Christoph Thuemmler · Chunxue Bai
Editors

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Preface

> "He who does not expect the unexpected will not find it, since it is trackless and unexplored"
>
> Heraclitus of Ephesus (535 BC–475 BC)

> "Your task is not to foresee the future, but to enable it"
>
> Antoine de Saint-Exupéry (1900–1942)

During the nineteenth and twentieth centuries the art of medicine was advanced, especially with regard to therapeutic interventions. Now the focus has shifted over recent decades, we are able to look deeper and deeper into the micro-cosmos, observing and analyzing molecular structures, such as DNA, and even go beyond this looking at atomic and sub-atomic level, our ability to foresee is growing stronger. While the elders could only treat conditions they could grasp with their hands, digital imaging became the ultimate diagnostic weapon of the twentieth century, making smaller and smaller structural changes recognizable. This allowed faster diagnosis and treatment of diseases. While today prevention is based on early recognition, tomorrow's medical strategies will be based on anticipation. While no man can foresee the future we can learn from the past and apply the lessons learned in the present, thereby enabling the future. Medicine has always been in a creative dialogue right at the interface of art, philosophy and science. The evolution of medicine has always been driven by a combination of soft and hard factors; human factors—such as the reluctance to change, social and societal forces—such as ethics, legislation and economics and technical progress such as the evolution of machines and computers. All of these factors have contributed to the emergence of e-health and m-health in the late twentieth century.

Now, at the beginning of the twenty-first century we find ourselves (almost) ready to individualize health care by not only sequencing individual DNA and tracking down intra-individual changes in real time, but also to turn our newly

gained wisdom into individualized "theragnostic" strategies, which has already started to fundamentally change healthcare and the way it is delivered.

Twentieth century healthcare was driven by statistical averages, which were reflected in values defining normality, the type and dose of medication prescribed, the surgical approach to be chosen, etc., future practice will be turning away from generalization and move towards the definition of individual real-time requirements. Personalized medicine or precision medicine will allow for individualized treatment anywhere, anyhow and at any time.

At the same time, health monitoring and management will become more personal and timely as new technologies will enable individuals to conduct routine health monitoring and management activities on the go using virtualization tools and cyber-physical systems based on Industry 4.0 design principles connecting the physical and the virtual world in real time. However, safety, security and privacy aspects are of utmost importance for Health 4.0 strategies to thrive and unfold their beneficial potential. New network technologies, such as the 5th generation network (5G) will enable ubiquitous access, enhance connectivity and allow the ad hoc orchestration of services, integrating patients, formal and informal carers, social workers and medical practitioners.

Smart algorithms will allow for the monitoring and enhanced management of especially chronic, non-communicable conditions such as asthma, diabetes, multiple sclerosis or cancer. The prime target of these technologies will be to enable lower qualified individuals to conduct the routine tasks of higher qualified individuals and identify patients in need of expert attention or intervention.

Virtualization in the health domain comes with the emergence of next generation mobile network strategies (5G). While the global pick-up rate of e-health and m-health technologies has so far been patchy and behind expectation, new network technologies will provide the missing pieces towards comprehensive care virtualization:

- 100 times more devices to be able to connect
- Reduction of latency times below 5 ms
- Improvement of coverage
- Enhancement of battery life
- Improvement of security, quality of service (QoS) and quality of experience (QoE)
- Enhanced bandwidth
- Enabling the (medical) Internet of Things

The Health 4.0 approach, which is derived from the manufacturing industry's well-known Industry 4.0 concept, will ultimately turn into a win-win situation for all stakeholders as it enhances and facilitates a collective approach towards a manageable future in the light of changing socio-economic conditions. However, Health 4.0 is a chance to turn these socio-economic challenges into economic opportunities given the fact that the average Chinese spending on healthcare is around 5% of the GDP while European spending is around 10% of the GDP and rising. This is only topped by the US economy where around 18% of the GDP is spent on healthcare.

It is thus exciting to see how the move towards virtualization under a Health 4.0 framework may enhance our capability to expect the unexpected and thus enable us to cope with emerging challenges such as the growing concern of resistance to antibiotics, malaria, viral outbreaks and cancer and increase effectiveness and efficiency of care.

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Chapter 1
The Case for Health 4.0

Christoph Thuemmler

1.1 Demographic Developments

There can be no denying that life expectancy in industrialized but also in emerging countries has significantly risen over recent decades. According to WHO figures life expectancy grew globally by 6 years between 1990 and 2013 (This trend does not reflect the conditions in Africa, where life expectancy even has decreased in certain areas) [1]. The overall increase in life expectancy between 1970 and 2013 was 10.4 years in the average for OECD countries, 12.2 years for China, 10.3 years for Germany 7.9 years for the United States (Fig. 1.1).

This development may explain the current growing number of elderly people in our societies but would not necessarily constitute a socio-economic challenge. The challenge as such results from the fact that at the same time fertility rates have been dropping dramatically (Fig. 1.2) [2]. In other words people are getting older and having fewer children to a point where without net migration from other countries the overall population would decline. Fertility rates are in particularly low in Germany, Italy, Greece, Japan, South Korea and Hong Kong where they are ranging far below the reproductive minimum of 2.1 to keep the population stable (Fig. 1.3). A reflection of both effects, namely increasing age and lower fertility rates is the so called old age dependency ratio. The old age dependency ratio is the ratio of older dependents—people older than 64—to the working-age population—those 15–64 years of age. The old age dependency ratio in 2014 has been 30 in France, 32 in Germany and Greece, 22 in the United States and 27 in the United Kingdom. In comparison China had an old age dependency ratio of 12 in 2014 [3]. However, although the figure for China looks comfortable on the first glance projections clearly show that old age dependency ratio is to rise dramatically over the coming 30 years, almost equaling European figures (Fig. 1.4).

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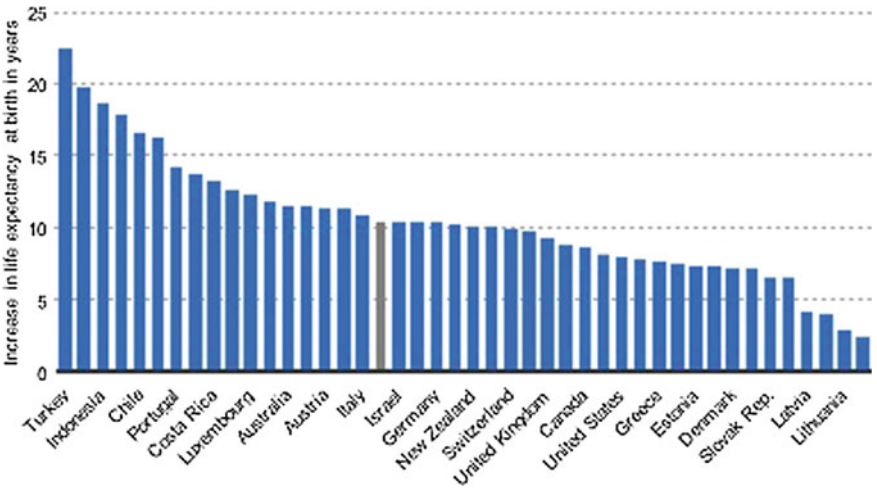


Fig. 1.1 Increase in average life expectancy at birth in selected countries between 1970 and 2013 (in years) (*Source* OECD)

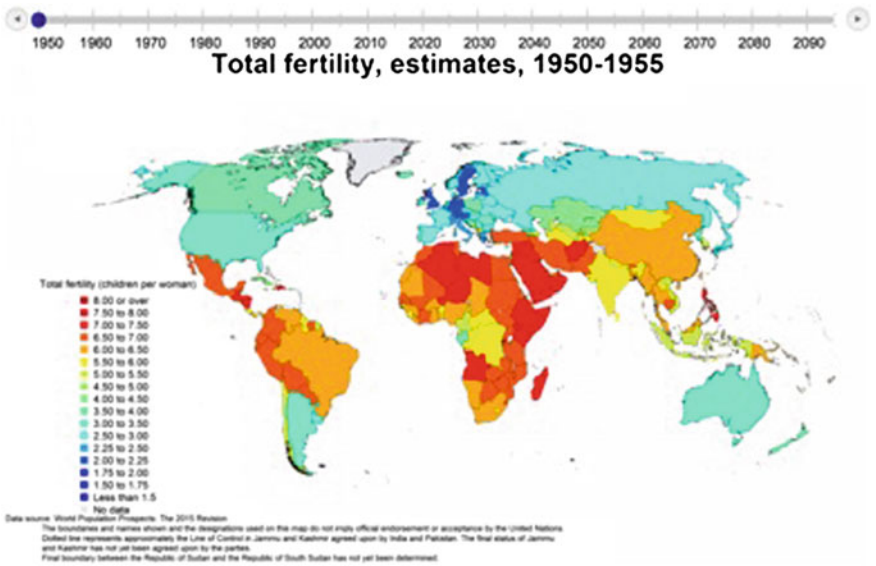


Fig. 1.2 Fertility rates 1950–1955 (*Source* United Nations)

According to Eurostat Germany will reach an old age dependency ratio of 50 % by 2035 and plateau from 2050 onwards at roughly 60 % [4]. Several European countries and China seem to have similar long-term projections hence why it is only understandable that these countries looking for shared solutions based on latest

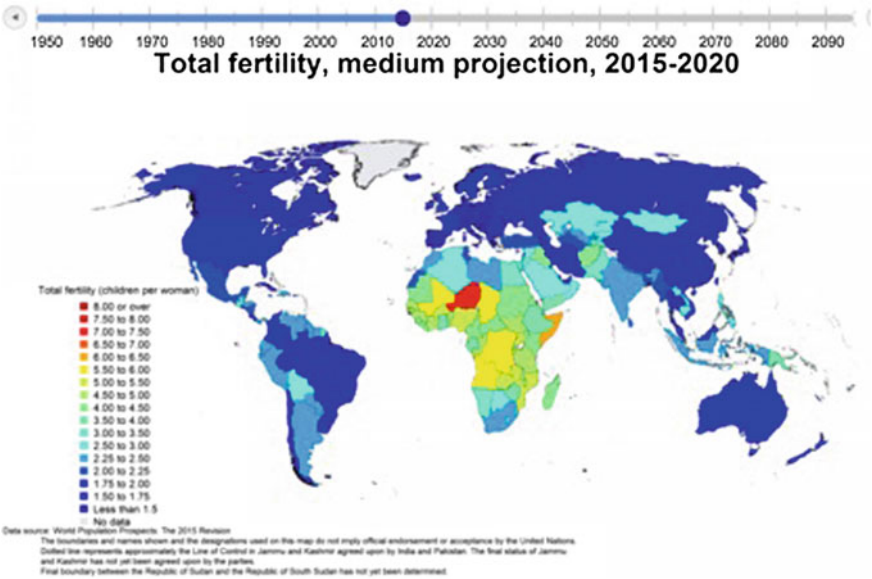


Fig. 1.3 Fertility rates 2015 (*Source* United Nations)

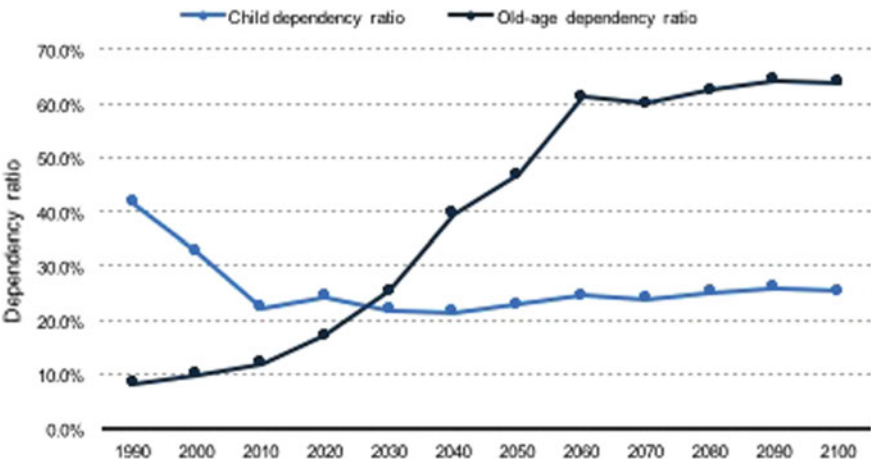


Fig. 1.4 Children and old-age dependency ratio in China from 1990 to 2100 (*Source* United Nations, National Bureau of Statistics of China)

health care and information communication technologies. As a matter of fact delivering care as we know it today will not be affordable for any society 20 years from now and many care elements will have to be delivered by non-professionals and machines. This includes robots and devices which will be connected via

Machine-to-Machine (M2M) protocols and automated, computerized services, which will be accessible via fast, wired and radio connections anywhere, anyhow and at any time.

1.2 Hospital Beds

The way healthcare is delivered has been undergoing major transformation for some time now. While in the 1970s hospital centered and professional focused approaches were the norm we can see and experience more and more evidence for the transition of this hospital centered and professional focused approach towards a distributed patient centered care model, where many care elements will be delivered virtually and by "informal" carers, meaning carers without formal professional training. One of the most outstanding trends is the shift of the point of care towards the periphery of the system. One of the main drivers is the irreversible change of the physical care infrastructure. According to OECD figures between 2000 and 2010 European hospital beds have been reduced at an average rate of 1.9 % per annum [5]. In Germany the number of hospitals has dropped from 2242 in 2000 to 1980 in 2014 (Fig. 1.5) [6].

In fact there is a sharp divide with regards to hospital beds per capita across Europe and globally. While Austria, Germany and Poland have 7.6, 8.2 and 6.5 hospital beds per 1000 population countries such as the United Kingdom, Italy and Spain have considerably less, namely 2.9, 3.4 and 3.1 beds per 1000 population. Interesting enough China has slightly more hospital beds per 1000 inhabitants than the United States, namely 3.8 per 1000 population in contrast to the United States

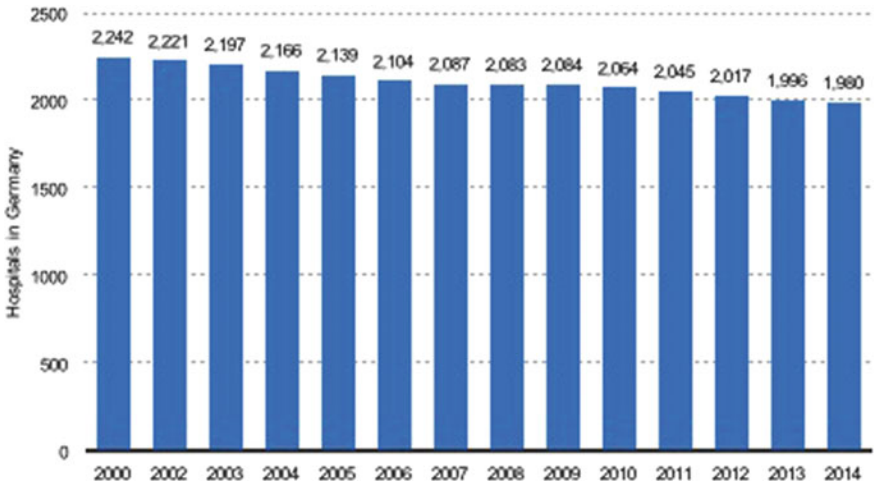


Fig. 1.5 Hospitals in Germany

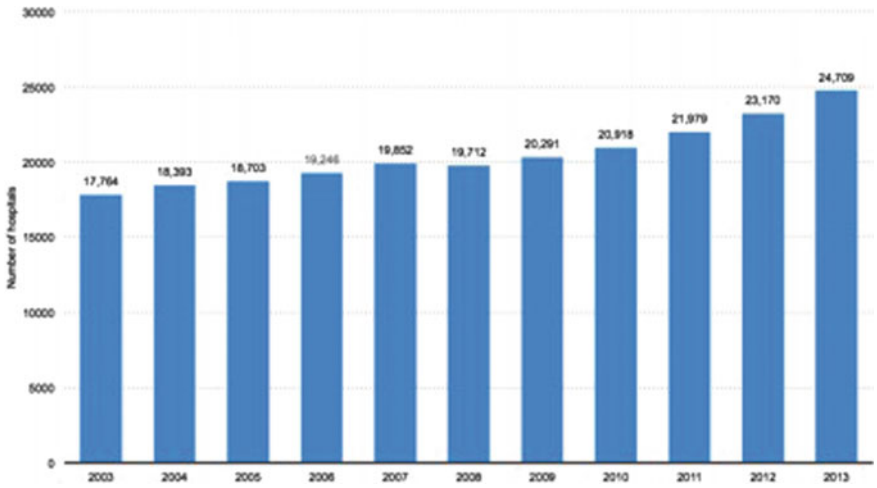


Fig. 1.6 Number of hospitals in China from 2003 to 2013

with 2.9 hospital beds per 1000 population [7]. However, while the overall number of hospitals has been stagnating in the United States, China, according to the Chinese Ministry of Health, has built around 7000 hospitals between 2003 and 2013 (Fig. 1.6). This does not mean that China is breaching the trend. The building of additional hospitals in China needs to be considered a compensatory step in support of the ongoing urbanization. However, there is growing awareness in China that the national demographic development is pointing at a significant increase of the average age of the Chinese society over the coming 3 decades and that the subsequent effects on the social systems cannot be managed by increasing the number of hospitals and hospital beds. In order to compensate for the ageing of the Chinese society over the next 30 years China would have to increase the number of hospital beds by an estimated 50 % of the current overall capacity, meaning 400 hospitals would have to be build every year. In the face of global economic downturn this seems not achievable and extremely unlikely.

Adding hospital beds seems to be counterproductive as on the one hand the capital needs to be found to build them (capital expenditure—capex) and on the other hand they need to be maintained, whereby currently more than 70 % of operation expenditure (operational expenditure—opex) goes into salaries and staff costs. The demographic projections including the provided information on the old age dependency ratios suggest that it will be difficult to find the staff to man hospitals mid and long term and it will be difficult to find the funding to cover the related costs. It seems that in the future hospitals will become means of last resort for conditions, which can under no circumstances and despite all modern technologies be treated outside hospitals.

1.3 Average Length of Stay

Overall the average length of stay typically expressed in days per episode has been declining globally. In Europe, especially for beds with curative and non-palliative or rehabilitation character the average length of stay dropped 1.8 days between 2000 and 2012 [8]. This trend has been ongoing since the eighties with much steeper declines in the early days fueled by the understanding that hospital stays might under certain circumstances be detrimental to a person's health and not always the best way forward. Good examples for detremental effects are the deterioration in mobility and muscle powers or the risk of nosocomial (hospital acquired) infections. Furthermore technological progress simply continues to provide a huge variety of solutions, which supports safe earlier discharges or in many cases allows for outpatient treatment of individuals with conditions which otherwise would have required hospitalization. Good examples is the surge of minimal invasive surgery in hospitals, outpatient cancer treatments and the reduction of hospital bed days for giving birth. Safer drugs also have expedited the management of chronic diseases and reduced the occurrence of side effects, for example the introduction of Insulin Pens and electronic blood glucose measurement devices, which have simplified the self-management of diabetes and reduced the number of accidental over- or under-medication. In Germany the average number of bed days per episode dropped between 2000 and 2012 from 11.9 to 9.2, in the United Kingdom from 10.7 to 7.2, in Switzerland from 12.8 to 8.8 and in France from 10.7 to 9.1. According to statistics published by the Chinese Ministry of Health in 2013 the average length of stay in China was 9.8 days, well in line with average European figures. Figure 1.7 depicts the drop in the average length of stay in community hospitals in the United States.

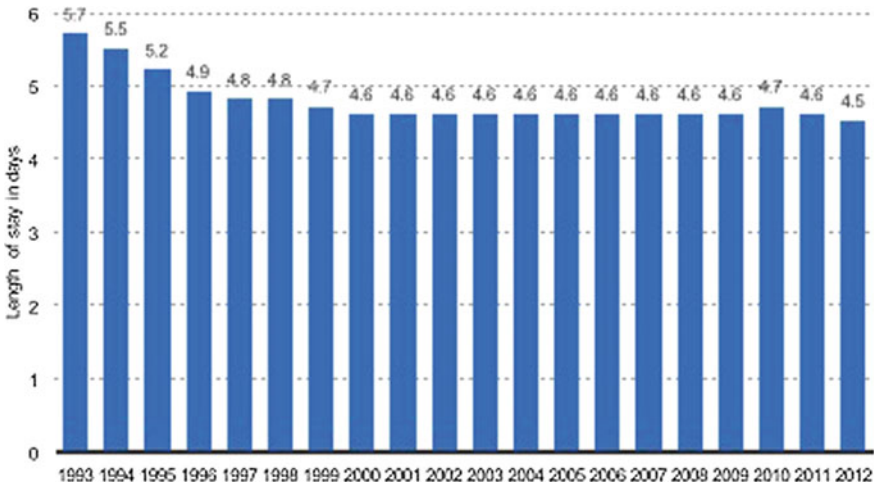


Fig. 1.7 Average length of stay in U.S. community hospitals 1993–2012 (in days)

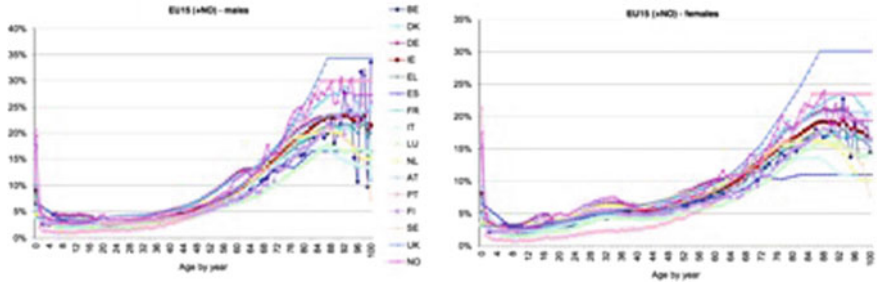


Fig. 1.8 Per capita spending by single age as percentage of GDP per capita (*Source* European Commission services, EPC)

1.4 The Health-Economic Burden of Ageing to Society

So far we found that people are getting older with fewer people to look after them and to pay for their care. At the same time the number of hospital beds have been reduced. But does old age mean higher health care expenditures? The issue has been subject to intense research and the results strongly suggest "that monthly health care expenditures for elderly people do increase substantially with age" [9, 10]. It seems that in particular the costs "from 5 years prior to death to the last year of life greatly overshadowed the 30 % increase in costs from age 65 to 85" [9]. Taking into consideration the data on old age dependency ratio we have to conclude that regardless of technological and pharmaceutical innovation this trend alone will be a massive driver for health care costs over the next 30 years. This sits very well with work on the economic and budgetary projections for the 28 EU Member States (2013–2060) recently published in the European Commission's 2015 Ageing Report [11]. Per capita spending by single age as percentage of GDP per capita is depicted in Fig. 1.8. Health care spending is clearly age dependent and there is clear evidence that ageing of the population will drive health care costs in the future.

