardless of their ethnicity or wealth. Digital information technologies, together with the concept of Society 5.0, will assist in implementing the United Nations (UN) Sustainable Development Goals (SDGs), particularly Goal 3, which looks at the use and integration of new technologies in improving healthcare, resulting in individuals living a longer, healthier and more productive

Z. Dlamini (✉) · R. Hull
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: zodwa.dlamini@up.ac.za; rodney.hull@up.ac.za

R. Mehrotra
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa

Indian Cancer Genomic Atlas, Centre for Health, Innovation and Policy Foundation, Pune, India
e-mail: ravi.mehrotra@gov.in

R. Khanyile · T. Molefi
SAMRC Precision Oncology Research Unit (PORU), DSI/NRF SARChI Chair in Precision Oncology and Cancer Prevention (POCP), Pan African Cancer Research Institute (PACRI), University of Pretoria, Hatfield, Pretoria, South Africa

Department of Medical Oncology, Faculty of Health Sciences, Steve Biko Academic Hospital, University of Pretoria, Hatfield, Pretoria, South Africa
e-mail: richard.khanyile@up.ac.za; thulo.molefi@up.ac.za

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life. The healthcare sector is a fundamental component of the economy, and as such, it requires that the individuals in the sector be in peak mental and physical health to facilitate maximal societal growth. It is common knowledge that health is wealth, and this is reflected by the rate of growth and development in societies and when their population is healthy. In its implementation, Society 5.0 will not only require new technologies but will also drive technological developments. Developments that will improve data analytical methods and geospatial surveillance for the prevention of chronic diseases. The implementation of Society 5.0 into healthcare systems will strengthen precision medicine approaches and invariably improve all spheres of human health. Despite the challenges such as human rights violations, security, privacy, safety and the impact on the energy crisis, these technologies will pave the way forward for improved healthcare systems and living.

Keywords Society 5.0 · Predictive · Preventive · Personalized and participatory healthcare · UN SDG3 · Digital information technologies · Precision medicine · Safety · Security · Privacy · Human rights · Energy crisis

1 Conclusion

Society 5.0 is an ambitious endeavour conceptualized in Japan. Its aim is to propel humanity from the current information-intensive reality to a more knowledge-based paradigm. This is conceived to be achieved through creating a human-centred society based on integrating cyberspace with the real physical world. Society 5.0 can be simply defined as a future intelligent, sustainable society. The aim of healthcare systems in Society 5.0 is to improve the longevity and productivity of individuals as well as quality of life and ensure health equity and equality, while driving the upliftment and use of cutting-edge technologies. This will be accomplished by using digital information technologies to minimize the incidence and severity of disease and optimize the use of medical resources. The intricacies involved in the management of cancer provide the perfect scenario to apply the principles of Society 5.0. By using the strategies of healthcare in Society 5.0, the incidence of cancer could be lowered by increasing the ease and speed of screening and diagnosis. At the same time, these strategies can improve access to quality personalized oncology services globally, including in low-middle-income countries (LMICs). LMICs have fewer resources with which to combat a disease like cancer. The strategies of smart healthcare, if implemented in these areas, will drastically improve the screening and treatment of premalignant and invasive diseases, resulting in improved patient outcomes. Technologies of the Fourth Industrial Revolution (4IR) allow for the generation, gathering, storage and analysis of large amounts of information. Their integration and application in Society 5.0 will allow for better personalized medicine.

Central amongst these 4IR technologies is Artificial Intelligence (AI). AI allows for the automated categorization, analysis, and interpretation of data to mimic human cognition and come to conclusions which can be acted upon. In healthcare, these

decisions include predictions of the best diagnostic approaches, prognostic predictors and treatment strategies. Achieving these goals involves exploiting AI for the betterment of all human life at both individual and societal levels. The potential role that AI can play in healthcare in Society 5.0 is demonstrated by its use of intelligence in drug discovery. This will drastically reduce the cost and production times for newly conceptualized drugs. The use of AI can also help ensure the safety, ease of use, and efficacy of these new medications, as well as reduce the occurrence of adverse drug events. These improvements will ease clinician decision-making and enhance the quality of patients' lives.