1.5 Outpatient Care

However, taking into consideration the reduction of hospital beds and the rising demand related to the ageing of our populations there has to be some evidence for compensatory strategies allowing health care providers to deliver care via alternative pathways. We already mentioned briefly the rise of minimal invasive surgery and the associated significantly shorter average length of stay. Since the early 1980s there are growing trends to implement day clinics for the treatment of a huge variety of conditions. In England the number of day only beds rose from 2000 to 2015 from 8155 beds to 12573 beds (Fig. 1.9).

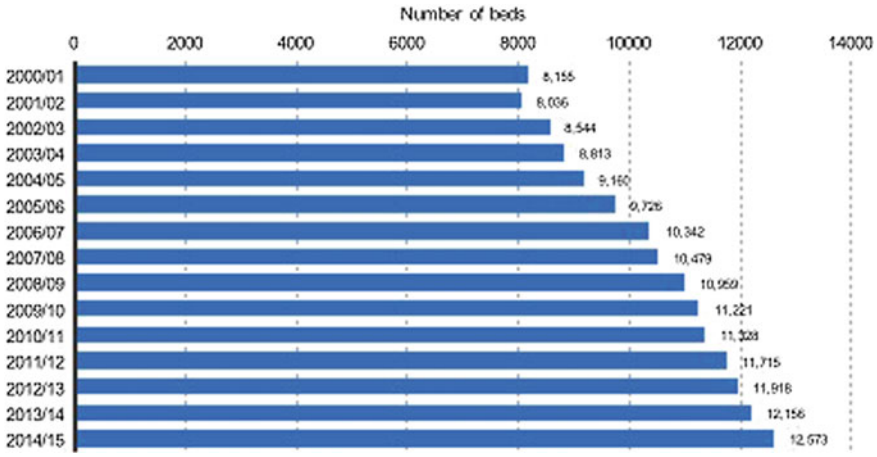
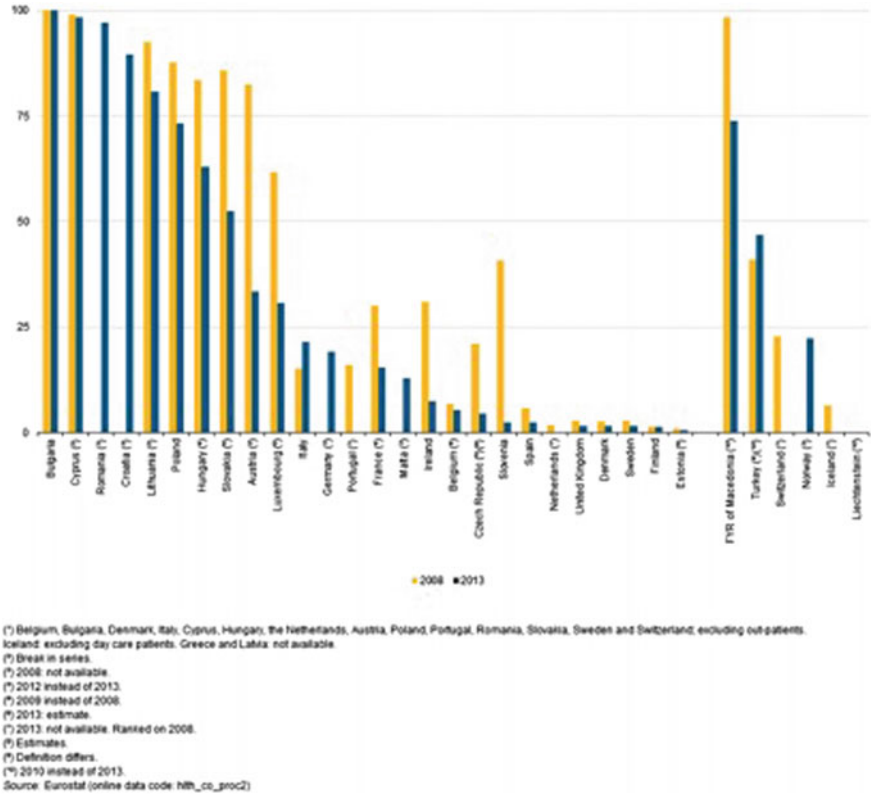


Fig. 1.9 Average daily number of day-only hospital beds available in England from 2000 to 2015 (*Source* HM Treasury)

On the other hand there is evidence for more and more surgical procedures to be performed outside hospitals or on a day surgery basis. Between 2008 and 2013 the percentage of cataract operations performed on an in-patient bases decreased significantly in a number of European countries, such as Austria, Poland, Hungary, Czech Republic and others (Fig. 1.10) [12]. But not all care is delivered in hospitals or primarily clinical facilities. The employer firm revenue of U.S. community care facilities for the elderly rose from 2006 to 2013 from 37 billion to 53 billion USD. In the United Kingdom the number of people employed in social work with elderly and disabled people has more than doubled from 2008 to 2014, from 125,000 to 264,000 per year [13]. Moreover, according to the National Audit Office UK in 2013 5.43 million so called informal carers, carers without a formal qualification, have been involved to provide social care to adults in England.

All the data available point towards a fundamental change in the way care is going to be delivered in the future. We see a reduction of hospital beds predominantly in Europe but also in the US. China has added hospital beds but this has mainly been driven by a backlog and a need to catch up with the standards set in the international community. The average length of stay in hospitals is decreasing and more care is delivered in day clinics, outpatient departments and in the community (nursing homes, patient homes, GP practices). In fact, the hospital is unlikely to remain the centerpiece of health care provision as care will be delivered in many different ways and settings. Also, progressive specialization will continue to fragment healthcare to a degree where it will be extremely difficult for GPs, patients and carers to sustain a general overview of the different dimensions of care and points of care and also administrative, billing and quality control elements (Fig. 1.11).



(*) Belgium, Bulgaria, Denmark, Italy, Cyprus, Hungary, the Netherlands, Austria, Poland, Portugal, Romania, Slovakia, Sweden and Switzerland: excluding out-patients.
Iceland: excluding day care patients. Greece and Latvia: not available.
(*) Break in series.
(*) 2008: not available.
(*) 2012 instead of 2013.
(*) 2009 instead of 2008.
(*) 2013: estimate.
(*) 2013: not available. Ranked on 2008.
(*) Estimates.
(*) Definition differs.
(*) 2010 instead of 2013.
Source: Eurostat (online data code: hlth_co_proc2)

Fig. 1.10 Share of in-patient procedures for cataract surgery, 2008 and 2013 in % (*Source* Eurostat)

Furthermore there will be growing involvement of carers without formal qualification who have to be considered a vital and affordable source for individual care packages who need to be integrated into the individual care plans and networks, alongside professional carers in a safe and secure manner.

1.6 Healthcare Costs and Spending

Healthcare costs are widely considered a burden to society and a threat to national budgets. But this of course is only one way of looking at it. Healthcare accounts in Europe for roughly 10 % of the GDP and in the United States for around 18 % of the GDP. Therefore healthcare can also be considered the biggest and fastest growing industry on earth, contributing large and reliable growth rates to the local economies. This of course is also related to huge commercial chances and opportunities. These opportunities are not necessarily limited to hospitals, the

Fig. 1.11 Fragmentation of Care

pharmaceutical industry or health insurers, but will become relevant to telecommunication providers, network operators and software developers. This process has already started. Denmark and Austria run nationwide platforms, which are instrumental to large-scale data collection and also allow their citizens to access their health data online [14, 15]. Health care costs have been rising continuously since the 70s in almost all countries in the world. In many countries the growth of healthcare costs has been well exceeding GDP increases in relative terms. Figure 1.12 provides a comparison of French, German, British and OECD figures. The economic crisis of 2007 is visible as a short slowdown in the otherwise steady increase. It is clearly visible that not even concerted austerity measures could curb health care expenditure growth. The slowdown of 2007 has been immediately compensated to an even steeper increase in the following years. In 2016 the UK government had no choice but to commit to increase the budget allocation of the National Health Service by 10 Billion GBP over the coming years to prevent a massive crisis. Due to most recent developments serious doubts have been casted on whether this figure will even be enough.

While typically in Europe a good approximation for healthcare spending as share of the GDP is 10 % this figure is considerably higher in the United States. In the

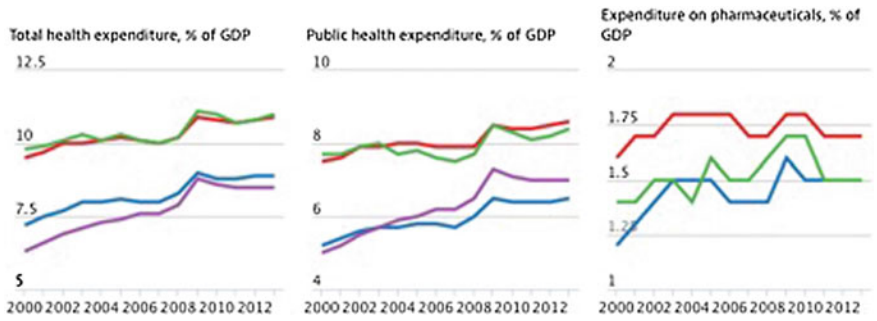


Fig. 1.12 Health expenditure as share of the GDP selected countries (*Source* OECD). *Red* France, *green* Germany, *purple* United Kingdom, *blue* OECD countries (no data for expenditure on pharmaceuticals as % of GDP were available for the United Kingdom)

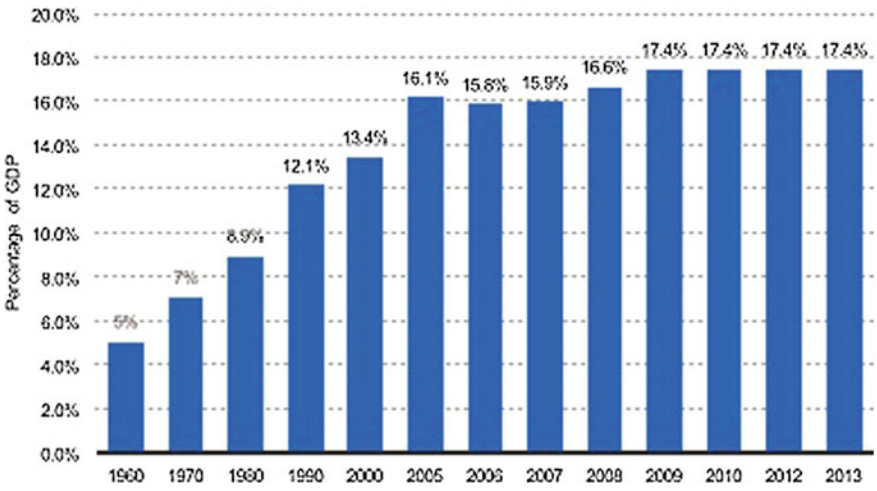


Fig. 1.13 U.S. national health expenditure as percent of GDP from 1960 to 2013 (*Source* CMS—Centers for Medicare and Medicaid Services)

United States the current overall spending on healthcare is around 18 % and expected to grow further. Figure 1.13 gives an overview about the U.S. healthcare cost development between 1960 and 2013 [16]. While the annual growth rate on public expenditure on health care and birth control in China has dropped from 2011 to 2014 from 32.5 to 9.8 %, the per capita expenditure of urban households on health care and medical services has risen from 25.67 Yuan in 1990 to 1305.60 Yuan in 2014 [17]. This equals a rise of more than 5000 per cent over 24 years (Fig. 1.14). It is pretty obvious that the growth rates in global health care spending are not sustainable on the long run. On the other hand there is a clear indication that governments and the wider public is willing, ready and able to spend significant amounts of their available funds on health and care.

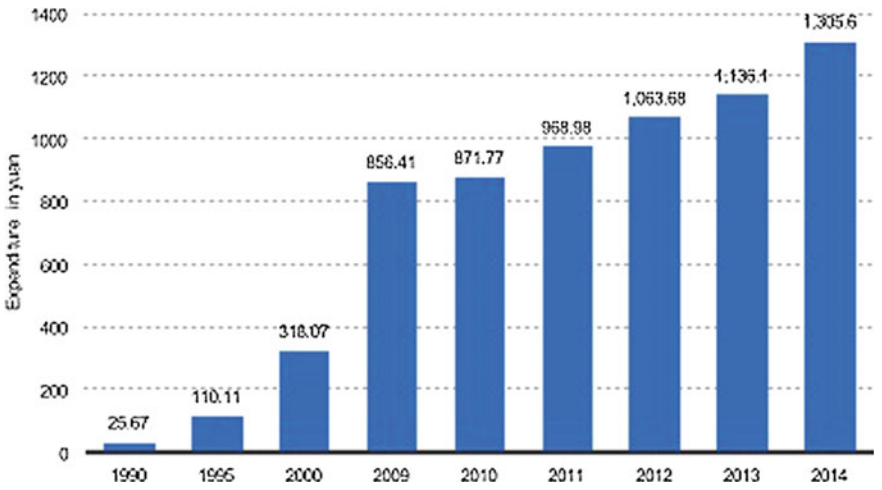


Fig. 1.14 Per capita expenditure of urban households in China on health care and medical services from 1990 to 2014 (in Yuan)

With regards to the implementation of Industry 4.0 principles in the health domain an outlook into the projections of global health care expenditure might be of interest. According to projections by the King's Fund based on data from Kibasi et al. (2012) there will be a significant increase in healthcare spending as share of GDP by 2040 in selected countries [18, 19]. Based on figures from 2007 two scenarios are offered in order to depict potential variation (Fig. 1.15).

While long-term projections in real term are notoriously difficult due to a huge variety of factors including in particular the long term prediction of the GDP trend analysis over the coming 5 years is relatively stable. In a recent projection by Deloitte healthcare spending in Germany is expected to grow from 411.5 billion USD in 2013 to 470 billion USD in 2018 [20]. According to the U.S. Centers for Medicare and Medicaid Services, CMS healthcare spending in the U.S. is expected to grow at an average annual rate of 5.8 % between 2012 and 2022. The expected growth for 2014 was 6.1 % and an average annual growth of 6.2 % was projected for 2015. By 2022 the overall health care spending in the United States is projected at 19.9 % of the GDP [21]. According to Forbes annual health care spending in the U.S. hit 3.8 trillion USD in 2014 and is on track to hit the 10,000 USD per capita mark in 2015 [22, 23]. Healthcare expenditure in China is predicted to reach 1 trillion USD by 2020 [24].

While on the one hand there can be no doubt that the health care industry is an industry with substantive growth potential there are considerable challenges due to the fact that at least the public component regardless of the private out of pocket spending needs to be financed by the national governments on a year on year basis. Due to an uncertain fate of national GDPs in the light of a decreasing work force and increasing old age dependency ratios governments are pushing for solutions to cool down the overheating health care market and keep care affordable. In the UK

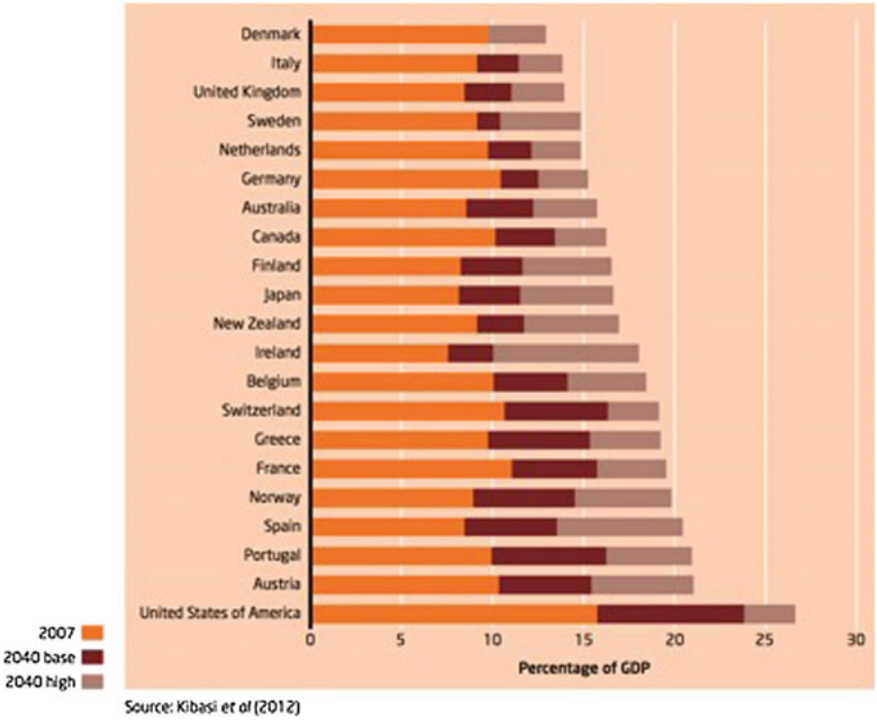


Fig. 1.15 Projection of potential growth in health care spending by 2040 by the King's Fund (*Source* Kibasi et al. 2012)

the National Information Board has published a report offering initial ideas to mobilize efficiency reserves in the English National Health Service—NHS. One of these strategies is to use Information Technologies, smart phones and smart devices to empower less qualified individuals to take on the routine tasks of higher qualified individuals, especially with regards to the provision of care for the elderly [25]. For some time now national governments have pushed for data exchange—and management platforms not only to exchange data among healthcare providers, but also to establish frameworks to empower patients to take on a more active role in the management of their own health. National health platforms such as ELGA in Austria and Sundhed in Denmark not only allow for collection of data on public health but also enable the integration of healthcare professionals and so called informal carers, relatives, friends and volunteers for the provision of individualized care in the community. As the classical one to one care models will simply not be affordable any more in times when a significantly larger share of the population is older than 65 years of age these data platforms are going to be instrumental in the progressive virtualization of care. There can be no doubt that additional technology will require initial investment over a considerable time before any positive effects will be visible. Considerable underinvestment into hospital IT in Europe and

elsewhere over many years has left legacy systems in a poor state and health care providers cannot be expected to exclusively carry the burden of a revamp of local healthcare infrastructures. Fortunately stakeholders such as pharmaceutical industries, telecom operators, network providers and patients are willing to support new initiatives based on latest information technology.

1.7 Mobile Phones and Smart Devices

The arrivals of mobile phones and portable computers in the late 1980ies was the start of an information communication technology revolution which not only fundamentally changed our lives but also the way how we are earning our money, do business, shop, bank and interact. Text messages and emails have emerged as communication standards. Online banking and online shopping have become widely accepted alternatives to the actual physical act of entering a bank or a shop. Purchasing of airline tickets is almost exclusively taking place over the Internet. We "google" our way through our modern worlds and promote ourselves through web pages, linkedin and on Facebook. The digitalization of our world is by many people considered a third industrial revolution, following a first industrial revolution through automation with steam and thereafter a second industrial revolution, namely the massive increase of productivity through the role out of electricity.

While the first relatively simplistic mobile telephones would allow for audio communication and the sending of text messages in 2G mode, today's smart phones are multifunctional devices with considerable build in storage and processing power, exceeding by far the specifications of the Apollo Guidance Computer (ACG), which was present at the Apollo 11 Mission which brought the first man to the moon. The ACG had approximately 64Kbyte of memory and operated at 0.043 MHz [26]. These days' modern smart phones hold typically a dual core 1.8 GHz processor and anything between 32 and 128 GB storage. Crucial for the context of this book is the fact that smartphones have turned out to become standardised mass products, which are available and operable almost everywhere on this planet. The amount of mobile connections exceeds more than 7.6 billion and thus the number of people on earth. There are more than 3.7 billion mobile subscriptions of which 2.6 billions are smart phones [27]. According to Ericsson the number of smart phones is set to more than double by the end of 2020, from 2.6 billion up to 6.1 billion [28]. At the same time 3G and 4G coverage is spreading, covering more and more geographical areas. The concept of 4G long-term evolution (4G LTE) is set to improve services by expanding into other underutilized frequencies, such as 800 MHz (LTE 800) and also seeking ways to integrate specific Machine to Machine (M2M) communication. M2M communication might be instrumental for the integration of a huge variety of medical devices such as

implants, artificial organs such as pace-makers, insulin-pumps, brain-pacemakers and others and might also be instrumental in the collection, integration and aggregation of data obtained from pharmaceutical products that might be IT enabled. 5G technology is now seeking to provide optimization with regards to providing connectivity of 100 times more devices per geographical area, reducing end-to-end latency to less than 5 ms and increasing the reliability, thus attempting to making a fast advanced network, such as 5G, serviceable [29].

1.8 Uptake of e-Health and m-Health Technologies

The effort to make integrated healthcare work utilizing e-health and m-health applications and latest network technology such as 4G LTE has sound economical foundations. Fueled by the permanently improving availability of smart phones and rapidly improving connectivity m-Health hardware and software is becoming increasingly popular. A forecast by the European commission predicts the global value of the m-Health market to be 17.6 billion Euro by 2017 (Fig. 1.16).

People already use a variety of applications, mostly for wellness and recreation purposes. However, the vast majority of data are generated by contemporary software and hardware products, which are typically not licensed for medical use under medical product regulations. Most software products are not standardized and there are ample security and interoperability issues. However, the contours of

Fig. 1.16 The Global m-Health market by 2017 (*Source* European Commission)

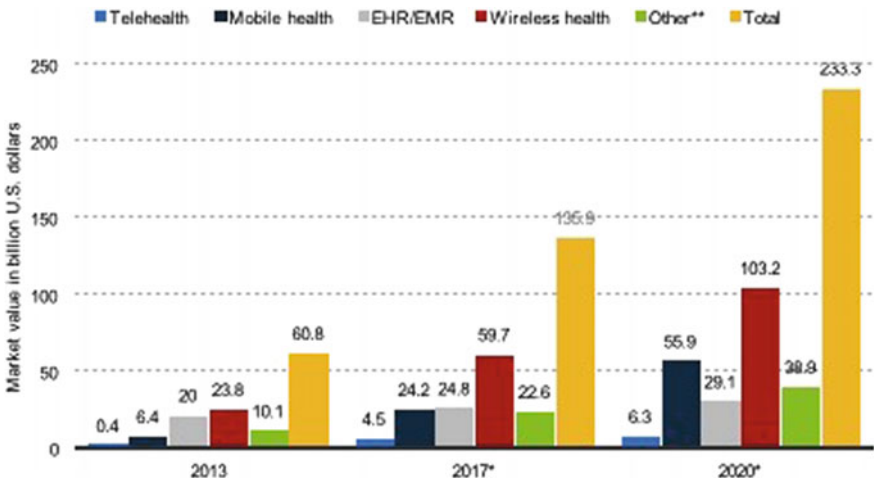


Fig. 1.17 Global digital health market from 2013 to 2020, by segment (in billion U.S. dollars) (*Source* Arthur D. Little, GSMA Intelligence)

emerging hyper-connected health and care platforms are already recognizable. Denmark and Austria have implemented integration platforms for health care providers which also allow citizens to monitor their electronic health records via a variety of devices such as smart phones, tablets and laptops [14, 15]. Most recent figures by GSMA Intelligence provide an overview over global digital health market including e-health, m-health, telemedicine, electronic health care markets and others (Fig. 1.17). The total market volume is expected to grow from 60.8 billion USD in 2013 to 135.9 billion USD in 2017 and to reach 233.3 billion USD in 2020.

The m-health market currently seems to be driven by sales in the United States and in Europe. According to figures provided by PWC the 2017 per capita spending on m-health in the U.S. is predicted to be 17.7 USD followed by 7.7 USD in Europe and 1.6 USD in Asia-Pacific (Fig. 1.18). Most recently the German federal government has announced a 100 million Euro initiative to boost the backbone development in the 33 German university teaching hospitals [30]. However, this can only be considered a starting point as Germany has an overall hospital count of roughly 2000 not to mention thousands of GPs, specialists, dentists and physio-therapists in free practice. 5G Whitepapers already discuss future options for health applications [29, 31, 32]. While over recent years one focus of the discussion has revolved around the Internet of Things (IoT), its sensing capabilities and the associated interoperability issues the focus in the application research community is now shifting more and more towards the integration of the virtual and the physical world. Cyber-physical systems are pushing the boundaries with regard to the integration of the virtual and the real world [33].

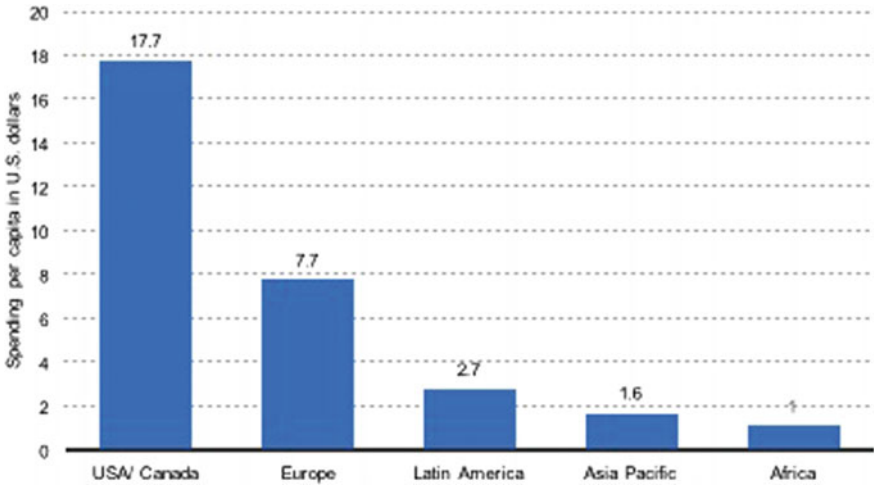


Fig. 1.18 Mobile health spending per capita in 2017, by region (in U.S. dollars)

1.9 Nomenclation, Norms and Standards

The Global Observatory for eHealth (GOe) published by the World health organization (WHO) defined in 2011 mHealth or mobile health as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices" [34]. However, there are no binding definitions and strict demarcations with regards to the different domains summarized under the label e-health. Very often terms such as telemedicine, telehealth, m-Health, e-Health, digital health, digital medicine and lately Precision Medicine and individualized medicine are used synonymously.

Efforts are under way to structure the relevant standards. However interoperability allowing an easy plug-and-play approach among components is still a challenge. Organizations such as the Association for Internet of Things Innovation (AIOTI) is working towards harmonization of the IoT domain within the e-health domain (Fig. 1.19). Other organizations, such as the European Telecommunication Standards Institute (ETSI) are working towards harmonization in the telecom sector contributing to the telecommunication element of e-Health. Standards such as ISO standards and IEEE standards also play a role in the healthcare domain and need to be considered. With regards to M2M there are several relevant standards to be considered.

On the regulatory side of things more and more regulations and legislative norms, such as the German e-health legislation are put in place and need to be honored in order to build stable business cases.

Fig. 1.19 AIOTI Standards mapping as per October 2015 (*Source* AIOTI)

1.10 Towards Health 4.0

Demographic and socio-economic shifts will enforce deep structural changes to the way health care is delivered in Europe, the U.S., China and elsewhere. On the one hand the number of people older than 65 will grow dramatically, while at the same time those in the working age between 15 and 64 will deplete rapidly. The lifting of the retirement age will not be sufficient to curb this trend. On the other hand health care costs will continue to grow due to the availability of new technologies, pharmaceutical substances and higher individual expectations towards health and care. One of the big trends currently is the implementation of integrated care platforms and the virtualization of care. Eventually, care cannot be delivered any more in one-onto-one settings but routine tasks and processes need to be automated and delivered from the virtual world into the real world. Distributed, virtualized services will be used to enable patients and lesser qualified informal carers to take on routine tasks, which otherwise would be delivered by qualified professionals. Hospital care will continue to become a last resort strategy for otherwise unmanageable conditions. Embedded and cyber-physical systems will enable and empower individuals to take a bigger stake in their care and in the administration of it. Patients and their carers might manage individual care budgets and decide for example when suffering from multiple, chronical conditions, which priorities to set with regards to the global management of their care. Health care systems in Denmark, Austria, Germany and the UK are working on the implementation of new services on top of the existing health care legacy systems designed to add value by

primarily increasing the efficiency. Google and Sanofi [35] just recently announced a 500 Million USD investment into a joint venture to offer management support to 600 Million people with diabetes by 2035. Vertical integration across selected services and the horizontal integration between different service domains will become increasingly important. Interesting enough there seem to be remarkable parallels with the manufacturing industry in Europe. In 2015 the Audi Foundation Professorship at Technical University Dortmund published a literature review on Industry 4.0 design principles [36]. As a result, 6 distinct design principles were highlighted:

- Interoperability
- Virtualization
- Decentralization
- Real-time Capability
- Service orientation
- Modularity

In Chap. 2, "Application of Industry 4.0 Design Principles in the Health Domain (Health 4.0)" we will examine if these general Industry 4.0 design principles are applicable in the highly regulated health domain and whether these design principles are compatible with the requirements resulting from the specific status of health infrastructure as "critical infrastructure". Critical infrastructures are infrastructures vital to the day to day functioning of public life.

1.11 Drivers Towards Health 4.0

In 2015 an initiative on what has been called Precision Medicine has been announced in the United States [37]. The idea was to manage especially chronic, non-communicable diseases in a more precise manner by collecting information ideally in real time from patients and process them with smart algorithms in order to describe the actual state of a patient more precisely and have a much better understanding about the current state of affairs with regards to the management of the health of a particular individual. This includes also the individual genomic analysis to be able to predict whether or not a patient and a certain condition might respond to a drug or pharmaceutical substance. This could mean that patients might be spared unwanted side effects in case it might be possible to predict that a therapy would not have a big impact on their particular condition. In Europe and other parts of the world the term "Precision Medicine" was perceived as somewhat misleading and it was felt by some that the emphasis should be clearly put on the individualization of care. However, in order to individualize therapy and adjust it more to the real time requirements of any given patient the most recent state of the condition needs to be assessed in real time using latest technology. Given the rapid progressive roll out of Internet of Things (IoT) technology it is safe to assume that in

principle the front-end technology to do so is available and that remaining interoperability issues are being addressed [38]. However, there are certainly challenges on the network level. The role of the emerging 5th generation mobile network (5G) as an enabler for the IoT has been frequently discussed and is widely accepted [39]. However, 5G is not a homogeneous, clearly specified technology. In fact, we can see the contours of it but so far it is not precisely defined. It is most likely that 5G will consist of a mix of technologies with different capabilities, operating on different frequency bands. While classical mobile phone frequencies will certainly be the backbone for video streaming and telephony, a huge part of anticipated future traffic will fall onto Low Power Wide Area traffic, utilizing alternative radio access technologies (RATs) such as Narrow Band—IoT(NB-IoT) or LoRa [40, 41]. NB-IoT has been recently standardized by 3GPP a relevant standardization body. Machine to machine traffic is also supported by several strong standards such as One M2M or HyperCAT [42, 43]. Most recently there have been suggestions to also use mm Wave technology to utilize frequencies in the upper part of the spectrum (15 GHz and beyond). US carrier Verizon has announced experimentation with mm Wave fixed mobile access for as early as 2017 [44]. Overall the technical prerequisites for the implementation of technologies for ecosystems in the health industry to support progressive virtualization of care and service deployment across domains and networks are almost there. New services such as smart pharmaceuticals, supply chain management from hospital to home, translation of care environments from hospital to home in almost real time have moved into the reach of patients, health care providers and professionals. There is a massive push by large cloud providers such as IBM and Google to place their public cloud products in the market [45, 46]. However there are question marks, at least in Europe, about the suitability of public cloud approaches in health care. There is a longstanding issue about the proof and monitoring of Quality of Service in public cloud infrastructures. It is unclear how patients, insurers and health care providers can assure themselves, that their data have been treated with the appropriate level of confidentiality, especially if data is migrated to or shared with out of state or even out of continent servers? Future solutions might result from software to data research, where not the data is moved to software but the software is moved to the data in order to meet growing privacy requirements [47].

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Chapter 2
Health 4.0: Application of Industry 4.0 Design Principles in Future Asthma Management

Christoph Thuemmler and Chunxue Bai

2.1 Industry 4.0

Industry 4.0 is a well-known industrial concept leveraging individualization and virtualization across different industrial domains. At its core Industry 4.0 strategies empower industries to evolve from manufacturers to service providers, allowing growing amounts of individualization and personalization as a service to client, customers and most likely to patients and formal and informal carers. Recently Hermann, Pentek and Otto proposed an Industry 4.0 definition and suggested Industry 4.0 core components and design principles for Industry 4.0 scenarios on the basis of a comprehensive and systematic literature review [1]. The aim of this chapter is to investigate the applicability of the authors' findings on to the health domain and in particular investigate the scalability of Industry 4.0 design principles into relevant sub-domains such as the pharmaceutical industry.

2.2 Industry 4.0 Components

Hermann et al. started their investigation by suggesting Industry 4.0 components based on their literature analysis. The proposed core components are:

- Cyber-Physical Systems
- Internet of Things (IoT)

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- Internet of Services
- Smart Factories

2.2.1 Cyber-Physical Systems (CPS)

According to Lee, Cyber-Physical Systems (CPS) refer to "integrations of computation and physical processes. Embedded computers and networks monitor and control the physical processes, usually with feedback loops where physical processes affect computations and vice versa" [2]. More recent work on CPS includes socio-economic factors into the definition stating, that "Through cyber-physical systems, the physical world is linked with the virtual world to form an Internet of Things, Data and Services" [3]. For the health domain concrete applications might be the connection of Body Area Networks and sensors in Smart Pharmaceuticals to disease management platforms with either autoregulatory feedback loops or feedback via accessories such as smart phones.

2.2.2 Internet of Things (IoT) and Internet of Services (IoS)

There can be no doubt that things as well as an Internet of Things (IoT) are playing an increasing role in the health care industry and in ambient assisted living, (AAL). The Hyper-connected Society is a vision where the Internet of Everything [IoT, Internet of Services (IoS), Internet of People(IoP)] will create added value and generate growth and prosperity by unleashing digital technological progress [4]. It is arguable if the IoS and the IoT can really be distinguished under an Industry 4.0 approach as the very objective of Industry 4.0 approach seems to be the virtualization of physical processes and its translation into services. However, for the health domain it is clear that things such as smart devices, biosensors, artificial organs, and smart pharmaceuticals are a reality, and one of the key targets of the European digital agenda is clearly to group services around these objects to virtualize the provision of care. The European eHealth Action Plan 2012–2020 is described by the European Commission as "The European Commission's eHealth Action Plan 2012–2020 provides a roadmap to empower patients and health care workers, to link up devices and technologies, and to invest in research towards the personalised medicine of the future" [5]. This clearly constitutes a justification for research on the medical Internet of Things and its enabling technologies such as the 5th generation network (5G).

2.2.3 Smart Factory

Smart factories are considered a key feature of Industry 4.0 and are defined as: "a factory that context-aware assists people and machines in execution of their tasks. This is achieved by systems working in the background, so-called calm-systems

and context aware means that the system can take into consideration context information like the position and status of an object. These systems accomplish their tasks based on information coming from the physical and the virtual world. Information from and about the physical world is e.g. position or condition of a tool, in contrast to information from and about the virtual world like electronic documents, drawings and simulation models" [1, 6]. Hospitals and distributed health care providing structures such as GP networks, community nurses, pharmacies, etc. can be without doubt considered "factories" which "context-aware assists people and machines in execution of their tasks." This happens for example through hospital information systems (HIS) or practise IT systems. Current flaws in health care environments are clearly that real time information is only available in a limited manner, so that work-flows cannot be depicted accurately. Sometimes it is not possible to establish beyond doubt where the patient or professional is located or what their current status is. The typical fall-out are disruption to operating schedules when the team is ready in the operating theatre but the patient has not arrived or if patients experience extended waiting times in A&E and outpatient departments. The smartness of "medical factories" might be lagging behind the "smartness" used in other industrial domains. However, this is likely to change in the near future as socio-economic requirements will force health care providers and national economies to find ways to enhance efficiency and effectiveness of health care systems.

2.3 Definition of Industry 4.0 and Its Scalability into the Health Context

Based on the findings of their comprehensive literature analysis Hermann et al. define Industry 4.0 as follows: "Industry 4.0 is a collective term for technologies and concepts of value chain organization. Within the modular structured Smart Factories of Industry 4.0, CPS monitor physical processes, create a virtual copy of the physical world and make decentralized decisions. Over the IoT, CPS communicate and cooperate with each other and humans in real time. Via the IoS, both internal and cross-organizational services are offered and utilized by participants of the value chain [1]."

Value chain organization is paramount to health care industries in order to enhance their effectiveness and efficiency in the face of growing budget pressure. Good examples for shortcomings are counterfeiting issues and unnoted expiry of drugs and medical consumables. Counterfeiting or selling of faked drugs can have a devastating impact onto the quality of care. "Counterfeiters have claimed around a third of the entire market—worth some $200 billion—and are implicated in the deaths of up to one million people each year due to toxic or ineffective drugs" [7]. The uncontrolled expiry of drugs and medical consumables is a substantive challenge to health care organizations in Europe and elsewhere worth billions of Euros

each year. Patient flow and patient pathways are the classical models of value chains within the health care industry and thus the health care industry is not any different from any other industry with regard to value chains. It is likely to benefit highly from the implementation of Industry 4.0 technologies and concepts. Future health care will definitely be structured in a modular manner as specialization grows and the global health care model is progressively shifting from a hospital-based professional oriented to a distributed, patient centred care model [8]. One of the core features of distributed patient centred care is that care elements and services are grouped around the patient. Cyber-physical systems (CPS) are not yet introduced to the medical domain but the process has begun. Pharmaceutical companies are working on smart pharmaceuticals, which are fitted with biosensors in order to enable and support the link between the physical and virtual world. Big Data strategies are being tested to cater for individualization and personalized care. New strategies such as Precision Medicine will be based on real time connectivity between patients (physical world) and cloud based algorithms and autonomous systems (virtual world). This will lead to individual combination of cross-organizational services which will be heavilly depending on real time information. This development is coming at a time where new care models call for individual patient budgets offering patients and informal carers more influence and control in managing their health and putting the relevant resources at their disposal [9]. This will have to be supported by new features and functionalities of 5G such as multi-domain orchestration and multi-tenancy.

2.4 Industry 4.0 Design Principles

Industry 4.0 design principles have recently been investigated through a comprehensive literature review by Hermann et al. [1]. The authors analyzed 51 publications related to predefined search terms and identified a set of recurring design principles closely linked semantically to Industry 4.0 and the predefined search terms. The following design principles have been proposed by Hermann et al.:

- Interoperability
- Virtualization
- Decentralization
- Real-time capability
- Service orientation
- Modularity.

2.4.1 Interoperability

The importance of interoperability has been highlighted frequently in the IOT discussion and has recently been pinpointed again in the context of health in the

EU-China white paper on the IoT [10]. In "smart factories" and "factories of the future" interoperability is crucial to enable the seamless flow of contextual information on all levels. Looking at biosensors as part of cyber-physical systems and their back-ends in the virtual domain seamless interoperability is important to enable the entire system loop to perform and continuously exchange information. In cyber-physical systems, it is also important that different services can be aggregated and integrated in order to establish the quantum leap from data readings towards the generation of meaningful information. In a report published by the European Commission on the public consultation on eHealth Action Plan 2012–2020 lack of interoperability has been identified as one of the main barriers preventing the large-scale deployment of eHealth in Europe [11]. In this context, there can be no doubt that interoperability is an important design principle of Health 4.0 solutions.

2.4.2 Virtualization

Hermann et al. highlight that "CPS are able to monitor physical processes" and that "a virtual copy of the physical world is created." According to Hermann et al. in Smart Factory plants "the virtual model includes the condition of all CPS." Doubtless these trends are valid for the health domain in many ways. The monitoring of physical processes is the very essence of what is happening in health related processes every day. Patients are being monitored by cyber-physical systems during surgical procedures involving anesthesia every day in a widely standardized process everywhere in the world. However, the sensors placed onto or into a patient by a medical practitioner during syrgery are island solutions. One key challenge is that in most cases these islands are closed loop systems and cannot be connected with other systems, for example the hospital information system (HIS). Also, due to the complexity of the system "human being," it is so far not possible to create a copy of the entire "physical world" at any time. However, in the health context a valid question is certainly in how far this is reasonable and necessary. The monitoring and virtualization of defined sections of the system might be sufficient until future technologies will allow for more extensive and easier virtualization. The challenge in the health domain is currently the seamless and autonomous virtualization anywhere, anyhow and at any time. This is of particular interest to new strategies, which are aiming to allow for individualization of therapies especially in order to treat chronic, non-communicable diseases [12]. Interesting enough the use of sensors to create CPS in order to enhance the value chain is a concept which is currently boosted by all major pharmaceutical companies for certain chronic, non-communicable conditions, including asthma. Details shall be discussed in the use case section on asthma later on in the paper. Summarizing the analysis, it is fair to assume that the design principles of virtualization seems to be valid for the health domain.

2.4.3 Decentralization

Decentralization in health care has been ongoing since the late twentieth century. Hospital bed numbers have been in decline almost all across Europe and OECD countries for years [13]. This trend is generally perceived as challenging as it does not seem to give sufficient credit to the demographic developments in most countries. On the other hand, more and more patients are being treated in GP surgeries, day clinics, their homes, and over the Internet. Market analysis by the European Commission suggests that mHealth market value will increase to almost 18 billion Euro worldwide by 2017 [14]. Also more and more devices are sold in a bit to measure fitness and wellbeing, such as fit-bits, smart watches, and others. However, there are concerns regarding the accuracy and suitability of these devices. Governance and liability issues are still pending and are so far not solved. The estimated amount of health and wellness related applications on the market is well beyond 100,000. In fact, Forbes predicts that "in 2016, users will trust health apps more than their doctors" [15]. Again only very few apps have been undergoing rigorous testing and even fewer offer guarantees with regard to accuracy.

While there can be no doubt that health care is moving toward a distributed patient centred model with patients, professionals and formal and informal carers increasingly using sensors, smart devices, smart phones, applications and cyber-physical systems, ever more sophisticated requirements are building up with regard to network and telecom providers. Distributed patient centred care requires a seamless and reliable flow of information across different networks and domains. The sophisticated requirements of various industrial domains including health care have led to a variety of white papers by the telecommunication industry [16, 17]. A recent document from the National Health Service (NHS) in England lays out strategy plans to utilize information communication technology to enable patients and their carers to shift more treatment from hospital to home without necessarily increasing the pressure on their outpatient services [18]. Herman et al. explicitly referred in their paper to the use of license plate technology such as barcode and radio-frequency identification (RFID) in Smart Factories in order to enable autonomous decision making. This practice has been used widely in the NHS in England and other national health services [19, 20]. Another important aspect is the consideration of the deployment of intelligence and processing powers into networks. Mobile Edge Cloud (MEC) computing has become more than a buzz-word. It is an attempt to support decentralized decision making at the edge of the network in order to reduce latency and enhance security. MEC is now a popular topic for major network technology providers.

Overall there can be no doubt that decentralization is an ongoing trend in the health domain causing a strong technology pull in order to realize Industry 4.0 design principles. This development is crucial in order to release efficiency reserves in health care and meet the socio-economic requirements of the next decade.

2.4.4 Real-Time Capability

Real-time capability is of general importance for any factory style operation regardless of which domain to ensure proper orchestration of processes. Part of the concept of Individualized Medicine or in the US Precision Medicine is clearly the real-time recognition of individualized requirements in a distributed manner. Patients should wherever possible be treated outside hospitals with exactly the amount of medication required to maximize therapeutic effect and minimize side effects. Disgnostic and therapeutic processes should confluctuate and form a spatio-temporal entitiy. This is related to the concept of "theragnostics" where therapy and diagnostics amalgamate and move closer to real time [21]. Real-time capability as a crucial requirement in the health domain in order to move closer to the implementation of personalised medicine, smart pharmaceuticals and supply chain management.

2.4.5 Service Orientation

Herman et al. give a high level overview of "customer centred" service aggregation where the IoT, the IoS and IoP may add to a set of individualized aggregated services in their Smart Factories vision. This vision is in principle also valid for the health domain and service orientation can therefore be acknowledged as a design principle of Health 4.0. Moreover there is a clear trend by pharmaceutical Industrys towards a shift from being a manufacturer of drugs to becoming a service provider in the health industry. The general underlying idea is to harvest "Big Data" from a huge variety of sensors in smart pharmaceuticals such as smart inhalers and Insulin pens in order to prevent exacerbation and serious episodes, reduce sick days and hospital admission and increase the quality of life, thereby cutting costs and dependencies. From a business model perspective this might mean that a pharmaceutical company not only will sell a drug but will sell disease management as a service. On the other hand procurers for health care providers might soon only accept products, which go beyond the bare delivery of drugs and the ability to deliver patient health data via a defined interface might be an entrance requirement to enter a tender. Patients might be able to authorize the use of their data as a service and sell the data to pharmaceutical companies to speed up trials. All of these scenarios are currently under discussion and the upcoming 5G networks will act as an enabler to boost the service orientation in the health domain. Eventually network slice technology and edge cloud technology will leverage service aggregation across different domains and networks.