The development of a disease, its progression and its management can be thought of as facets of a single process, one which warrants an active, integrated response from all stakeholders. This can be effectively achieved by appropriately leveraging all available resources. This includes the engineering of health-related information, which is another example of these cutting-edge technologies and health informatics. The Internet of Things (IoT) allows for the connection of physical objects with sensors, processors, and software, therefore, enabling efficient gathering and exchange of data. We already have a large body of knowledge concerning the layout of medical IoT systems, including knowledge of the components involved in their functioning and communication networks. Currently, this knowledge has only had minimal, real-world practical implementation. This is especially true in under-resourced communities because of cost issues. Technologies such as the IoT need to be expanded to remote populations in lower socioeconomic areas to facilitate remote diagnosis and patient monitoring. Pilot projects with carefully planned financing strategies have been carried out to test their use in remote diagnosis and patient management. Key to the success of these projects will be establishing the robustness of these technologies in these environments. A digital twin is a virtual representation of a real-life object. Digital twins can be used to virtually model individuals or populations. For instance, in healthcare, they can be used to model patient responses to various treatments or to screen high-risk patients, resulting in early diagnosis and treatment. An intelligent digital twin, combining data, knowledge, and algorithms (AI), has the capacity to accurately simulate public health and medical situations. Simulations may be individual or population-specific and these can be used to model medical situations such as disease progression, drug interactions, treatment efficacy and the spread of disease. Virtual modelling can make accurate predictions and inform clinical practices.

Devices used to remotely monitor patients require the integration of embedded software that regulates these devices. This embedded software controls their computer fogging functions, automated physical systems and AI algorithms. These devices and the level of integration within them are about to change the way medicine is practised, helping to realize healthcare within Society 5.0. These medical cyber-physical systems (CPS) permit remote patient monitoring through sensor technology, digitalization of data storing, mining, and sharing and allow the transmission of alerts to care providers. The processing and storage of big data by these devices are facilitated through the integration of AI with cloud/fog computing. Digitally assisted patient management systems allow for rapid, less invasive and

effective patient care. The security of CPS requires the development of reliable autonomous security patches. These patches would detect security breaches or vulnerabilities and eradicate the threat before it can cause any harm. The unsolicited access and manipulation of electronic data is a major issue for many of these technologies. This is especially true for facilities that store patients' medical records in electronic computer systems. Blockchain technology is a solution to this problem as this technology prevents data corruption or record manipulation without a common consensus. Blockchain technology functions as a digital ledger monitor, which sends alerts every time the data is accessed. This gives the owner control over who accesses the data, as well as who's allowed to manipulate it. The owner controls this using a digital signature, making this technology secure and reliable. This technology will significantly enhance the implementation of the other information-based technologies required for healthcare in Society 5.0. Besides security, Blockchain can also perform various healthcare functions, such as medicines tracing (drug discovery, development and distribution process), smart contracts and healthcare insurance mediation. The challenges facing this technology, such as throughput, latency, security, usability, size and bandwidth, are not insurmountable and solutions to these problems are actively being sought.

The smart digital technologies required to make Society 5.0 and healthcare in this society possible are not without their various challenges and issues (Fig. 1). Despite its challenges, these technologies offer innumerable promises for truly personalized healthcare to be ignored. Another promise these technologies offer is the democratizing of healthcare. Currently, the cost of 4IR technological advances puts them beyond the reach of many emerging nations and individuals. This cost factor is currently prohibitive, unscalable and therefore unsustainable, particularly in LMICs where they are the most needed. The governments of these countries need to make a collective and conscientious effort to invest more in these technologies, as they can effectively improve preventative medicine. The long-term effect of this will be a return on these investments, as the current financial burden of disease treatment outweighs the initial investment in disease prevention.

Additionally, in many cases, these new technologies operate in ethical grey areas. This is because they can be misused, resulting in safety issues, poor clinical decision-making, and violation of human rights and values. As such, governments, regulatory bodies and international cooperatives, like the UN, must effectively regulate these technologies to prevent harm. There are also legal and human rights issues surrounding these technologies, ranging from the protection of privacy, informed consent to intellectual property laws. Most important is the question of who bears legal liability when the technologies cause harm to an individual. New laws and regulatory bodies need to be created to control and enforce laws concerning these issues. These ethical issues can be remedied, and harm minimized by cautiously implementing these technologies following extensive testing and auditing.