2.4.6 Modularity

Herman et al. state that "Modular systems are able to flexibly adapt to changing requirements by replacing or expanding individual modules. Therefore, modular

systems can be easily adjusted in case of seasonal fluctuations or changed product characteristics." The advantages of modular systems have been already proven for the health domain as part of a recent large-scale research project funded by the European Commission [22]. Under the FI-STAR project modular software components (Generic Enablers and Specific Enablers) were utilised to create new functionality by simply recombining the different active groups. The application of rules reflecting norms and standards together with software modules has proven to be an effective way of building code faster and establishing new functionalities from predefined building blocks [23]. In the future software modules and algorithms will be offered by vendors such as Google and IBM Watson and will be readily deployed as Software to Data in hospital or health care facility edge clouds. FIWARE, a pan-European initiative has already published a catalogue where the features and interface specifications of modular software elements are highlighted. User may assess and evaluate the catalogue in order to choose from a variety of products to suit their needs [24].

2.5 Safety, Security, and Resilience

Hermann et al. do not touch in their article onto the security dimension. However, from the point of view of the health domain this is an aspect, which cannot be left uncommented. Health care is considered a "critical infrastructure" vital for the day-to-day running of any state. The protection of the functionality of health care infrastructure and the privacy of the personal data is paramount. This might be different from a Smart Factory where security breaches might cause economic losses or structural damage but does not trigger massive liability for personal "secrets" or loss of lives. From a Health 4.0 perspective safety, security and resilience need to be considered hard design principles to protect confidentiality and prevent all stakeholders from incalculable and unpredictable risk. Trust is one of the fundamental principles of health care and is a legal requirement anchored in national legislation and European directives. While there might not be an immediate need to prioritize safety, security, and resilience as a general Industry 4.0 requirement these topics are basic requirements in the Health 4.0 domain. As such, we are suggesting to extend the design criteria established by Hermann et al. for the health domain.

2.6 Health 4.0

Health 4.0 is a strategic concept for the health domain derived from the Industry 4.0 concept. The aim of Health 4.0 is to allow for progressive virtualization in order to enable the personalization of health and care next to real time for patients, professionals and formal and informal carers. The personalization of healthcare will be

achieved through the massive use of CPS, (Edge) Cloud computing, the Internet of Everything including things, services and people and evolving mobile communication networks (5G). With the help of cyber-physical systems, software building blocks and Big Data tools (algorithms) "objects" will be virtualized involving a spatial temporal matrix. The virtualization will enable the analysis of snapshots of the physical world in next to real time and allow for theragnostics. This again will allow for Prsonalized/Precision Medicine.

2.7 Health 4.0 Use Case: Narrow Band–Internet of Things (NB–IOT) Hyper-Connected Asthma Inhalers

Asthma is a chronic respiratory disease with symptoms such as wheezing, shortness of breath, chest tightness, cough, and reversible airflow limitation. Symptoms and airflow limitation both change over time. The prevalence of asthma ranges from 1 to 18 % in different countries. Currently, there are about 350 million patients with asthma worldwide, and about 30 million in China [25]. In Scotland the prevalence of Asthma is 18 %. The large-scale epidemiological survey of asthma among children in China in 1990 and 2000 indicated that the prevalence of asthma in children increased by 64.84 % in 10 years. Each year approximately 25 million people worldwide die from asthma. The societal burden of asthma is significant. It is in the interest of all stakeholders, including patients, doctors, carers, and pharmaceutical companies to reduce the societal burden while at the same time to increase effectiveness and efficiency of asthma therapy as well as the perceived quality of service.

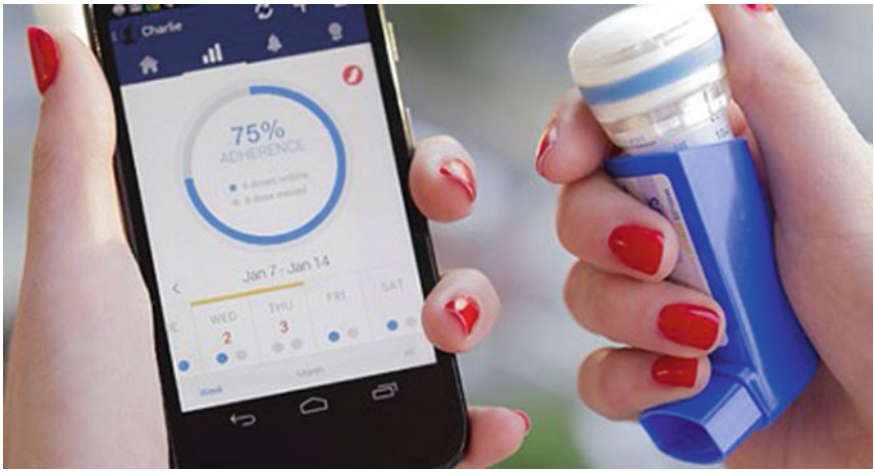

Fig. 2.1 Teva smart inhaler development 2016

New technologies including the IoT, industrial internet, network slice technology (such as the Chinese mIoT), next generation network technologies such as 5G, Narrow Band IoT (NB-IOT), LoRa, Big Data, CPS, edge cloud computing, and new strategies for the safe and secure aggregation of services hold the key for new and massively improved treatment strategies for asthma, allowing for progressive individualization of asthma treatment anywhere, anyhow and at any time and the integration of pharmaceutical and non-pharmaceutical therapy. First conceptual strategies in the asthma domain have been developed by the pharmaceutical industry. Smart asthma inhaler concept studies are available from Teva (Fig. 2.1), Boehringer, GSK, Astrazenica and others [26–30].

In 2004, a global survey involving 29 countries showed that only 5 % of asthma patients could achieve complete control of standardized treatment. Recent studies demonstrate that about 45 % of patients fail to achieve good asthma control in Europe [31]. The reason is mainly because of poor adherence to the treatment of asthma [32].

2.8 Improving Asthma Control Through Cyber-Physical Adherence Management

The improvement of asthma requires adherence and long-term behavioral changes. In order to achieve these objectives latest technologies from the areas of 5G, IoT, Big Data, cloud computing and security have to be orchestrated in order to generate interactive, cyber-physical systems, which can operate in real time. First technology proposals are available based on micro sensors embedded in asthma inhalers. Initially smart phones have been suggested as back-end device to store data and provide processing intelligence by establishing connections to the pharmaceuticals via Bluetooth. Smart phones can serve as gateways to share data with remote servers thus enabling amalgamation of data and big data analysis. Although the use of smart phones as processors and potential gateways is possible in principle some questions have been raised with regards to its reliability, suitability and practicality. Typically asthma patients use not only one single inhaler but two or more different types of aerosols or powder based medications. Many patients store several units of each kind in different places to ensure that it is readily available if needed. All in all this means that several inhalers would have to be connected to the phone via Bluetooth at any time, which is a challenge to battery life and also to the phone's blue tooth router. Another challenge is a conflict with regard to reliability between mobile phones and medical devices in general. While mobile phones generally operate on a "best effort" basis some medical devices are considered "mission critical." "Best effort" and "mission critical" refer to the quality of service (QoS) and can mean very different things. While "best effort" means that data may or may not be sent, "mission critical" offers guarantees with regards to the reliability of a device or process. Clearly, in the interest of the quality of care and quality of experience medical devices to manage

asthma cannot operate on a best effort basis as this would jeopardize the very key objectives of asthma therapy, namely maximizing adherence and minimizing the occurrence of severe asthma attacks, hospitalization, and death. Other important aspects include energy efficinency and data protection. Using smartphones as gateways might seem more energy efficinet on the first glance. However, using Bluetooth to connect to the phone and then using the phone to access the radio network is everything but energy efficient. Given the fact that asthma inhalers could account for more than 1 billion connections in 2025 this should be investigated more closely. With regards to security Bluetooth and phone signals cannot be assumed to be safe to the standards legally required in the health domain.

Alternative technologies are at hand to significantly improve the current Bluetooth-based smart pharmaceutical strategy for the treatment of asthma. Narrow Band—Internet of Things (NB–IOT) technology is a low power wide area radio access technology (LPWA RAT) which seems promising. It has recently been standardized and accepted by 3GPP, the global relevant standards organization and is ready to use (technology Readiness Level (TRL) 7–8). Similar technologies have been successfully implemented into smart electric meters and lately into water meters to establish water consumptions of households more accurately. However, this does not mean that smart phones and tablets will not play a role in individualized asthma therapy in the future. Patients will use their smart devices to manage their personal data and obtain therapy recommendations as video downloads. They will also be able to authorize and follow up on the use of their data by medical professionals and researchers.

NB–IOT modules offer an interesting and viable solution in order to allow for enhanced connectivity by utilizing different segments of the spectrum in comparison to smart phones. Typically NB–IOT utilizes significantly lower frequencies (around 800 MHz) than mobile phones (typically around 2 GHz). Due to its physical properties lower frequency waves show better penetration and reach. However, data amount and bandwidth is limited due to requirements for energy efficiency of the devices. The question will be can a cost increase of 3–10 % for the medication be justified through the value added by providing Industry 4.0 features, such as cyber-physical capability, modularity (several drugs and sensors to be connected at the same time), service orientation and interoperability (several services and cyber-physical systems may be aggregated to achieve better asthma control).

In general crucial requirements for Health 4.0 based smart pharmaceutical asthma therapy are:

- QoS needs to be predictable
- Safety and security. Privacy is paramount
- The technology needs to be network agnostic and interoperable
- The technology needs to be safe, secure and resilient
- Connectivity anywhere, anyhow, at any time
- Global product and service interoperability and network capability for global service orchestration

Currently shared demonstrators in Europe and China are under preparation. Standards and interoperability have been discussed during the EU-China dialog on the IoT and have been included in a recent EU-China white paper on the Internet of Things (IoT, mIoT) [10].

2.9 Medical Internet of Things (mIoT) in China

Lack of knowledge about asthma and lack of proper management are important causes of asthma aggravation and high mortality. With the successful application of mIoT in the management of heart disease and diabetes, mIoT is now applied in the management of asthma. Asthma education is an important part of asthma management. With mIoT and 5G, all kinds of video and audio material related to asthma education can be delivered to the mobile terminals of asthma patients, enhancing patients knowledge about asthma and integrating pharmaceutical and non-pharmaceutical therapy. In addition, mIoT makes the assessment and monitoring of asthma easier. For example, asthma patients could complete their asthma control tests and asthma control questionnaires on their cell phones routinely, so that physicians could monitor the condition of their patients regularly. On the other hand health authorities and service providers could utilise the mIoT to assess the dynamics of the condition and the interaction with environmental or behavioural factors.

2.9.1 5G Driven Personalized Asthma Care

The treatment of asthma is frequently based on the use of different types of inhalers to apply pharmaceuticals. However, so far commercially available inhalers do not include CPS to inter-connect the physical with the virtual world and support personalized medicine strategies. This is about to change. While latest generation of sensor technologies now enable the capture of important therapy key performance indicators (KPIs) at the point of care such as adherence, physiological parameters and timing 5G will provide multi-frequency connectivity and multi-modal capability including NB–IoT and mobile telephony to enable the information exchange between the physical and the virtual world. This will in particular enable the use of theragnostic algorithms and also offers the possibility of easy and seamless integration of pharmaceutical and non-pharmaceutical therapy.

The use of smart inhalers will:

- Reduce the number of serious incidents
- Enhances the efficiency of pharmaceutical therapy
- Improve the quality of experience of patients and professionals
- Reduce the number of hospital admissions, sick days and outpatient visits
- Improve documentation and individual risk analysis.

2.10 Conclusions

There is plenty of evidence suggesting that Health 4.0 should be considered a subset of Industry 4.0. Due to the definition of health infrastructures as a critical infrastructures safety (safety, security and resilience) has to be accepted as a mandatory additional design principle in Health 4.0. Mobile phones are unlikely future gateways for smart pharmaceuticals as their current limited Bluetooth routing capability, limited battery life and their "best effort" paradigm make them incompatible with the requirements of smart asthma therapy and general personalized medicine approaches ("mission critical" QoS, multi-tenancy). However, smart phones and tablets will play a role for the reception of video files and reports. Smart pharmaceuticals enabled through 5G technologies including NB–IoT are close to market and will be available within the next years. This will trigger new business models. The pharmaceutical industry might shift from a manufacturing industry to a service industry by taking on new responsibilities beyond the mere manufacturing of pharmaceutical products.

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Chapter 3
Data Traffic Forecast in Health 4.0

Alois Paulin

3.1 Introduction

The fourth technological revolution is a big expectation traversing all domains of human conduct: Industry 4.0 is *the* twentieth-first century buzzword per se, denoting significant advances in the modernization of manufacturing and giving rise to new ecosystems. Its public-sector instantiation is Health 4.0, where similar transformations are expected to occur. The field of healthcare is without doubt a rich pasture: its archaic organizational structures are a promising prey to challengers, its data a mysterious hidden treasure, and its volumes of revenue a territory teasing to be conquered. From this perspective, Health 4.0 is about the search for reformation by means of information technology.

There is little doubt that a total transformation towards Health 4.0 is about to happen—it is not a matter of *if*, but merely a matter of *when*. How such a transformation will look like is hard to predict, but it is likely that it will be a transformation from hospital/professional-centred health care (patient in hospital) via distributed patient-centric care (multiple care-providers) to a globalized and self-administered Health 4.0. This chapter is about exploring this transformation with regard to the status quo of its evolution on the one hand, and about creating an understanding of the implications of such a transformation on the other. To this end, Sect. 3.2 aims to provide a theoretical understanding of the fourth generation as such, in order to lead the reader to a workable insight into the economic and technological gains and implications of 4.0 technology. Section 3.3 describes the modern technological landscape as routinely used in hospital healthcare environments in modern Western hospitals. Section 3.4 exerts the method of the Gedankenexperiment (thought

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experiment) [1] to argue for changed infrastructural requirements for future healthcare environments in the context of applied Health 4.0.

3.2 Understanding the Fourth Generation

The fourth technological generation is about the introduction of information and communication technologies (ICT) into the functions of a given domain, whereby ICT assumes the role of a channel for steering and controlling these functions, allows for the introduction of artificial intelligence, inclusion of new stakeholders and technical agents, and the extension of functionality to a previously technically unsupported extent. Aside from this, the fourth generation acts as a gateway to establishing and fostering new ecosystems, which develop from the possibility to seamlessly interact and interconnect through open application programming interfaces (API), accessible standards, and open technology. Health 4.0 loans the "4.0" attribute from Industry 4.0. In the domain of manufacturing and producing tangible outputs, the fourth generation is a clearly explainable concept, whose analogy can be transferred to the domain of (health-)care provision.

This section shall first (Sect. 3.2.1) provide an overview over the four generations of controlling *structure*, which play a crucial role in understanding the fourth generation. (These four generations are: *mechanization*, *automation*, *computerization*, and *informatization*.) Section 3.2.2 shall then outline the trend towards establishing digital ecosystems, and the added-value digital ecosystems imply.

3.2.1 From Mechanization to Informatization

The technological generations, in a nutshell, stand for different ways to controlling structure: the first generation of control was *mechanization*, the second *automation*, the third *computerization* and the fourth is *informatization* [2]. *Informatization* is used to "denote the ability to control concepts, systems, or things by means of information technology" [2]; although the term *virtualization* is often used in a similar sense as *informatization* will be used in this chapter, the difference needs to be outlined: A virtualized entity (such as, e.g. a virtualized car in a computer game) is an entity that exists entirely in the virtual dimension of its hosting environment (e.g. the computer game as such), without having real-world effect (e.g. a virtual car crash would not hurt the driver); in this sense, virtualization can be legitimately used when e.g. virtual healthcare data is being used for the observation of pandemics, or virtualized patient records are exchanged online. An informated entity on the other hand likewise may imply virtualization, but goes beyond what this term offers as it creates a link between the informated entity and a "tangible" real-world effect: an infusion pump that can be controlled from the virtual environment is thus *informated*, rather than merely virtualized.

While mechanization and automation have been well-known at least since Antiquity [3], computerization and informatization are available for roughly two (or one, respectively) generations only. This section aims to define and delineate these terms, to provide a normative understanding within the scope of this chapter. The differences between the terms shall be demonstrated based on heterogeneous systems/functions/activities as shown in Table 3.1.

3.2.1.1 Mechanization

A basic approach to control structure is through mechanization. Mechanization in the scope of this discussion shall be understood as the mode of operation of multistage systems, where the transitions between the stages are conducted entirely by human- or animal-based power and actions. The transitions between the stages then are along determined, planned paths.

Manually operated mechanical systems are, for example the pin-tumbler lock, the piano, or the mechanical loom. While all these mechanical systems address functionality that was known already before (locking a door using a cross bar, making music on a santoor, weaving cloths using a hand loom), the level of sophistication, the ability to increase precision and efficiency, and the ability to further advance the systems in an unpreceded manner generated added value beyond the limitations of non-mechanized systems.

The core principles of mechanization are the modularization of action and the identification of mechanize-able sub-processes: modularization enables sub-tasks/-processes to be addressed and evolved separately from the entirety of the system. In case of the Jaquard loom, which today is regarded as a crucial step towards both industrialization and even information technology [4], the design of the pattern was not a just-in-time activity of the weaver, but has been outsourced to *programmed* sub-procedures of a mechanical system. Likewise, the high specialization required to produce an accurate series of tones from the santoor has been leveraged to the array of strictly separated keys of the piano. The principles of splitting-up activities and processes into sub-components play also a crucial role in the optimization of manufacturing and general work processes: division of labour into individually controllable sub-processes enabled the evolution of the assembly line, decentralized production, etc.

3.2.1.2 Automation (Power-Based Transitions)

Automation bases on the chained/linked execution of processes, which as a whole comprise an automated system. While automation can be enabled, triggered and controlled through many forms of forces ranging from manual (and animal-based) labour to quantum-level processes, for sake of the present treatise *automation* shall be distinguished from *mechanization* by the general ability of a system to transition between states *without* requiring explicit manual or animal-based assistance during

Table 3.1 Transformations of functionality from mechanization to informatization [2]

Functionality/legacy system	Mechanized	Automated	Computerized	Informated
Santoor	Piano	Pianola	Keyboard	MiDi, Virtual Piano[a]
Loom	Mechanical loom	Power loom		CAD/CAM
Writing	Typewriter	Electric typewriter	Electronic typewriter	Word processing software
Washing dishes	Cochrane's (1887) hand-powered dishwasher	Modern (post-war) dishwasher	Microprocessor-controlled and sensor-assisted washing cycles	"Internet of Things"
Industrial manufacturing	Interchangeable parts/modularization	Conveyor-based assembly line	Robotized manufacturing	"Industry 4.0"

[a]http://virtualpiano.net

the transition. Thus, automation will typically involve the existence of a natural power source, like for example wind, flowing water, temperature, or pressure, or a controlled power source like electricity, or steam. Accumulation of power, as in the electrical battery, the water tank, or the clock spring, can further serve as a power source to enable transition between states of a system.

Using automation to control a system enables modes of its utilization beyond the abilities of mere mechanization. While use of automation in production-oriented contexts boosts productivity—as in the case of the power loom or the automated assembly line, automation can be used as well to increase the power of devices, such as the crane or lift, or the precision of a system, as in the case of the clock, or similar high-precision automata.

3.2.1.3 Computerization

Further advances with regard to precision and functionality were introduced through computerization—programed procedures, which were partly already known in pre-computerized systems, as in the case of the Jacquard loom, were now replaced by computerized procedures, which could be developed, maintained and applied with magnitudes higher speed and sophistication than before. A computerized system, according to Oxford's dictionary of English, is a system that has been converted to be operated by computers. Computerized systems allow software-based functionality like user interaction, virtualized controls through, e.g. touchscreens, and electronic display of advance data. The reliance on software allows for software-based tuning and expansion of the system. As such, computerization can provide improvements to functionality (e.g. electronic typewriters that provided basic spell checking features), expedite work processes (e.g. computerized accounting), or unleash large-scale potentials, like in the case of computerized assembly lines.

Characteristic for computerized systems is that the prime objective of their computerization is to boost performance, to enrich functionality, or to optimize production costs. The computerized dishwasher, for example will be steered by a chip, and may expose a digital interface for configuring the washing cycle; the computerization will thus enable the manufacturer to diversify its product range by alternating the software and user-interface features, with the main hardware system remaining exactly the same.

The result of computerization is thus a purpose-built system in which information technology is utilized to cater for functionality, which can be assumed to remain sealed from unauthorized transformation. When the system is designed and developed, the focus is thus on functionality and efficiency, rather than on features of the internal design of the system as such.

3.2.1.4 Informatization

Although both computerized and informated systems base on software, their approach differs significantly: while former focuses on efficiency and utility of the system for the functionality provided by the system, latter focuses on enabling ways to enrich the functionality of the system at run-time, thus enabling integration of independent stakeholders into the ecosystem shared with the informated system. With informatization, the leap into the digital dimension (the cyberspace) happens, which enables the generation of new forms of interaction, production and perception [5, Sect. 2].

The *computerization* of the piano yielded the electronic keyboard, which is not only significantly cheaper to produce, but can provide advanced functionality like different categories of tones, direct coupling to sound processing devices, etc. The *informatization* of the piano's functionality however goes beyond the provision of electronic tones: standards such as the *music instrument digital interface* (MIDI) translate tones into the digital dimension, where they can be controlled and transformed through a myriad of tools, and communicated through a myriad of systems, while still remaining an informated melody that can be heard in the real world. The result of a system's informatization are thus informated entities, which can be created, controlled, and transformed within the digital dimension, while remaining able to result in real-world effect, e.g. providing the basis for the melody to come to life.

Examples of thoroughly informated systems are for example the Web's technology stack (HTTP, HTML, CSS), or the open document format (ODF). Different kinds of informated systems are developer frameworks like .Net, Java, or the Java-based Android, on top of which software engineers craft further computerized and informated systems; yet another form are platforms like Facebook, Wolfram Alpha, or Google, which provide Web-based access to their functionality for peer-production of computerized or informated systems on top of them.

What informated systems have in common is a multi-level access to the underlying system, which is a feature of its design. Thus, while the informated ODF letter might have been composed with word processing software, where it is displayed as a neatly typeset document, on the level beneath lies a zipped folder structure containing XML files that describe how the document *can* (or perhaps: *should*) be visualized. These XML files however can be also accessed (read access and write access) using other tools and software systems, and so changed and amended outside of the original word processing environment, resulting in changes to the original informated document. Likewise, while most users might interact with a Web page through the Web browser of their choice, the browser is only an optional way to interact with the system. In the case of developer frameworks, the multi-level access is assured through the share-ability of programming libraries, while Web-based platforms offer dedicated APIs for developer access to provided functionality.

3.2.2 The Trend Towards the Ecosystem

It is the very multi-level paradigm of *informated* (i.e. fourth generation) systems, which allows for the rise of mighty technological ecosystems that trigger disruptive progress and unprecedented economic value. The multiple levels are aligned according to the principle of the three technological ecosystems [6]: the base technology (abstract models, non-deterministic technology), the primary ecosystem (economic activities surrounding the instantiation of base technology), the secondary ecosystem (use-oriented artefacts, such as manifested in computerized systems), and the tertiary ecosystem (artefacts designed for co-creation, such as represented by informated systems).

The power of global players of the dotcom era, like eBay, Uber, Airbnb, Alibaba, Facebook, Twitter, Google, or Apple, is owed to the possibilities of the secondary ecosystem. The products of these companies are themselves part of the secondary ecosystem, whom they helped to rise to prominence and economic might. With the creation of tertiary ecosystems by providing APIs, these companies significantly expanded their outreach and increased revenues by harvesting the fruits of their digital fields.

Economic power of the technological ecosystems has meanwhile reached impressive levels: California's economy—substantially due to the power of Silicon Valley, is said to be the Eighth largest economy in the world [7]—outperforming the economies of Russia or Italy. The existence of these global players, however would not be possible without the underlying existence and perpetuation of the primary ecosystem, whose surplus know-how and innovative spirit pioneered and remains fuelling the innovations leading to the secondary ecosystem (cf. [8] for an excursion through a zealotic IT developer's mind-set).

The massive economic value contained in technological ecosystems has triggered political pursuits aimed at opening-up the health sector to allow for the inclusion of new stakeholders, and to enable the reuse of data. The basic idea hereby is that new stakeholders will be able to create added value by digging through existing data, an idea which in principle is shared by the open data movement [9]. Health 4.0, however goes beyond the humble aim of sharing data—it is about realizing the full potentials of the technological ecosystems.

3.3 Data Sources and Data Traffic in Modern Healthcare

Deep into the twentieth-first century, healthcare routine yet leaves plenty of room for improvement with regard to adopting fourth generation technology. In a nutshell, technology is used extensively in remote monitoring of vital signs, the transfer of body imagery, and the exchange of patient records, advanced use beyond that however, such as e.g. comprehensive governance of patient data, multi-stakeholder

access to patient information, informational self-determination, event-based patient routing, track-and-trace systems, or APIs to access, are virtually not to be found.

The findings summarized in this section are derived from a study conducted in late 2015 at an advanced German university hospital, which investigated the use of computerized and informated systems in everyday use. These observations give an insight into the daily routine of professional healthcare providers, which is a necessary basis to understand the further potentials for informating healthcare.

The technology-supported activities in hospital routine fall in four broad use categories: the monitoring of vital signs, the creation of digitized body scans, the storage and exchange of patient records, and communication between units. This selection deliberately excludes technology used in direct care provision, such as robotic surgery, which is dealt with in more detail in Chap. 5. The technology used in scope of these categories is largely automated, or computerized, respectively, with an exception being imagery and structured reports, which are virtualized, but not informated.

3.3.1 Cross-Domain Access to Patient Records

The patient records are the most essential information about a patient and are part of many steps in the pathways patients traverse during the care process. In a hospital environment, dependent on the complexity of the wards, one or multiple *hospital information systems* (HIS) exist, which store the information on the in-hospital treatment process, patient diagnoses, billing and other administrative issues. The information from the HIS can be then accessed by the various wards involved in the care process, as well as interfaced with adjacent systems.

The observed hospital used the SAP system for its HIS; SAP is a well-known modular enterprise resource planning system, which provides a broad range of solutions to support and virtualize workflows in various business scenarios. Interaction with the SAP system works through the frontend *presentation server*, which is the client application through which the user interacts. The frontend interacts with the *application server* in the backend, which in turn interacts with the *database server*. The user interaction with the system is conducted through so-called dialogue steps, whereby client-side inputs are collected and pushed at the end of the dialogue step to the server.

Administrative (text-only) interaction with the HIS inflicts moderate data traffic on the hospital network. At an estimated 50 concurrent users of the system, network data traffic of 25–50 kbps would apply caused by the client–server interactions with the SAP HIS.

An ongoing trend is to increase stakeholder involvement by sharing patient records through central state-run infrastructures. Germany as of 2016 was about to commence base research towards such infrastructure, which aims to provide centralized access to care data [10], while its neighbour Austria in beginning of 2016 already began rolling-out a nation-wide system for online access to patient health

records accessible to the data owners (i.e., the patients) and care givers alike, the *Elektronische Gesundheitsakte*—ELGA cf. [11]. ELGA is grounded legislatively in the Health Telematics Act 2012 (*Gesundheitstelematikgesetz 2012*), and is planned to gradually assume a role of a national backbone for all interaction related to the patient data (medical records, etc.) available.

3.3.2 Patient Monitoring

Monitoring of patients' vital parameters is conducted in various settings, like for example during intensive care, or during anaesthesia. The parameters captured include blood pressure, oxygen saturation, body temperature, pulse, respiratory frequency, blood sugar, blood gas analysis and estimated drainage quantities. The thus monitored vital signs give insight into the patient's status, which is crucial for deciding on actions required to keep the patient in a stable position. Indicators such as a sudden change in respiration or blood pressure will signify patient instability such as internal bleedings, organ instability, phasing-out of the anaesthesia, or similar and call for emergency action of the staff.

Vital signs are captured by *computerized* read-only devices, which show the data on local displays. These solutions come in form of black-box systems tailored to the real-time demands of the monitoring environment, with optional export of data through the hospital network for telemonitoring and archiving purposes. At the observed hospital's inpatient ward only the blood gas analysis was captured automatically and sent directly on to the *patient data management system* (PDMS) server, the other vital parameters are assessed and written down manually in the patient file, on paper.

Data rates of biosignal monitoring devices have been collected by Vouyioukas et al. [12, 13]; according to them the generated data amounts usually to less than 10 kbps; according to Vergados et al. [14] sensor resolution is 12/16/24 bits with sample rates ranging from 5 to 50,000 Hz, yielding in data output in the range of 80 bps to 600 kbps, respectively.

3.3.3 Images and Multimedia

The vast majority of modern hospital data traffic caused by routine operation is attributed to imagery and multimedia. Large quantities of images are produced by the radiology department in form of various body scans, such as X-Ray, ultrasound, CT (*computer tomography*), or NMR (*nuclear magnetic resonance*) images.

The images are stored at the hospital's central PACS (*picture archiving and communication system*) in form of DICOM files. DICOM (*digital images and communication in medicine*) is a de facto standard meta container for storing digital images for medical purposes, which supports rich meta information, as well as

multidimensional images [15]. Each DICOM image comes with a vast array of metadata, including patient demographic information, acquisition parameters, identifiers of the operator, practitioner and referrer, and image dimensions, amongst other data. Modern PACS servers support advanced operations, such as JPEG 2000 streaming, which allows for increased speed of access to details in high-resolution images or composite images where applicable. DICOM clients are available for a broad range of devices, including handhelds, which makes DICOM imagery at least in theory available to any stakeholders (including patients) with permission to connect to the PACS server.

At the observed hospital the amount of data thus collected amounts to roughly 500 GB lossless-compressed imagery per month, with a maximum of ca. 80 simultaneous connections observed so far. DICOM images will vary significantly in size depending on the complexity of the nested images. A single X-Ray or CT image for example will start at ca. 256–512 kB, but may easily reach the size of several ten MB [16]. DICOM files will typically include whole series of images, entire patient cases, or snapshots of body regions represented as many hundred fine layers as produced, e.g. in the course of an NMR scan. Thus resulting DICOM files will easily reach to several 100 MB or even several GB of data.

The PACS is routinely and repeatedly accessed by the different wards involved in the provision of care for plain informative purposes, consultation on a patient's status, etc. The DICOM images are *virtualized* insights into the patient's body, with parts of their information contained coming with a potential for informatization that would come handy to assist in in-body navigation, or smart/personalized medication.

A further large source of data traffic is the transmission and streaming of multimedia contents. Video technology is largely deployed to enable minimal-invasive in-body treatment, where laparoscopic and endoscopic cameras enable surgeons to perform operations through small holes or even natural body cavities rather than fully opening the body. During surgery video technology is deployed for supervision, precision, and counselling purposes, where external experts can be called-in to assist via video streaming.

In the observed hospital, the video streams are often captured and archived for educational/research purposes, however, a systematic approach that would enable advanced analysis and sharing of this material is not applied.

3.3.4 Out-Hospital Data Interactions

Interactions with out-hospital stakeholders include interactions with emergency units, established doctors, research agencies, the general public, suppliers, the patient and its kin. The interactions along these relations allow plenty of room for increased informatization beyond the status quo. As of present, the interaction in general is unstructured and usually improvised.

3.3.4.1 Emergency Mobile Units

Emergency mobile units (emergency ambulance, rescue helicopter) communicate over dedicated national telecommunications systems, such as the German BOS[1]-Funk, a well-established non-public mobile VHF land radio service [17], or the emerging TETRA (terrestrial trunked radio) systems.

Between the mobile units and the hospital as such, routine communication is not foreseen. The communication (if any) is conducted via voice over radio or mobile networks. Since the role of the emergency physician is to stabilize the patient or to conduct life-saving measures, no dedicated e-health systems were used on the relation between the mobile unit and the hospital in the observed German case. In Germany, the emergency physician typically will inform the control station via BOS-Funk on a first diagnosis of the patient's condition, whereupon the control station will check online for availability of required facilities in near-by hospitals, such as a shock room. Thus, in Munich, the Emergency Services Association (Rettungszweckverband München) operates a Web service, which displays an overview over the availability of services provided by the participating hospitals [18].

3.3.4.2 Established Doctors and Patients

Interaction with established doctors in the observed setting is yet predominantly confined to old-fashioned paper-based transfer of information, despite technology available and ripe in theory. Systems such as the Austrian ELGA aim to modernize communication in this regard; however as of 2016 the systems are yet at very early stages of implementation.

In the context of patient data however one often forgets that the data at stake is not merely data *about* the patient, but rather, data *owned by* the patient, who, in legal terms is the *data owner*, while the care-giving stakeholders on the other hand are merely *data processors*. In a nutshell this means that the patient is supposed to be able to control its data, access it, and use it as it pleases. This in turn, would be—at least in theory, an interesting possibility for patient-centric systems to interface with hospital information systems (or similar) to generate added value. As the owner of the data about it, the patients should be in the position to partake in potential commercialization of the data, or other endeavours that derive added value from the data at stake.

3.3.4.3 Suppliers

Electronic links to suppliers of hardware systems for remote maintenance purposes, automated software updates, and interfacing with suppliers of goods for

[1] *Behörden und Organisationen mit Sicherheitsaufgaben*—Agencies and Organisations with Security Tasks.

system-supported stocks supply management are some of the rare possibilities for the automated interfacing between the hospital and its suppliers of goods and services. Interconnected systems for assisted restocking with supporting suppliers are becoming increasingly relevant in streamlining the supply chains.

A further systematic advance of hospital virtualization and informatization, however would intensify the opportunities along the relation between care providers and their suppliers, with the ability to introduce competent track-and-trace systems for the used pharmaceuticals and instruments, and use thus generated data for advanced analysis of treatment performance, personalization, or streamlining the operational costs.

3.4 Future Traffic Characteristics

Section 3.3 provided an overview of the data characteristics of present-day care provision environments. With regard to the expected future data traffic mix, certain trends can be already identified based on thus collected insights, which shall be explored further below: One such trend is linked to the issue of data ownership and data governance and the empowerment of the data owner—Sect. 3.4.1 shall explore this trend and its implications; another trend is the utilization of track-and-trace solutions for (reverse) supply chain management and drug safety assurance (Sect. 3.4.2); or the increased de-centralization and globalization of health care, which shall be dealt with in Sects. 3.4.3 and 3.4.4, respectively.

3.4.1 Trends in Data Governance

Healthcare data is very specific data—unlike data which is collected for traditional purposes of commerce, transport, logistics, or control over manufacturing processes, healthcare data is a special kind of personal data, which is subject to detailed legal regulations, policies and jural decisions.[2] Data used in the healthcare domain is so-called *personal data*, which is a legal term, which in the scope of European Union's legislation (EC Directive 95/46/EC—*Data Protection Directive*, and Directive 2002/58/EC—*e-Privacy Directive*) denotes (1) *any information*, which is (2) *relating to* (3) *an identified or identifiable* (4) *natural person* [19]. The characteristics of thus handled data have a vast influence on the characteristics of emerging information systems that will be rolled-out in the future.

Aside from this, future information systems will need to take into consideration that access to the thus collected and stored data might be requested by multiple heterogeneous stakeholders. The *data subject*, i.e. the person, who the data is about,

[2]The here outlined provisions belong into the context of the European Union.

is the legal owner of the data, and thus entitled to know which data is collected and entitled to receive access to the collected data, to demand its rectification, and in certain cases, its destruction. Aside from the data subject, access to the data in the healthcare domain can be requested by third parties for reasons of research, disease prevention/control and for other purposes of governance bodies. Access to the collected personal data thus can be requested by a set of stakeholders with justified interest, which cannot be fully foreseen at design time of the information system. A further level of complexity is introduced, as the data subject is eligible to know with whom the data has been shared and who is in possession of its data, in order to demand deletion/rectification of the data. The resulting constraints imply new demands to information system designers and developers, who need to take into account complex requirements, which might unforeseeably change in the future due to interventions by law [20].

In order to accommodate for these constraints, new principles of data governance have been introduced in the past years, most importantly the concept of *fine grained access control* (FGAC), and *fair non-repudiable message exchange* (FNR) —cf. [21]. FGAC refers to the ability of databases to govern access to core data based on access policies, which take into account the contents of the data query, the context of the request, and the identity of the requester. Unlike with traditional approaches, which categorize access permissions based on the pre-assigned role of the requester, FNR does not rely on roles, but rather on the complex context. Technologies for FNR have been described by Bertino et al. [22] and Paulin [23], who focus on FNR technologies that utilize SQL query rewriting for governing access to the data. Standardization efforts have been conducted by OASIS, which provides the eXtensible Access Control Markup Language (XACML), while IBM introduced the Enterprise Privacy Authorization Language (EPAL).

Fair non-repudiation (FNR) reveals its utility when personal data that must be exchanged between two entities must be exchanged in such way, that the exchange cannot be refuted by any of the participating parties. This way, a non-repudiable trace chain is coined, which then can be accessed by parties with a vested interest. A state-of-the-art summary on FNR has been provided by Paulin and Welzer [24], where an internet-based approach is described for the direct message exchange between two technical systems.

Future health systems will rely on a combination of FGAC and FNR to provide sustainable technology for the governance of data in public-sphere domains like health care, public governance, or public education, i.e. in domains, where governance of access to personal data is subject to public domain policies and influenced by the legal domain [21]. This will allow for multi-stakeholder access and a transformation from monopolistic public-sphere domains to participative technological ecosystem in which added value is generated through shared access to data in the thus created *internet of jural relations* [2, 20, 25].

The importance of participative ecosystems is shared across the board of emerging technological realities, including the *Internet of Things* cf. [26], *Open Government Data*—OGD [27, 28, 9], and *Smart City* urban technologies [6]. This omni-stakeholder paradigm has already proved itself as an economy-fuelling

mechanism in the domain of Web and Internet technologies as such [6, 8], and is already being pursued by emerging backbone-infrastructures, such as the Austrian ELGA [11].

With regard to future data traffic characteristics, it is impossible to make any near-realistic predictions on how multi-stakeholder access will impact data flows and interactions involving data subjects, data processors, data providers, and data consumers. Given that data at present is held in a locked environment with no technological provisions for free technology-mediated sharing, whereby access to data is chiefly governed by individual institutional agreements, i.e. human-mediated contracts, the effects which a shift from human-mediated contracts to technology-mediated contracts would have, can under no circumstances be feasibly estimated.

For comparison, the Internet's global data volume exchanged over undersea cables was in 2000 roughly one terabit per second (Tbps), rose by 2005 to roughly 10 Tbps, and boomed till 2013 to 70 Tbps [29]. Needless to say, before the dotcom boom in the late 1990s, the traffic levels were not yet counted in terabits—in 1997 CISCO estimates a global IP traffic of 200 Mbps,[3] which by 2002 rose to 800 Gbps [30].

A similar boom can be reasonably expected by the systematic opening-up of medical data, which a multitude of stakeholders would be able to access and transform into added value within dedicated ecosystems. How strong this boom is going to be however depends on several crucial factors, which are impossible to predict or quantify, such as the usefulness of data, the ability to easily interface it by technical means, the organizational setting, etc. With regard to the *usefulness of data* lessons learned come from the field of OGD, where the opening up of the government data in many cases was a failure—the reason being not technical obstacles, but rather the value of the content; on the other hand, the government files opened on WikiLeaks were of high value and accordingly the technical implications (data traffic, etc.) were a class of its own.

3.4.2 *Track and Trace Systems: Reverse Supply-Chain and Drug Safety*

In close relation with the emerging trends from the *Internet of Things* (IoT), an increasing labelling and virtualizing of medical *things* is expected to shape the future of health provision. Package-level identifiers in the domain of pharmaceuticals (and even other goods, such as alcohol) are already well-established in countries such as China, Iran, or Brazil, where they serve as a mechanism to ensure authenticity of the items at stake, and to curb the trade of counterfeit goods.

[3] 100 GB/h = 800 Gb/h = ca. 0.2 Gbps.

The trend to control (track) the movement of items along the supply chain in the domain of a given governance agency is persistently taking shape also in Western domains, such as the USA, the EU or UK. In the EU, directive 2011/62/EU, stepping into effect in 2017, mandates a European track-and-trace system, by which the EU follows the steps of Asian, African and Latin-American countries with the objective to protect its markets from criminal pursuit in the medical domain.

Advanced bi-directional track-and-trace systems (also known as reverse-supply-chain), such as the one explored by the European FI-STAR (*Future Internet Social-Technological Alignment Research*) project [31] lay strong focus on sustainability by adhering to the principles of the *omni-stakeholder paradigm* as outlined in Sect. 3.3.1.7, as well as providing a universally scale-able solution that fits both macro-environments (track-and-trace of items on the scale of a large political area), as well as micro-environments, such as individual hospitals, or departments; thus, the track-and-trace system deployed within the FI-STAR project was tested both on a nation-wide scale in the UK, as well as a department-level scale at a surgical ward, where in-body items and tools used during surgery were tracked in order to increase safety and efficiency [32, 33].

Extensive use of omni-stakeholder systems has significant impact on the characteristics and extent of future data traffic both on-premises, as well as beyond. Bi-directional track-and-trace relies on periodic queries against the supply chain by multiple stakeholders, such as consumers, merchants, wholesale agents, government agencies, researchers, etc., which in their entirety impose significant micro-traffic against the central chain system, comparable to the traffic experienced by social media providers. In order to estimate thus upcoming traffic characteristics, insights from latter are a valuable source.

Twitter, for example, is said to register around 6.000 new tweets each second [34]; according to estimates by Alexa, twitter.com is visited roughly 1.160 times each second (this probably excludes the individual channels as such). If a Europe-wide bi-directional omni-stakeholder track-and-trace system would be deployed, traffic estimates of similar grade may be a feasible amount to count with, under the assumption that multiple agencies would systemically access the system on a regular basis. At an average message length of 1.280 bits (Twitter's 160 characters in UTF-8 encoding) that would mean an average interaction stream of ca. 3 Mbps (request + response) affecting the central system.

3.4.3 Central Infrastructures

Central infrastructures for the storage and maintenance of patient data, such as the Austrian ELGA system, are the undisputed trend of virtualized healthcare systems. Patient information is as of current stored in local databases on-premises (cf. Sect. 3.3.1) in central hospital information systems. The ongoing trend however is to extend/replace these local solutions for global (in terms of at least nation-level)

systems, which would open-up medical data to external healthcare providers in the scope of patient-centric healthcare provision.

Such central infrastructure is then mainly about mediating access to patient records. Estimations of the data traffic context can be made based on estimated access to thus stored information. In the case of the Austrian ELGA system, an estimated 142 million read-accesses per year has been taken into consideration as part of the system's architectural planning [35, Chap. 13], which applies to a country of roughly 8 million inhabitants, a total of roughly 100,000 care providers that will be subjected to using ELGA, and an estimated 25 million medical findings created each year (ibid.). That amounts to roughly 13.5 read-accesses per minute, assuming an 8-hour workday and 365 working days in a year.

Also Germany has recently taken up this trend [10], aiming at interconnecting 33 university hospitals at a first step. Germany, as a country of roughly 80 million inhabitants, features more than 2,000 hospitals and more than 130,000 established doctors (compared to 450 hospitals and 20,000 established doctors in Austria [35, 213]).

On a side-note: This trend is yet only a national one, which does not take into consideration trans-national exchange of data, as it is compulsory in the context of trans-national unions such as the European Union. Leaving out focus on this particular topic is expected to lead to similar challenges in the future as have occurred in the case of the European electronic identity.

3.4.4 Computer Vision & AI

Computer-assisted diagnosis and treatment, aided by pattern-recognition, artificial intelligence, and computer vision in general, is an emerging reality of future healthcare, which finds application in cancer diagnosis [36] or surgical treatment [37]. Modern application however remains confined to local environments.

Given the ongoing political tendencies to opening up medical data, e.g. [10], imagery and other complex data sets are expected to be available in the future to a broad range of stakeholders for remote access. The extent to which data is going to be shared will vary from exchanging data as such—that would imply large quantities of data transferred over the Internet, to sending analytical algorithms directly to the data according to the *software-to-data* paradigm [38].

The software-to-data paradigm is a preferred option with regard to data privacy implications, but is then restricted to systemic analyses of large, invisible, anonymous sets of data. The software-to-data paradigm is most certainly applicable in diagnostic pursuits as described in [36] where a standardized remote set of data can be examined by algorithms that are "pushed" to it, and also applicable in cases where remote algorithms could be "pulled" towards the data to provide added value, as such would be the case in the surgical set-up described by Feußner and Wilhelm [37]. This, however, works only as long as no human interaction is

required to either validate the system's findings, to innovate beyond the system's capabilities, or to train artificial intelligence.

An increasing utilization of imagery and multimedia for system-aided diagnosis, in conjunction with globalized research and diagnosis efforts, will significantly impact data transfer characteristics. The expected future implications might be similar to those posed by the BitTorrent protocol, which as of 2015 accounted to 2.67 % of North American downstream Internet traffic [39]. The BitTorrent traffic is relevant for comparison, since the content streamed is predominantly large files of several hundred MB to several GB in size, which are downloaded sporadically, rather than streamed systematically.

3.4.5 Globalized Ecosystems, Peer Production, and Self-help

Peer production denotes self-organized remote collaboration on undertakings within the digital realm, whereby the stakeholders usually do not know each other in person. Peer production is a state-of-the-art paradigm of the cyberspace culture as well as software development, known best for concepts, such as open-source software development [8] and organized social causes like the *Anonymous* group, Internet security [40], or content production in online fora, social media, bulletin boards, or systems like Wikipedia. Peer production is the paradigm par excellence of the tools that built cyberspace as we know it and the core paradigm that gave cyberspace its content.

This is the point where ecosystems (see Sect. 3.2.2) evolve naturally out of the zealotry of individuals that take an active role in the peer production of tools, systems, or content. Peer production meets a global market and the self-help attitude of cyber communities, and has been found to attribute positively to care processes [41–43, 44].