Another challenge is the impact these technologies will have on the current energy crisis. One of the biggest barriers of these technologies is the lack of resources required to implement them. They require storage capacity, cloud computing capacity, computational power, raw materials for manufacturing the required

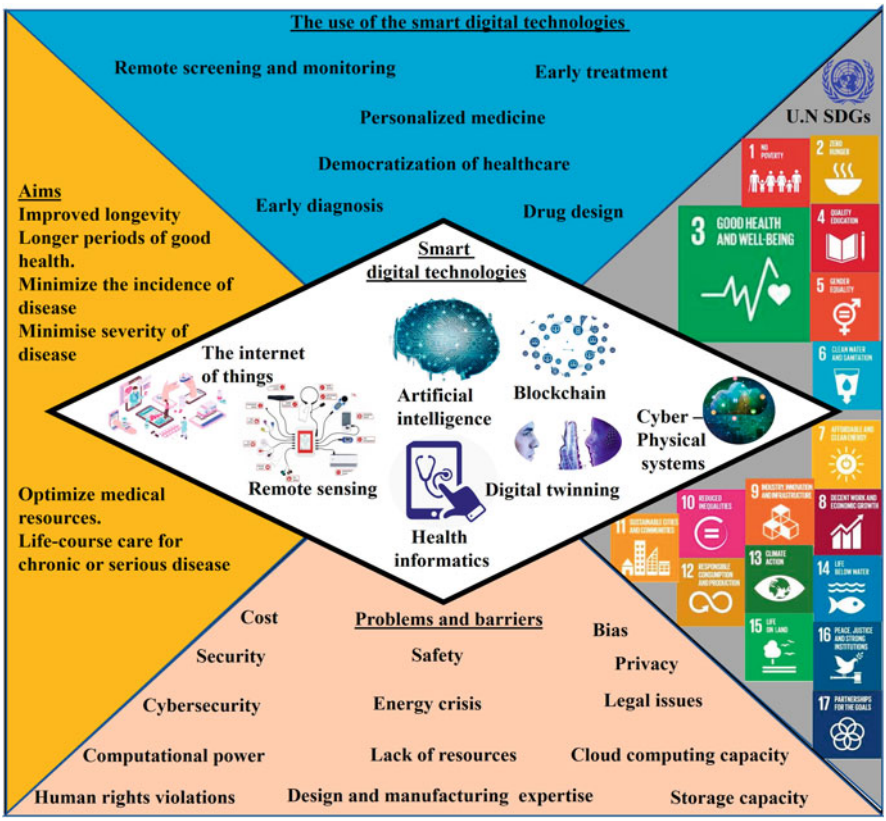

Fig. 1 Summarizes the aims, expected outcomes, technologies and challenges facing healthcare in Society 5.0. The aims of healthcare in Society 5.0 are shown in the *orange* quadrant. They include a longer life with more extended periods of productivity due to a lower incidence of disease or decreased severity of the disease. The central *white* diamond shows the technologies used to implement healthcare in Society 5.0. The issues with and barriers to the implementation of these technologies are shown in the *pink* lower quadrant. These include cost, ethics and legal rights. Society 5.0, especially healthcare in Society 5.0, will help the world realize the UN's sustainable development goals. For healthcare, the most obvious will be SDG 3, Good health and well-being. However, the implementation of these technologies will result in progress being made in many of the other SDGs. Finally, the *blue* quadrant lists the actual applications of these technologies in healthcare that would allow us to achieve the aims of healthcare in Society 5.0

hardware, expertise for the design, and manufacturing of both hardware and software, and this will consume large amounts of energy. The implementation of Society 5.0 will require a reliable supply of energy. If this challenge can be overcome, the benefits that these technologies will provide outweigh the challenges. For example, AI, IoT and digital twinning have the potential to manage, monitor and adjust the consumption of energy resources (Sifat et al. 2022; Nandury and Begum 2015). Smart grids (SG) would improve the flow of data and electricity within the electricity

system networks (ESN) and allow for the replacement of conventional fossil fuel–rich grids with distributed energy resources (DER) (Kumar et al. 2020).

This book has attempted to introduce the concept of a novel, human-centred healthcare system, delivered through implementing an innovative, knowledge-based approach known as Society 5.0. It has raised the different digital technologies which will make this possible and described how these technologies would help fulfil the fundamental promise of healthcare in Society 5.0, which is a longer and healthier life. It has also discussed how these technologies will contribute to achieving the sustainable development goals set forward by the UN. Society 5.0 will lead to a healthcare system that is predictive, preventive, personalized and participatory rather than reactive. In this way, it can provide improved healthcare from the cradle to the grave by increasing productivity, quality of life and longevity.

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