With the governed opening-up of one's personal medical data to global communities, the boundaries of social media will erode and new services and markets will become available. Already today expats tend to interact with their home physicians via the Internet by sending them body scans, and diagnoses conducted locally, as the services offered by the home physicians are considered of higher quality or efficiency, as compared to those in the country of residence. Opening-up and standardizing medical data will open new avenues for a global economy of services of an unprecedented scale.

3.4.6 Entertainment

More than 70 % of today's Internet bandwidth use (downlink) is used by streaming services [45, 6] for entertainment, such as NetFlix or YouTube. Astonishingly, not all hospitals yet provide entertainment options or Internet access to their patients,

partly due to security concerns and technical bandwidth limitations. Even though entertainment has not much to do with the primary functions of healthcare provision (others might object, after all, a relaxed and entertained patient might cure faster), providing entertainment to patients in forms of video streaming and the like will play a significant role in the future of communication requirements of stationary wards.

A proper separation of data traffics, such as achieved through the provision of prioritized, dedicated network slices for professional traffic, and low-priority slices for entertainment, is thus expected to contribute its share to the complexity of future network infrastructure for in-hospital use.

3.5 Conclusions: Forecasting the Next Generation

The killer-applications of today's Internet and Web—e.g. BitTorrent file sharing, Google search engine, Facebook social media, or Skype communication, etc., are all focused on mere communication. When it comes to Health 4.0, the matter at stake goes beyond communication, which makes a comprehensive prediction of its future evolution impossible. As a matter of fact, Health 4.0 is the natural evolution of an already heavily computerized domain into an informated one, which means a paradigm shift comparable to the transition from classical telephony to digital communications which evolved later into the Internet and the Web. Much like it was a pure speculation to predict how the Internet would evolve in the decades following its introduction around 1970, it is a mere speculation to predict how Health 4.0 will impact the evolution of the cyberspace as we know it today. From the lessons learned through the evolution of the Internet, and later the Web (it *does* makes sense to observe both technologies' evolutions separately), one can however reasonably assume that the technological ecosystems [6] evolving from the availability of medical data will perpetuate themselves, tightly followed by regulative, legislative, political and judicative measures that will keep the public sphere involved in healthcare-related matters.

In predicting the future traffic characteristics, one might be tempted to simply statistically scale up existing circumstances (such would probably work in the case of transmitted body scans), as one would do when forecasting the growth of an emerging social media provider (taking into account the progress of competing providers), communications hardware producer, or telecom operator. However, such forecast would doubtlessly lack proper scientific rigour, as it would necessarily have to ignore the intrinsic paradigm shift that the transition to the fourth generation of health technology would imply.

At the end of the day, there are three possible paths future health care will follow: stagnation, patchwork progress, or paradigm shift.

3.5.1 Stagnation

The first way of evolution is plain stagnation, keeping things as they are. Professional healthcare is yet today heavily relying on tools and technologies which have been invented and produced decades ago with no truly path-breaking innovations happened since. Many of the technology yet in use today in the observed hospital, such as infusion pumps, anaesthetics monitors, EKGs, defibrillators, respiratory ventilators, etc., are serving duly for many decades.

Stagnation is a normal evolution of technology and a sign of ripeness; Gartner's hype curve [46] is illustrating the progress of a technology hype, which again is a natural part of a technology's evolution. Technology in sensible domains such as transportation (aviation, cars, trains, ships, etc.), military, jurisprudence, and also health care will typically remain fairly stable and conservative, but will nonetheless remain open to minor modernizations.

Assuming stagnation as the dominating factor to forecast the future of healthcare, one can assume things to remain pretty much as they are to rest on Gartner's *plateau of productivity* for decades to come, much like science and technology have remained stagnant for many centuries in the past with occasional decades of disruptions caused by the discovery of radically new materials, or ways of manufacturing.

3.5.2 Patchwork Progress

The second possible evolution is a non-systemic, patchwork progress determined by local patches of progress, strong overall heterogeneity of the technology in use throughout the domain, myriads of competing standards, suppliers, and providers of technology, whose objective is to achieve a vendor-lock-in situation in order to turn their investments into long-term sinecures. The patchwork progress is a well-known phenomena from domains such as digital government [6, 47], which is hard to overcome, as systematizing it would affect a broad range of stakeholders in whose interest it is to maintain a balanced status quo in the shared domain. The outcome of such non-systemic evolution can be observed in the domain of digital government, where disruptive transformation of the system has not occurred, but instead, a mere digital channel for interaction with government agencies has sporadically been added on top of the existing repertoire of the well-established bureaucratic culture.

In terms of future data traffic expectations, this type of evolution will not move mountains either, like it has not done in digital government. Neither will this type of evolution result in a domain-covering fourth generation of healthcare provision, but will instead remain on the level of second- and third-generation artefacts, i.e. on the level of computerization, automation, and the like.

3.5.3 *Paradigm Shift*

A paradigm shift would be the ultimate transformation from a provider-centric to a patient-centric care paradigm, featuring "smart" (cf. [48] for a comprehensive analysis of this term) healthcare technology and the entanglement of global care ecosystems. The great economic opportunity of future care provision may well be found in the fourth generation, if the evolution of ecosystems is taken for granted [6].

Such paradigm shift, then, would not only thoroughly shuffle existing relations, but would mean a *big bang* for new ecosystems to emerge, much like the *big bang* of the Internet and the Web created cyberspace and the dotcom economy. Not much can be predicted with seriousness about the consequences of such big bang, aside from the expectation that it would be massive.

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Chapter 4
Smart Pharmaceuticals

Bruce G. Bender, Henry Chrystyn and Bernard Vrijens

Abbreviations List

COPD	Chronic obstructive pulmonary disease
ECS	Extensive Care System
FENO	Fractional exhaled nitric oxide
HCP	Healthcare professional
MDI	Metered-dose inhaler
MEMS	Medication Event Monitoring System
PMI	Precision Medicine Initiative

4.1 Introduction

This chapter introduces key themes that are emerging from the rapidly developing field of smart pharmaceuticals, focusing especially on monitoring, improving clinical control, and achieving appropriate use of the medication, which ultimately aims to maximize the potential for benefit and minimize risk of harm. A lack of formal pragmatic controlled studies and service evaluations inevitably means that many of the assumptions being made have limited evidence to support them.

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We highlight these areas of uncertainty to help inform the research agenda. We also consider the most important barriers that organizations planning to implement these devices need to overcome to realize the potential benefits. By considering these barriers concurrently with the evolving evidence base, appropriate and rapid employment of smart pharmaceuticals can ensure seamless integration with medical systems and practice, and address emerging regulatory, ethical, and legal issues.

4.2 What Are Smart Pharmaceuticals?

There is currently no consensus definition of the features that constitute a smart pharmaceutical. For the purposes of this chapter, we define a smart pharmaceutical as an electronic package, delivery system, or pill that offers one or more examples of "intelligent added value." As part of this, most smart pharmaceuticals offer electronic connectivity (e.g., wireless connection to an internet-enabled device or direct internet communication) that allows communication to a remote system that can compile, store, and analyze the data.

Intelligent added value can take several forms. For instance, smart pharmaceuticals can precisely monitor drug exposure, which in turn can be used effectively to improve clinical control. As discussed below, smart inhalers for people with asthma or chronic obstructive pulmonary disease (COPD) can offer feedback not only on time of intake but also on critical parameters such as disease control, appropriateness of inhaler technique, or dosing consistency. A more advanced illustration of smart pharmaceuticals is provided by several closed loop artificial pancreases that are being developed to permit more physiological glycemic control by tailoring real-time insulin delivery based on continuous, remote monitoring of blood glucose levels [1]. Artificial pancreases exemplify the way in which smart pharmaceuticals can offer dynamic dose calculations and tailor delivery by monitoring vital signs or biomarkers.

Dosing history data collected by smart pharmaceuticals could facilitate self-management and a collaborative consultation. In the simplest form, smart pharmaceuticals can remind patients that a dose is due and record when the package or inhaler is opened. More sophisticated systems can confirm when a dose is delivered: for example, an inhaler that measures the inhalation could confirm that a dose had been taken, rather than simply that a dose had been prepared. Systems can collect data on adherence at the individual level and population level (also referred to as micro- and macro-level data). This in turn could help patients and HCPs identify issues that hinder adequate adherence and improve the diagnosis of treatment-resistant diseases. Smart pharmaceuticals could also collect data on risk factors, which, if handled tactfully, offer powerful educational opportunities and allow patients and HCPs to identify and address counterproductive behaviors.

Collated, "de-identified" data from many patients can provide metadata that could contribute to ongoing "big data" initiatives that aim to improve economic and

clinical outcomes, and identify novel insights into therapeutic optimization and pathophysiology.

It is already clear that smart pharmaceuticals could foster the development of emerging healthcare models; Robert Drury from the University of Wisconsin explains that the Extensive Care System (ECS) [2] "takes advantage of the continuing advances in biosensor technology, computing power, networking dynamics, and social media to facilitate not only personalized health and well-being, but higher quality, evidence-based preventive, treatment, and epidemiological outcomes." Drury argues that ECS could "challenge the acute-care episode model" [2].

The time is right for these approaches. For example, according to the Pew Research Center, 64 % of American adults owned a smartphone in 2014, an increase from 35 % in 2011 [3]. Moreover, smart phone use in previously low-penetration markets, such as the socioeconomically deprived and older people, is increasing. For instance, 50 and 71 % of those with household incomes of less than $30,000 a year and $30,000–$49,999, respectively, owned a smartphone [3]. In a survey conducted by the Pew Research Center, 62 % of smartphone users reported using their device to obtain health information—a higher proportion than those who reported using it for online banking [4] (Fig. 4.1). It is predicted that smartphone use will grow, with 70 % of the world's population using smartphones by 2020 [5].

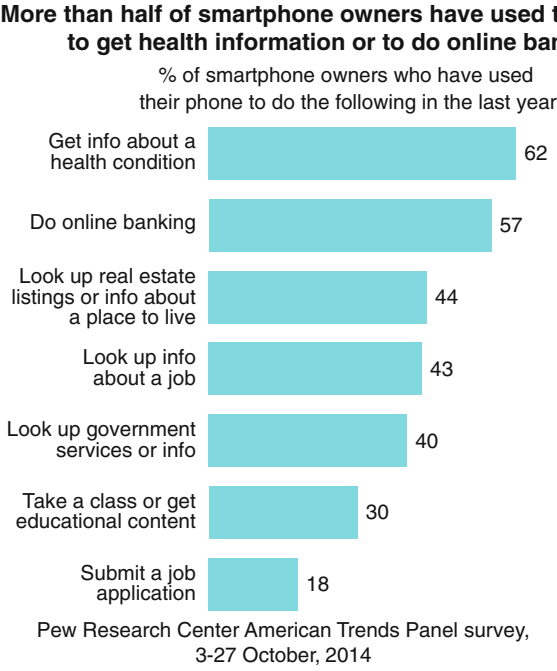

Fig. 4.1 Percentage of smartphone owners who used their phone to get online information in the year 2013/2014. With permission from [4]

Realizing the potential offered by smart pharmaceuticals depends on overcoming several hurdles, some of which are discussed in this chapter. Most importantly, the technology must organize and personalize information, while being seamlessly integrated with the person's care pathway. This integration with healthcare differentiates smart pharmaceuticals from the more consumer-focused "health apps" currently on the market. However, developers of smart pharmaceuticals can learn something from successful consumer apps, such as the importance of allowing patients the ability to interact with and control some aspects of the technology. This interactivity will encourage uptake and help dispel any perception that use of smart pharmaceuticals entails unwelcome vigilance of the patient.

Regulatory authorities and governments need to ensure that legal frameworks keep pace with technological advances. An improved regulatory and legislative framework will help ameliorate concerns over data protection and allow smart pharmaceuticals to become fully integrated in the care pathway. Unless the latter issue is effectively addressed, such devices will continue to be used more by patients who look after themselves and are prepared to invest in their well-being rather than those with the most to gain, such as patients who are unengaged in the management of their condition, patients with limited health literacy, or patients with more severe/uncontrolled disease. This selection could lead to disenfranchised patient groups and undermine the potential benefits offered by smart pharmaceuticals in particular and Health 4.0 generally.

4.3 Examples of Smart Pharmaceuticals

4.3.1 MEMS®—The Origin of Smart Pharmaceuticals

The first smart pharmaceutical system, known as the Medication Event Monitoring System (MEMS), was initially tested in 1977 [6]. The MEMS system incorporated microcircuitry into pharmaceutical packages of various designs, such that the maneuvers needed to remove a dose of drug were detected, time-stamped, analyzed, stored, and communicated to the appropriate caregiver to initiate corrective action. To date, MEMS has been used primarily in research and drug development for compiling drug-dosing histories in ambulatory patients. It has not been broadly adopted into patient care improvement programs, although some reference centers do use it on a regular basis. It provides a thorough characterization of medication adherence, with clear distinctions between initiation, implementation, and discontinuation. It is, of course, an indirect method of estimating when and how much drug is administered, but it has been shown to predict drug concentration in plasma [7]. The experience is captured in published work that today covers over 700 peer-reviewed papers [8].

4.3.2 The "Smart Pill"

Another example is an ingestible sensor developed by Proteus that, once in the stomach, communicates with a wearable sensor patch. It records the time the medication was taken and can collect additional data, including rest, body angle, and activity. This information is communicated to the patient, for example using a mobile phone. With the patient's consent, HCPs, caregivers, or both can access the data over the web [9]. Future, oral smart pharmaceuticals could target drug release at specific sites of gastrointestinal pathophysiology. A nondigestible smart pharmaceutical could collect samples from the gastrointestinal tract to facilitate diagnosis and track progress [10, 11]. Such insights could help tailor the dose based on the severity of gastrointestinal disease.

While these methods offer a promising future, they currently present some drawbacks, including patient intrusiveness, safety issues, the risk of false-negative event detection, and the burden on the patient of having to continuously wear an adhesive skin patch to capture information sent from the ingested sensor. There would also be significant hurdles in getting ingestible smart pharmaceuticals approved by regulatory authorities.

4.3.3 Preliminary Examples of Smart Pharmaceutical Devices in Respiratory Disease

There has long been interest in electronic monitors for inhalers for the delivery of drugs for asthma and COPD. For example, the SmartMist (Aradigm Corporation, Hayward, California, USA) was a device launched in the 1990s that was loaded with a standard metered-dose inhaler (MDI) canister [12, 13]. Inhalation flow was measured using a pneumotachometer and the device could be programmed to deliver the drug at a certain point in the inhalation cycle. Inhalation timing and accuracy were recorded on the device and could then be transferred to a personal computer. The ChronoLog or MDILog (Medtrac Technologies, Lakewood, USA) was a small device that was attached to the MDI [13]. It recorded shaking and the time of actuation. Using a thermistor, it measured inspiratory effort and recorded whether there was no inhalation, an inhalation at the correct time, or a late inhalation. While ahead of their time in many ways, these early smart inhaler devices had limited success in the clinic because they were standalone products that were not well integrated into a broader disease management model. Some devices were found to be unreliable (e.g., the MDILog [14]) and this highlights the need for contemporary devices to be tested thoroughly and be shown to provide accurate recording of dosing.

SmartTrack pioneered a sensor that fits over a standard inhaler and an audio-visual reminder alerts users when they miss a dose. In one study, school-aged children with asthma who received the reminder had improved adherence and took

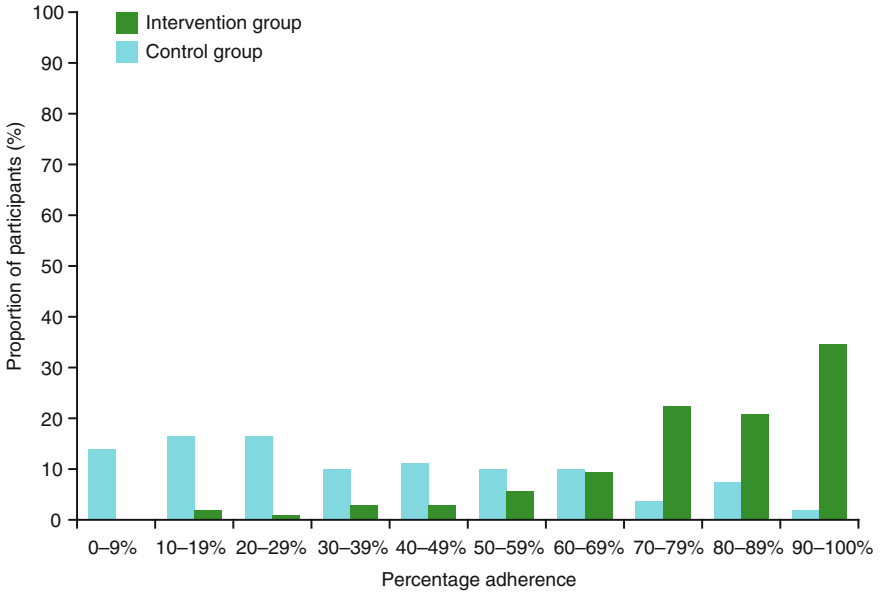

Fig. 4.2 Percentage adherence in patients with a previous asthma exacerbation aged 6–15 years receiving an electronic monitoring device (n = 110) or control (n = 110). With permission from [15]

a median of 84 % of their inhaled corticosteroids compared with 30 % in those who did not receive the reminder (Fig. 4.2) [15]. SmartTrack did not indicate whether the dose was inhaled or whether inhaler technique was correct.

GeckoCap (Teva, Petah Tikva, Israel) and Propeller (Propeller Health, Madison, WI, USA) are examples of systems that include sensors that connect to the inhaler and detects when the inhaler has been actuated. The data can be uploaded to an app or a cloud-based system. These sensors do not indicate whether the drug has been taken or whether inhaler technique was correct. In contrast, next-generation smart inhalers should record the inhalation profile and indicate whether a dose was inhaled and whether inhaler technique was adequate. A group at Trinity Center for Bioengineering, Dublin, Ireland, has investigated the feasibility of using acoustic measurement to detect steps in dose preparation (e.g., actuation of an MDI), detect inhalation, inspiratory flow rate, and volume (from a dry powder inhaler) [16–18].

4.3.4 Preliminary Examples of Smart Pharmaceutical Devices in Diabetes

There is also considerable interest in the field of diabetes management to optimize glycemic control based on key parameters such as dosing history and biomarkers. For instance, LabStyle's Dario™ system allows people with diabetes to measure

glycemic control using a monitor that plugs into the headphone socket of a smartphone or tablet computer [19]. The app logs blood sugar levels and patients can track carbohydrate intake, insulin use, and physical activity. Users view the information chronologically or compare time segments. A calculator helps users adjust their insulin dose based on carbohydrate intake, blood sugar concentration, and glycemia target. HCPs, parents, and other caregivers can access the data on a cloud [19]. Dario is not integrated with an insulin delivery system. Nevertheless, the growing number of apps used by people with diabetes illustrates the rich, relevant, and actionable datasets that could be collected automatically from smart pharmaceuticals.

The above examples demonstrate proof of principle of the benefits offered by smart pharmaceuticals, although—as the following discussion illustrates—they barely scratch the surface of the potential outside the clinical trials space.

4.4 Smart Pharmaceuticals' Potential Impact on Adherence

Medication adherence is a key parameter that the clinician should assess during a care pathway and as such it can be considered the "fifth vital sign." For example, when a patient shows a suboptimal therapeutic response, checking adherence is a prerequisite before changing or escalating therapy. Indeed, many people with supposedly "resistant" disease—including difficult-to-control asthma [20, 21] and resistant hypertension [22]—are probably not adherent in the first place.

4.4.1 The Epidemiology of Poor Adherence

It is now well accepted that patient nonadherence to prescribed medicines is endemic and therefore a central issue in the quality and economics of ambulatory medical care and drug trials. However, many studies examining the epidemiology, causes, and consequences of suboptimal adherence have been poorly designed. In particular, few studies adequately differentiate the three essential components of medication adherence—initiation, implementation, and discontinuation [23]:

- Initiation refers to the patient taking the first dose of a medication.
- Implementation refers to the way in which a patient's actual dosing corresponds to the prescribed regimen, from initiation until the last dose.
- Discontinuation marks the end of therapy. Persistence refers to the time between initiation and the last dose, which immediately precedes discontinuation.

A meta-analysis of 16,907 patients enrolled in 95 clinical trials highlighted that adherence was usually underestimated by pre-electronic methods and is clinically

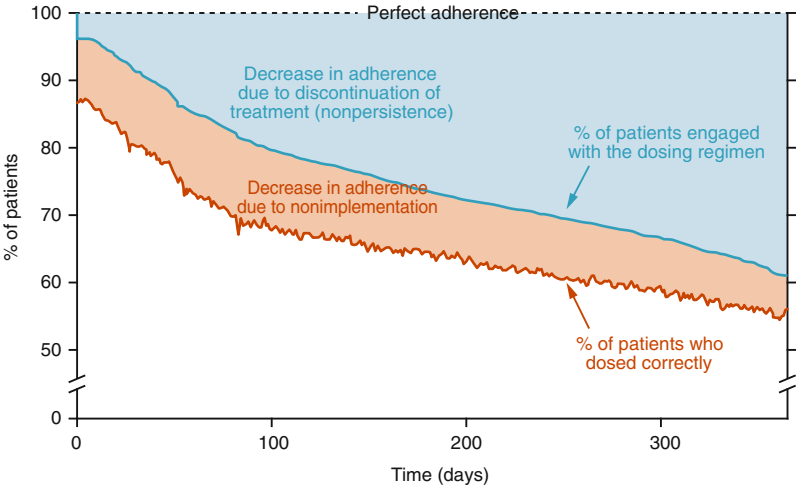

Fig. 4.3 Time course of adherence based on persistence (*blue line*) and adherence based on correct execution (*red line*) among 16,907 patients prescribed oral medications for one of a variety of medical conditions. With permission from [24]

under-recognized as a frequent cause of failed treatment or underestimated effectiveness [24]. Figure 4.3 shows the time course of adherence based on persistence (blue line) and adherence based on correct implementation (red line) from this meta-analysis. The decline of the blue line indicates permanent discontinuation; the red line shows the percentage of patients who dose correctly on each day and therefore varies from day to day. The pink area between the blue and red lines shows the shortfall in drug exposure arising from missed doses (suboptimal implementation) while the light blue area shows the shortfall in drug exposure caused by decreased persistence.

In a retrospective analysis of pharmacy claims including 167,907 patients, persistence to six classes of agent used in the treatment of chronic diseases declined rapidly in the first 90 days of therapy and then continued to decline at slower rates (Fig. 4.4) [25]. Mean 12-month adherence was 26 % for prostaglandin analogs (used in the treatment of glaucoma), 61 % for statins (used in cardiovascular disease), 60 % for bisphosphonates (used for prevention of bone fracture), 72 % for oral antidiabetics, 66 % for angiotensin II receptor blockers (used in cardiovascular disease), and 35 % for oral agents used to treat overactive bladder.

An analysis of 195,930 prescriptions reported nonadherence rates over one year of approximately 30 % for newly prescribed medications for chronic conditions, including hypertension (28.4 %), hyperlipidemia (28.2 %), and diabetes (31.4 %) [26]. Forty percent of patients do not fill their original prescription for a cardiovascular medicine. About 50 % of those who start a cardiovascular medicine discontinue within a year [27].

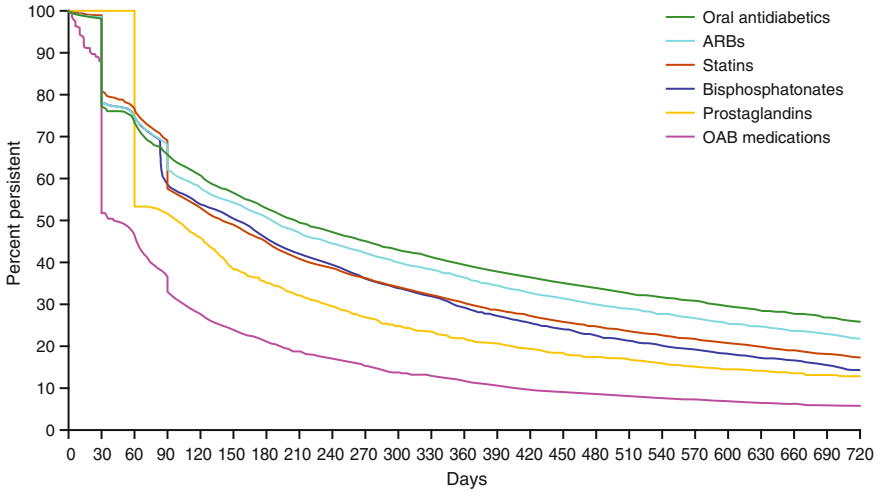

Fig. 4.4 Time to discontinuation of six drug classes, allowing for 30-day treatment gap, among 167,907 patients. With permission from [25]

Future studies using smart pharmaceuticals might be able to identify crucial errors in dosing that can jeopardize treatment outcomes. In some cases—such as reducing viral load in the initial treatment of HIV and hepatitis C virus—full or almost total adherence might be necessary. For example, most antiretroviral regimens for HIV require almost perfect implementation of the dosing regimens to optimize clinical outcomes and avoid resistance [28]. Such insights could facilitate consultations with patients and potentially lead to development of new extended-release and other formulations to overcome some hurdles to adherence.

Notwithstanding the methodological limitations alluded to above, nonadherence is estimated to account for between 3 and 10 % of total healthcare costs in the USA [29]. Healthcare costs reached $3 trillion in 2014, according to the Centers for Medicare and Medicaid Services [30]. Therefore, the economic burden imposed by nonadherence could reach $300 billion. Several cost drivers account for this expenditure, including worsening disease progression, complications, adverse events, hospitalizations, emergency department visits, and death [31, 32]. For example, in a study from the USA, after adjusting for potential confounders, each 25 % increase in the proportion of time without inhaled corticosteroids was associated with a doubling of the rate of asthma-related hospitalization [33]. Data collected by smart pharmaceuticals could, as discussed below, help optimize the use of increasingly scarce healthcare resources and reduce the economic toll exerted by poor adherence.

4.4.2 Using Technology to Improve Adherence

In a study of people with difficult-to-treat asthma, when presented with evidence of their dosing patterns, 88 % admitted poor adherence after initially denying that they failed to follow the HCP's advice [21]. This finding underscores that feedback can lead to a more open and focused discussion about adherence [34]. Indeed, a systematic review suggested that objective monitoring of adherence with inhaled corticosteroids and feedback about behavior improved asthma outcomes in adolescents [35].

Against this background, there have been many attempts to use technology to improve adherence, although these have had limited success. There is some evidence, for example, that inhaler reminders improve unintentional nonadherence in people with respiratory diseases. In a study of 143 patients with moderate to severe asthma, adherence (based on prescribed daily doses) was 73 % in those who received twice-daily inhaler reminders for missed doses plus adherence feedback using a monitoring device clipped to the inhaler compared to 46 % among controls. However, there was no difference in asthma control or severe exacerbations after adjusting for exacerbation history. In other words, the improvement in adherence did not translate into differences in asthma control [36].

Given the ubiquity of mobile phones, it is perhaps not surprising that several studies have assessed the effectiveness of reminders, delivered by text message, to improve adherence. The first of these studies, published in 2008, found that adolescents valued a text message service consisting of daily reminders to use an inhaler, health education tips, and safety messages [37]. Studies have shown a modest benefit of text message reminders. A meta-analysis, assessing health promotion interventions using text messaging, included 19 randomized controlled trials conducted in 13 countries (Fig. 4.5) [38]. Overall, text messaging was associated with a small-to-medium effect size (mean $d = 0.329$), which compares favorably with other health promotion interventions, such as print-based, computer-delivered health, and message framing interventions. Text messages on smoking cessation, physical activity, and—to a lesser extent—weight loss and primary care appointments were the most successful. Text messaging about preventive medications did not show a significant effect, although this conclusion is based on limited evidence. Another meta-analysis of 2742 patients enrolled in 16 studies showed that text messaging more than doubled the odds of medication adherence compared with no text messaging (odds ratio, 2.11, 95 % CI, 1.52–2.93) [39]. An example of a successful randomized trial of text messaging is the TRIMM study, in which African–American obese/overweight patients were randomized to tailored text messages or standard care [40]. At 6 months, text messaging was associated with greater mean weight loss and the degree of engagement with messages was correlated with weight loss. Patients' attitude to text message reminders is clearly important yet, in a survey of 989 patients with glaucoma or ocular hypertension, only 47.5 % reported text messaging would help adherence [41]. Respondents for whom text messaging would be beneficial were more likely to be aged below

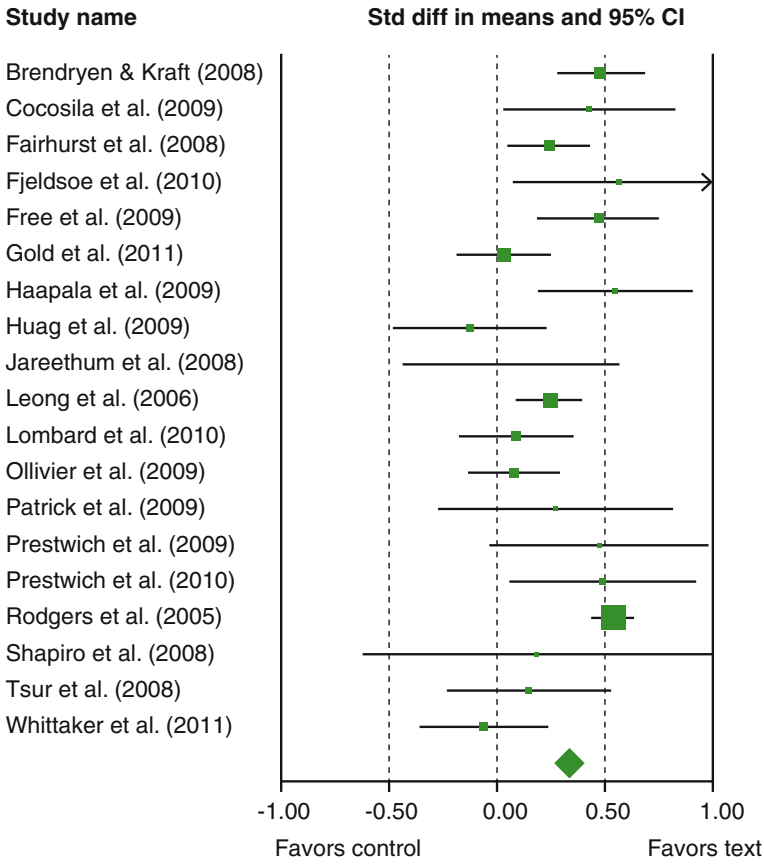

Fig. 4.5 Effect size of text messaging-based interventions on health-related outcomes. With permission from [38]

40 years and more likely to be African-American. Other studies suggest that reminders do not improve adherence: for example, in a study of 230 patients receiving antiretroviral therapy, text message reminders linked to late doses detected by real-time adherence monitoring did not significantly improve adherence and had no impact on viral suppression [42].

Further studies should use the taxonomy outlined above to ascertain whether text messaging has a differential effect on initiation, implementation, and discontinuation [23]. Cost-effectiveness should also be incorporated into future studies: many of applications designed to improve adherence (e.g., mobile phone apps) can be built at low cost and would need to produce only small changes outcomes to have an overall beneficial effect.

To date, most studies investigating the utility of apps or text messages have been small and have measured adherence by self-report, which is prone to desirability and recall bias. Furthermore, respondents may provide answers that conform to their

perceived expectations of the "right" answer and what they think the HCP wants to hear. In addition, few subjective scales that purport to measure adherence have been shown to agree with MEMS or clinical outcomes across multiple diseases [43].

Pill counts or pharmacy refills offer an alternative to self-reporting of adherence. However, these methods are biased and offer only sparse information about adherence—there is no guarantee that the pills have been taken and prescriptions may be filled before the patient needs another supply.

Against this background, integrating new technology into a "smart" system to use multiple capabilities and improved care coordination could better identify the factors that influence adherence. Capturing dosing history data is likely the biggest step toward improving the efficacy of treatment. Other data—such as the geographical location where administration took place—may add explanatory power, although this will probably be much less than dosing history. The optimal data sets need to be characterized using pragmatic clinical studies and service evaluations.

4.5 Smart Pharmaceuticals' Potential to Monitor and Improve Clinical Control

Smart pharmaceuticals move beyond most previous technology-based adherence interventions to offer the potential to monitor and improve clinical control of a range of diseases. Such developments are possible owing to the increasing number of biomarker sources that are accessible without blood sampling (e.g., tears, sweat, and saliva). Robust clinical evaluations need to ascertain the specificity, selectivity, and predictive value of many of these biomarkers to determine which could inform pharmacological management.

Emerging proof-of-concept studies show that monitoring clinical control and adapting management is possible. The growing number of closed loop artificial pancreases has already been noted. Furthermore, in 2014, Alcon/Novartis licensed Google's "smart lens" "for all ocular medical uses." The smart lens has embedded miniaturized electronics including noninvasive sensors. As a result, one version of the smart lens can continuously measure glucose levels in tear fluid and upload the results wirelessly to a mobile device [44]. Although the method needs validation in large-scale studies, patients could adjust their insulin dose to maintain glycemic control.

Exhaled breath offers another potential source of biomarkers, such as fractional exhaled nitric oxide (FENO) [45]. Further research is needed into the clinical utility of biomarkers in asthma and COPD.

4.5.1 Monitoring and Improving Disease Control in Asthma

Pressurized MDIs entered clinical practice in 1956 [46]. Over the last 60 years, numerous bronchodilators, corticosteroids, and other anti-inflammatories, delivered

by a range of devices have reached the market for COPD and asthma. Despite incremental innovations in respiratory drugs and inhaler design, poor adherence (see above) [47–49] and inadequate technique are common. Indeed, up to 94 % of patients, depending on the inhaler, assessment and instruction method, and level of health literacy, do not use their inhalers correctly [50, 51]. Common problems include not exhaling before inhalation, not holding the breath after inhalation, incorrect inhaler position, and incorrect dose metering [50].

Smart pharmaceuticals can help overcome these issues and facilitate the regular assessment and reinforcement of correct inhalation technique, which is essential to improve management [50]. Potential benefits of smart pharmaceuticals for the patient and for research are summarised in Table 4.1. An ongoing study, for example, is assessing a device that makes an acoustic time-stamped record when the inhaler is opened, and analysis of this record allows HCPs to determine the steps involved in using the inhaler [52].

Existing medical devices illustrate that delivery of respiratory interventions can be adjusted according to breath dynamics and capture variables, such as respiratory rate and inhalation parameters. For example, auto-adjustable continuous positive airway pressure (C-PAP) devices reduce sleep parameters and snoring index, as well as improving subjective sleep quality [53]. Philips' System One C-PAP device compensates for variable resistance characteristics related to different masks; analyses ambient temperature, relative humidity and flow; and optimizes humidity [54].

The I-neb Adaptive Aerosol Delivery System releases medication only when the patient inhales, and pulses the delivery of medication into 50–80 % of each inspiration, based on a rolling average of the last three breaths. I-neb provides continuous audible and tactile feedback to the patient reassuring the user that treatment has been delivered successfully [55]. In addition, this device can record tidal inhalations and the data on usage can be downloaded.

To develop the new generation of smart pharmaceuticals that will improve outcomes in respiratory disease means moving beyond using a vacuum pump to

Table 4.1 Potential values of smart pharmaceuticals in asthma management

For the patient	For research
Identification of errors in dose preparation and inhalation could aid device training	Identification of critical errors
Optimal drug delivery according to breath dynamics	More realistic inhalation modeling and development of improved inhalers
Detection of changes in breath parameters, medication use, and/or symptoms could warn of exacerbation	At population level, identification of patterns that are associated with exacerbations
Warn of need for refill	Could be useful for studying persistence within populations
Warn when a dose is overdue and prevent overdosing	Could track the relationships between dose timing and symptom control
Information that will aid self-management, e.g., information on nearby environmental triggers	Identification of associations between environmental factors and medication use

model inhalation through the devices. Most current studies stop assessing inhalation at 30 L/min, despite the fact that many patients can achieve this flow rate and does not represent a minimum flow rate. In addition, vacuum pumps produce an un-physiological "square wave" model of inhalation. New methods use a more physiological model that measures, for a dry powder inhaler, inhalation flow against time; acceleration that de-aggregates the powder; and inhalation volume [56]. People with very weak flow may not de-aggregate dry powder.

Analyzing these complex data to derive insights that inform the development of new inhalers can prove challenging. However, artificial neural networks integrate numerous variables across a range of peak inspiratory flows and volumes. Neural networks have offered unprecedented insights into the relationships between in vitro data, subject characteristics, and in vivo outcomes [57]. To take one example, the insights offered by neural networks could lead to devices able to compensate for the weak inhalation profiles common in respiratory diseases, such as severe exacerbations of asthma or COPD.

Smart inhalers might also be able to collect data that identifies prognostic markers for exacerbations of COPD and asthma. Numerous studies show that declining peak flow readings and increased beta$_2$-agonist use precede dangerous exacerbations [58–60]. For example, peak expiratory flow typically declines for several days before an asthma exacerbation (Fig. 4.6). This decline is especially

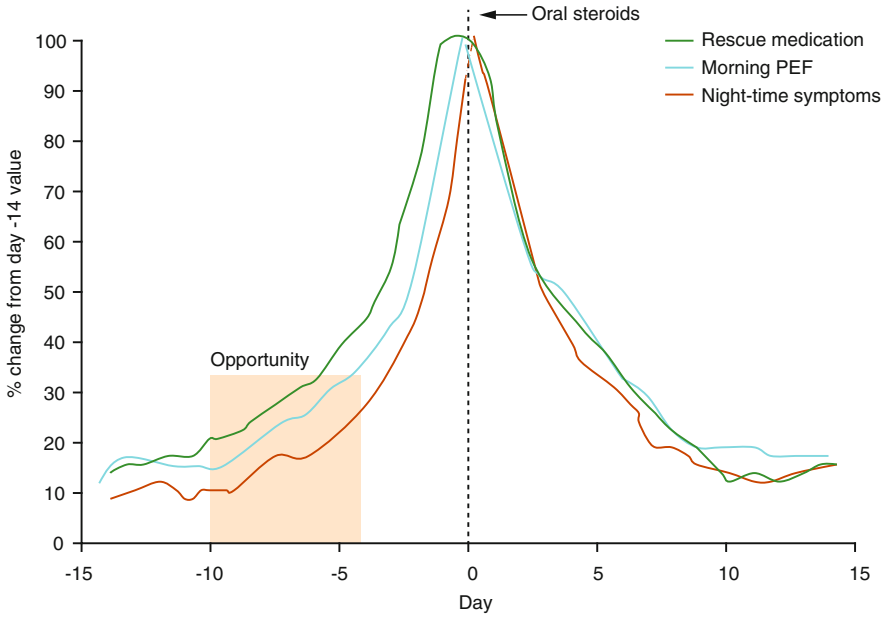

Fig. 4.6 Percentage change from day−14 in rescue medication use, morning PEF and night-time symptoms before and after an asthma exacerbation (day 0) in post hoc analysis of 242 patients who suffered 425 severe exacerbations in the FACET trial. PEF, peak expiratory flow. With permission from [60]

marked in the 2–3 days immediately before the exacerbation. Symptoms and use of rescue medication also increase over this period [60].

The new generation of smart inhalers may be able to detect changes related to pulmonary function and combine those data with data on use of rescue medication and symptoms to identify a heightened risk of exacerbation. The inhaler could then prompt patients to change behavior (e.g., increase controller medication) to prevent an exacerbation.

Asthma action plans could include such monitoring to improve self-management and reduce the risk of a severe exacerbation and the associated healthcare costs. At a population level, analysis of data collected by the smart inhaler could identify patterns that are associated with exacerbations. This could help inform the development of treatment algorithms and management guidelines.

4.6 Barriers Hindering Use of Smart Pharmaceutical Among HCPs and Patients

The potential benefits offered by smart pharmaceuticals apply to numerous indications and settings. Therefore, smart pharmaceuticals will need to be accepted among a wide range of HCPs, including (depending on the healthcare system and local contracting arrangements) specialists, GPs, nurses, physician assistants, and pharmacists. This acceptance depends on robust pragmatic clinical studies and service evaluations with relevant outcomes that clearly articulate and demonstrate smart pharmaceuticals' benefits to patients and health systems [61]. HCPs need to see how an app or smart pharmaceutical could improve care, satisfy patients, save time, and improve outcomes. For example, data provided by smart pharmaceuticals may facilitate greater use of clinics coordinated by nurses, physician assistants or pharmacists, which can help reduce the pressure on doctors and limit costs at a time of rising demand. However, there is a need for cost-effectiveness analyses and service evaluations in routine clinical practice to demonstrate these benefits [62]. Purchasers are likely to require these data to support the reimbursement of the smart pharmaceutical/app, which is, of course, essential for uptake by HCPs.

Selective use of smart pharmaceuticals can help drive uptake and improve cost-effectiveness. For example, smart pharmaceuticals could be used in selected patients, such as those with supposedly treatment-resistant or high-risk disease, for a defined time, to help monitor and manage nonadherence and poor clinical control. In the case of asthma, HCPs could provide a smart device to monitor asthma to people who, in the last 6–12 months, had used more than the recommended amount of bronchodilator, or had experienced an exacerbation.

Once an appropriate behavior is achieved, the HCP could confirm control or adherence using, for example, clinical outcomes and data from pharmacies, such as refill frequency or the proportion of days that patients have access to medication (e.g., medication possession ratio or cumulative medication gaps) [27]. The use of smart pharmaceuticals by people who already adhere or show adequate clinical

control would probably waste money and other resources. Indeed, further studies need to identify the patients most likely to benefit from smart pharmaceuticals in each indication.

Smart pharmaceuticals offer the prospect of real-time monitoring of clinical control, although this requires careful consideration before implementation. For example, real-time monitoring could send an alert to a doctor or another HCP when control worsens or another "red flag" is identified. This raises medicolegal issues: if the clinics were expected to monitor real-time data and an alert were missed, it could be liable for the consequences. Moreover, some patients may feel that this degree of reporting represents an unacceptable level of intrusion and scrutiny. Therefore, the medicolegal consequences of potential real-time monitoring need to be clarified, if the patient and HCP agree that this approach is clinically warranted and acceptable.

4.6.1 Reporting to the HCP

The output of any smart pharmaceutical system needs to be organized logically and lead to a clear and easy-to-follow pathway to improve care. The aim is to organize information and show interventions with the touch of a button so that the system improves clinic efficiency and requires no additional time from the HCP. Table 4.2 summarises some ways in which smart pharmaceuticals could help physicians in day-to-day practice. Usually, data collected by smart pharmaceuticals will be included with other clinical information into a report for the HCP. Such reports could save time, reduce duplication (e.g., primary care and secondary care HCPs performing the same evaluation), and facilitate clinical consultations. HCPs are, in the authors' opinion, more likely to welcome summary reports that can be used during a consultation than "real-time" data and alerts.

Table 4.2 How smart pharmaceuticals could help physicians

Benefits	Secondary benefits for the physician/clinic
Provide a summary report, which could form a basis for structured conversations on adherence and promote shared management	• Increased efficiency • Decreased duplication
Provide support for patients at particular risk of poor implementation (e.g., adolescents with asthma, learning disabled, elderly)	• Reduced need for repeat visits owing to poor control
Guide treatment decisions by confirming adherence before stepping up to the next level of treatment	• Easier requests for funding • If more patients are receiving the appropriate therapy: reduced need for repeat visits
Provide guideline-based recommendations	• Treatment can be delivered by nonspecialists
Facilitate clinics run by nurses, pharmacists, or healthcare assistants	• Increased clinic efficiency

Nurses, physician assistants, pharmacists, and other HCPs could review the data before passing to the doctor, if necessary. It has been shown that community pharmacists can provide valuable patient support that results in measurable benefits in adherence [63], and in many healthcare systems, community pharmacists are in a good position to review the data provided by a smart pharmaceutical system, discuss the implications with the patient, and make recommendations on dosing technique and adherence. In some cases, pharmacists can also make changes to the regimen and in other cases; they can pass the information to the treating physician to make these changes.

While potentially empowering consultations, HCPs' communications skills vary. Not every HCP is able to employ shared decision making to engage and empower patients. Smart pharmaceuticals, apps, and other high-tech innovations can be a helpful step toward higher quality consultations. However, HCPs have to know how to use the data and technology to successfully engage patients. Providers and manufacturers may need to offer support and education to ensure that HCPs derive the full benefits from technological advances. Once the benefits are demonstrated, HCPs will be more likely to promote the app and engage in the education and training to use it effectively and efficiently.

Currently, however, many HCPs appear to be reluctant to recommend apps to patients, which could hinder uptake of smart pharmaceuticals. In a recent survey, 41 % of doctors surveyed agreed that health apps could be a "game changer." Nevertheless, only 36 % said they are likely to recommend an app to patients. Currently, the main reasons for recommending mobile health apps are: diet and weight loss (70 %), general health and fitness (65 %), health monitoring (53 %), smoking cessation (49 %), and adherence to medicine (45 %) [64]. Younger HCPs may be more willing to use smart technology than their older colleagues.

In part, the reluctance to recommend apps might reflect the fact that many are aimed more at consumers than designed to meet HCPs' needs. To realize their potential, smart pharmaceuticals need to be fully integrated into routine clinical care and medical records. Current standalone apps and adherence devices, in the authors' experience, tend to appeal to motivated patients, rather than those patients who most need support, and are of limited value. People with diabetes can use such apps during consultations to demonstrate their glycemic control and insulin use. However, there are few such examples. Therefore, manufacturers and healthcare providers need to demonstrate that the smart pharmaceutical reduces work, increases efficiency, delivers information that facilitates rapid application, and seamlessly integrates into current practices.

Despite these barriers, smart pharmaceuticals offer the potential to engage and improve the skill and knowledge of patients and HCPs, as well as organize information in a manner that is helpful and that directs patients and HCPs toward solutions. For example, building or changing a habit depends on recording current behavioral patterns. Smart pharmaceuticals can collect a dosing history, which can then be used to make patients and HCPs aware of the behavior and start a focused discussion. The smart pharmaceutical can then ascertain the extent to which the discussion results in behavioral change. As such, electronically monitored dosing helps patients develop a medication-taking habit [65].

4.7 Barriers Hindering Use of Smart Pharmaceutical Among Patients

Apps and smart pharmaceuticals have the potential to build bridges between HCPs and patients. However, a feeling that monitoring clinical control and adherence is obtrusive ("Big brother is watching") could damage the patient-HCP relationship and could hinder uptake and acceptance.

Therefore, the smart pharmaceutical and any associated app should offer patients control over the collection and communication of data to themselves, the HCPs and purchasers, and other organizations. The importance of control and that the system should not act as a persistent reminder of the disease was underscored by the meta-analysis of the efficacy of text messaging-based interventions for health promotion. Allowing participants to set a schedule and interventions that were used with decreasing frequency was more effective than texting on a fixed frequency, such as once a month [38].

In the authors' experience, patients tend to accept data collection if they can see how the information can help improve their care. Patients must not feel the technology is being imposed; they need to give "permission" for the system to be used and for their data to be collected, stored, and shared [66]. Selective use of new technology to address a particular issue with adherence or clinical control (see above) can help patients to see the value of and accept the smart pharmaceutical. Patients like to feel in control.

In addition, smart pharmaceuticals that monitor disease and build the habits that drive adherence need to be sympathetic to a person's routine and to the reluctance of some people to be seen using a device or taking medication in public. Automatic and unobtrusive data collection helps build a daily habit of medication taking and monitoring. HCPs, purchasers, and manufacturers should appreciate that the motivation and social attractiveness of taking a medication or monitoring a disease is different from, for example, doing sports, stopping smoking, or starting a diet. People want to take their medications and monitor their disease activity rapidly, nonintrusively, and in privacy—then forget about it for the remainder of the day. As a result, social media may have only a small role within a smart pharmaceutical system.

Developers also need to be mindful of differences in the popularity of technological features among different patient groups. Texting, for example, is ubiquitous. The Pew Research Center found that all 18–29 year olds in the USA used smartphones to text message, compared to 92 % of those aged 50 years and over [3]. The proportion using their smartphone to access the internet was 97 and 80 %, respectively. The proportions using social networking (91 and 55 %), video (75 and 31 %), and music (64 and 21 %) were all higher among 18–29 year olds than those aged 50 years and over [3]. Smartphone ownership is very high among Black and Latino populations, and the percentage of Black and Latino respondents reporting using their smartphone to research a health issue was 67 and 73 %, respectively, [67]. Moreover, respondents from these groups reported relying on the smartphone

for internet access more heavily than White respondents. App and smart pharmaceutical developers need to consider these behavioral differences, along with manual dexterity, physiological senescence (e.g., declining lung function), and potential cognitive impairment, when designing apps and smart pharmaceuticals that are to be used by older people.

4.8 Regulatory Barriers Hindering Use of Smart Pharmaceuticals

Implementation of smart pharmaceuticals depends on resolving several regulatory issues. Table 4.3 summarizes some of these barriers and how they might be resolved. Inevitably, regulatory frameworks lag behind the pace of innovation. Indeed, as mentioned above there is not yet a clear definition of a smart pharmaceutical or of the standards required. For example, apps developed by "consumer" companies may use different coding systems for diseases than software in clinical use. This needs to be standardized to ensure seamless integration. Patient confidentiality and security are critical and need to be assured.

In particular, there is a need to harmonize regulation of apps and devices originating from medical companies with those developed for consumer-focused products. Nonmedical companies currently do not face the same scrutiny as pharmaceutical companies when they introduce a Health 4.0 product. Pharmaceutical companies need to provide more robust data than is required for the 510(K) or CE approval of apps and devices. Figure 4.7 shows which apps are subject to FDA regulatory approval [68]. This discordance could stifle innovation by pharmaceutical and other medical companies.

In addition, companies need to address areas that are not core to their competency, such as software development, cyber attack defenses, and data protection. Each element needs to be thoroughly beta-tested. This may result in novel partnerships between pharmaceutical and nonmedical companies, exemplified as that between Novartis and Google. Regulatory frameworks will need to be responsive to these market dynamics. Given the clear benefits offered by smart pharmaceuticals,

Table 4.3 Regulatory barriers and potential solutions

Barrier	Potential solution
Different coding systems for diseases	Harmonization of coding systems
Differences in regulatory requirements for products produced by consumer manufacturers and those produced by pharmaceutical companies	Consistent application of regulatory requirements
Requirements relating to data protection and defense against electronic threats	Collaborations between pharmaceutical and computing companies

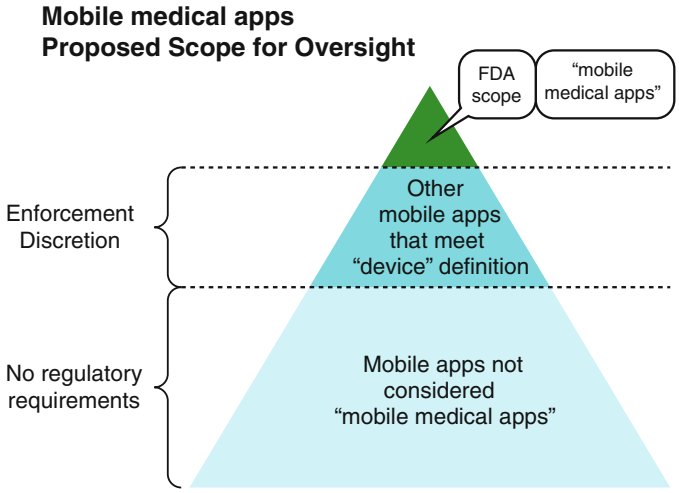

Fig. 4.7 Apps that require FDA approval. With permission from [68]

alluded to above, addressing these regulatory issues should be a priority to prevent disincentives from becoming entrenched.

Regulatory authorities also need to consider the impact of smart pharmaceuticals on clinical studies. Data have been collected electronically for years by using patient self-report and electronic measures. Smart pharmaceuticals could take this a step further: by tracking medication adherence and monitoring biomarkers and disease outcomes, smart pharmaceuticals may help improve the efficiency of clinical studies. As adherence to prescribed dosing regimens has a greater impact than any other factor on reducing variance in drug response and improving the effect of treatment, incorporation of smart pharmaceuticals to measure and optimize medication adherence in clinical trials could provide invaluable information on dose-dependent efficacy and safety [7]. Such innovations might help reduce the cost and duration of clinical studies. The benefits might be especially marked if clinical trial data sources can be combined into an integrated single product that has capability to capture large amounts of clinical trial data.

4.9 Smart Pharmaceuticals' Potential to Provide Data for Research

Many common diseases are pathologically complex, dynamically influenced on several levels from the genome to epigenetic mechanisms, and phenotype to the environment. The risk of developing type 2 diabetes, for example, arises from the interaction of genetic and biological factors with the obesogenic environment and

food choice. The risk of developing COPD is influenced on numerous levels from the genetic to policies over smoking.

Against this background, big data initiatives aim to facilitate a move to preventive, disease-modifying interventions by integrating very large data sets from a range of sources and levels. The Precision Medicine Initiative (PMI) is an example of this approach and takes into account individual variability in genes, environment, and lifestyle. The PMI is currently recruiting a research cohort of a million or more Americans who contribute their health data over many years to improve health outcomes, fuel the development of new treatments, and catalyze a new era of data-based and more precise preventive care and medical treatment [69]. Ongoing and future big data initiatives can provide an unprecedented evidence base of meta-studies (such as modeling and decision analysis), pharmacovigilance, and outcomes research [70].

Smart pharmaceuticals have the ability to collect large volumes of micro- and macro-level metadata in which the data from many patients are de-identified and collated. The analysis of these data may reveal previously unrecognized correlations and aid treatment individualization. However, the metadata collected needs to be relevant and actionable. For example, in respiratory medicine, metadata collected by smart pharmaceuticals could quantify the effect of lung function, symptoms, medication use, and environmental factors such as temperature, mold levels, altitude, comorbidities, lifestyle, environment, and genetics on outcomes. In other clinical settings—such as for expensive agents or drugs with a narrow therapeutic window—metadata collected by smart pharmaceuticals could be integrated with variables such as age, race (as a surrogate for pharmacogenomic variation), and renal function. Those parameters might predict pharmacokinetic and pharmacodynamic profiles allowing more accurate dosing (more akin to dosing based on body surface area or body weight), thereby minimizing waste.

Analysis of large rather than small data sets is more likely to identify high-risk patients and other subsets that may gain the greatest benefit from using smart pharmaceuticals and show the highest incremental cost-effectiveness for the payer. Such studies are important for the uptake of smart pharmaceuticals, as there is currently relatively little evidence.

While such advances will improve outcomes, the legal and ethical implications of using data collected by smart pharmaceuticals need to be clarified. For example, identifying behavioral or other risk factors associated with a disease or poor treatment outcome could influence insurance and employment prospects. Legal safeguards need to prevent employers and insurance companies restricting employment and healthcare based on data collected by smart pharmaceuticals. Moreover, even among HCPs, stigma and social disqualification still surround certain diseases, such as COPD, obesity, and addiction [71–73]. HCPs might be more reluctant to invest time and resources, or engage in education, to use smart pharmaceuticals in stigmatized conditions. Legal and ethical safeguards also need to ensure that certain groups do not become disenfranchised from the benefits offered by smart pharmaceuticals.

4.9.1 Big Data in the Clinic

Big data could be integrated with expert systems that improve the quality of consultations by nonspecialists and potentially reduce referrals to specialists. In this vision, the clinician follows a management algorithm, based around guidelines (such as the Global Initiative for Asthma [GINA] and Global Initiative for Chronic Obstructive Lung Disease [GOLD] in respiratory medicine) and symptom scores. Big data collected at a population level could allow the HCP to optimize the drug, regimen, and self-management plan based on the appropriate management guidelines. The impact in the individual patient could be tracked by monitoring clinical control and medication adherence. If sub-optimally managed compared with the population data, smart pharmaceuticals offer the opportunity to use behavioral and decisional models to improve outcomes. As discussed above, showing patients their record engenders awareness of their adherence and can act, if presented appropriately, as a stimulus for change [36].

Big data could lead to a "whole-system perspective" of healthcare, while the increased connectivity exemplified by smart pharmaceuticals should facilitate seamless, integrated care. Importantly, there is a need to incentivize data sharing between different parts of a healthcare system.

Unfortunately, there is already a bewildering number of smartphones, tablets, and other internet-enabled technologies, apps, and electronic records. These multiple platforms could, in theory, discourage use. There is, therefore, a need to ensure that apps and smart pharmaceuticals are fully integrated with healthcare systems and that systems are standardized across companies to reduce the burden on clinicians and healthcare services.

In other words, realizing the potential of smart pharmaceuticals in clinical practice depends on ensuring vertical (e.g., all devices in a disease area) and horizontal (across disease area) integration of the database and platforms. Vertical integration allows seamless transition between, for example, inhalers to improve adherence or improve clinical control. Horizontal integration is especially important for conditions associated with numerous comorbidities, such as COPD, which is associated with, for example, lung cancer, asthma, sleep apnea, cardiovascular disease, diabetes, skeletal myopathies, osteoporosis, and psychiatric disorders [74].

4.9.2 Persuading Payers

Nonadherence compromises clinical efficacy and increases costs [26, 27, 29, 31, 32]. Declining peak flow readings and increased beta$_2$-agonist use precede dangerous exacerbations, which are important cost drivers in COPD and asthma [58–60, 75, 76]. Therefore, improved adherence and better management of chronic conditions through enhanced monitoring and individualized care has the potential to reduce healthcare costs.

There is currently little economic evidence supporting smart pharmaceuticals. It seems plausible, in the authors' opinion that smart pharmaceuticals could, for example: identify over- and under-use of medication; identify "waste" and inefficiencies; slow disease process by, for example, earlier identification of exacerbations; and achieve greater efficacy. Medication usage data can be used to identify high-risk patients who stand most to benefit from focused intervention [77]. However, there is an urgent need for economic evaluations, which will probably need to be performed from the perspective of each healthcare service. Data from the USA may not be directly applicable to individual European countries, for example. In addition, the direct and indirect costs associated with asthma and COPD vary between countries. Indeed, a recent study identified "tremendous variation in per capita annual costs of asthma and COPD" between countries [78].

Funding is the main barrier hindering uptake of smart pharmaceuticals, especially given the current dearth of economic and service evaluations. Senior management in payer organizations will welcome big data that facilitates planning and optimizes resource allocation, but these need to offer demonstrable and relevant benefits. Showing that a smart pharmaceutical results in behavioral changes (e.g., improved adherence) is unlikely to prove persuasive. Outcomes need to be economically quantifiable and relevant to the payer (e.g., reduced admissions, referrals, or primary care consultations). Pragmatic controlled studies using databases (e.g., refill rates as a surrogate for adherence and admissions) could form the basis of the evidence base supporting smart pharmaceuticals, which payers will generally accept.

Once accepted by the payer, guidelines, organizational protocols, and treatment pathways should include the smart pharmaceutical and the use of the metadata to ensure uptake by individual HCPs to realize these potential cost and clinical benefits. Eventually, HCPs' concordance with these guidelines, organizational protocols, and treatment pathways, as well as their patients' adherence to drugs and clinical control, could allow outcome-based funding of HCPs. Such data would also enhance HCPs' and patients' accountability and responsibility. Indeed, smart pharmaceuticals might encourage the development of a consumer-based market.

It is possible that in the USA and some other countries, incentive schemes by employers might be a greater stimulus to the uptake of smart pharmaceuticals than health insurers. In the USA, big employers are incentivizing employees to adopt healthy choices [79]. Big data and the introduction of smart technologies facilitate such initiatives. The way that this integrates with conventional healthcare remains to be seen.

In the USA, there is interest in Value-Based Insurance Design (VBID), which encourages use of services when the clinical benefits exceed the cost and discourages the use of services when the benefits do not justify the cost [80]. In some systems, copayments (contributions from the patient) are lowered for interventions that are considered to have high clinical benefit and low cost (e.g., beta-blockers) regardless of the use of the intervention provided they are used in patients without contraindications; in other systems, copayments of certain medications considered to have high clinical benefit and low cost are lowered for patients who are considered to derive most benefit (e.g., antidiabetic agents in diabetic patients). Maeng et al. evaluated a VBID program in which individuals with certain chronic conditions

could choose to receive selected antihypertensives, antidiabetics, and lipid-lowering agents with a $0 co-pay [81]. This program led to a reduction of $144 per-member-per-month in total healthcare spending compared with a comparison group in which the $0 co-pay was not applied. Usage data from smart pharmaceuticals could be used to derive the relative value of particular agents in particular populations and monitor the implementation of a value-added insurance scheme.

4.10 Future Prospects

Further in the future, data collected by smart pharmaceuticals could aid reimbursement, by, for example, establishing a value proposition (e.g., reduced hospitalizations and other "downstream" costs) that supports a higher acquisition price for the smart pharmaceutical compared to conventional medicine.

As data collection with smart pharmaceuticals becomes established and the data sets mature, it is plausible that payers could use the data to model and examine the costs and consequences of implementing new technology or changes to services. Large payers already routinely monitor the economic effects of changes in the medicines available and the way they are used. Metadata captured by smart pharmaceuticals allows such analyses in more detail and with greater accuracy than is currently possible. However, it is likely to be several years before these databases are sufficiently populated to allow these types of analyses.

In the future, pharmaceutical companies will consolidate their presence in emerging markets, such as China and India. The ability to deliver smart pharmaceuticals in these markets depends on addressing a number of issues including reimbursement, working with non-Western political structures and protection of intellectual property. It is not yet clear how these issues will play out. But the potential is clear.

For instance, in developing countries and emerging markets, a remote village could have an automated kiosk that can take samples, diagnose disease (based on a finger-prick blood sample, for example), offer a web-based video consultation with a HCP, and have medication delivered by a drone or through the mail. While such centers are technologically possible, funding remains a barrier. This example may be pure speculation, but it underscores the potentially transformative benefits offered by smart pharmaceuticals.

4.11 Conclusions

Smart pharmaceuticals were introduced about four decades ago with the MEMS. Since then, they have been primarily used in research and clinical trials, but their uptake is expected to grow exponentially with the ongoing digital revolution. Estimated global sales of smart drug-delivery systems have increased from $139 to $197 billion, between 2009 and 2014 [16]. Future smart pharmaceuticals can

strategically overcome the limitations of some of the current examples, including patient intrusiveness, safety issues, and the risk of false-negative event detection. The proper integration of smart pharmaceutical systems into medical care is a prerequisite to support the patients who need the most support rather than being chosen by the most motivated patients. Selective implementation of the use of smart pharmaceuticals in specific patient groups may be a more rational approach rather than aiming for universal use or marketing to motivated patients.

Future smart pharmaceuticals could collect a range of micro- and macro-level metadata that can offer new insights into disease, aid service design, and facilitate personalized medicine. Increasingly, these data can be consolidated into reports that offer actionable insights for HCPs and patients. However, some HCPs may need support to develop the consultation and communications skills to realize the potential offered by smart pharmaceuticals to, for example, improve adherence and disease control.

Meanwhile, developers need to remain aware of the importance of engaging patients to maximize uptake and acceptance. In particular, the smart pharmaceutical and any associated app should offer patients control over the collection and communication of data to themselves, HCPs, and other third parties. Scaling up smart pharmaceuticals depends on vertical and horizontal integration of the database and platforms.

The objective of this chapter is to provide a long-term view of the future potential benefits of smart pharmaceuticals. Consequently, many of the benefits outlined in this chapter are speculative: there is a pressing need for pragmatic clinical trials, service evaluations, and cost-effectiveness analyses to confirm that smart pharmaceuticals will yield clinical, patient-orientated, and economic outcomes. For example, some of the methods to monitor and improve clinical control require validation. Studies designed to investigate interventions aimed at improving medication adherence need to take into account the initiation, implementation, and discontinuation of treatment. While further research is vital, smart pharmaceuticals offer an exciting and growing opportunity to improve care with significant potential benefits for individuals, health systems, and societies worldwide.

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Chapter 5
Surgery 4.0

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5.1 Introduction

Surgery is a manual medical discipline and insofar digitalization of surgery could be considered as irrelevant. The contrary is true. It will be demonstrated in this article that digitalization is the key for the survival of modern surgery.

Surgery is situated in a triangle between the quality of outcome, the expenses and the therapeutic trauma (Fig. 5.1).

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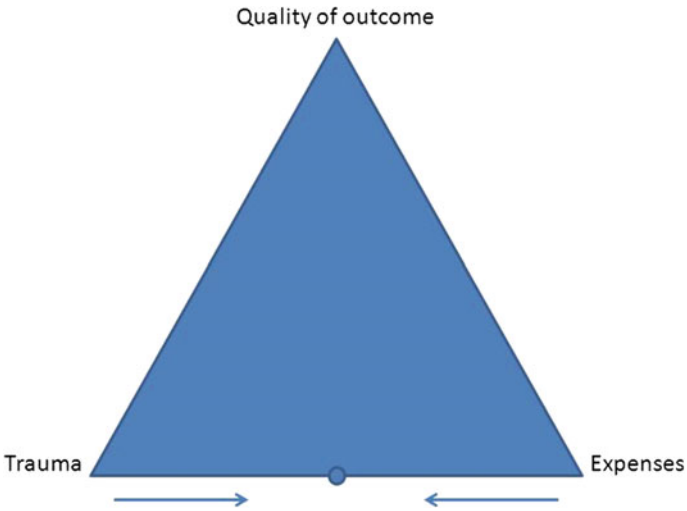

Fig. 5.1 The "magic" *triangle*: Both the expenses as well as the surgical trauma have to be reduced. Simultaneously, the quality of outcome has to be augmented continuously. At first glance, these three aims appear to be completely incompatible. Improving the quality of care is inevitably linked with higher costs and minimally invasive interventions are always more expensive than conventional ones. It is hypothesized that a comprehensive use of e-health is a chance to master this conflict

The problem of contradicting aims, however, is not an issue unique to surgery. In industry, the situation is comparable: The products must continuously become better, but the costs have to be reduced and public acceptance has to be maintained or even improved.

The answer industry has found to solve the dilemma is "Industry 4.0". This is a collective term which describes the combined use of cyber-physical systems, the internet of things and the internet of services to improve the chain of value organization. In other words, the computerization of manufacturing helps to make processes more effective, faster, safer and less expensive [1].

The idea is convincing. Accordingly, the surgeons should be very attentive to observe this new development. If this approach is successful, they should look for options to adapt the principles of "Industry 4.0" to the specific conditions of surgery, leading, perhaps, to a "Surgery 4.0" model. This article aims at the identification of future fields of application in surgery.

The operating room is the "profit centre" of a surgical unit. It will be the main focus if the idea of "Surgery 4.0" is discussed. Nonetheless, the whole chain of surgical care delivery has to be considered including pre- and postoperative care as well as decision making and surgical training and education.

At a closer look, "Surgery 4.0" is not less complex and challenging as "Industry 4.0", but equally—or even more—promising.

5.2 The "Collaborative Operating Room"

5.2.1 Context Awareness

The idea of context-awareness was originally derived from the concept of pervasive computing. Special investigative research on the term began in 1994.

Whereas pervasive computing strives to provide transparent use of computing facilities to users anytime and anywhere, independently of the environment, context-aware systems focus on providing the right service to the right user at the right time. Context-aware systems acquire context, analyze and interpret the context and modify the system behaviour for the user's changing situation. In other words, context-aware systems adapt their services to the user's need without explicit intervention from the user, thus working at least partially autonomously.

Making the context information available to the computer system is the first essential key issue of context-aware systems. Data retrieval by sensors plays a central role, complemented by other sources of information.

Sensing technology is already well-developed today and allows for the application of context-aware systems [2], context-aware file systems [3], context-aware security [4], context-aware activity recognition [5], context-based searching [6] and even intelligent healthcare systems [7]. To the best of our knowledge, however, surgical activities in the OR were not yet considered. Data retrieval and capturing is certainly not as easy in the surgical environment as compared to a technical system, e.g. of an airplane. Some special aspects are presented below.

The next challenge is to interpret the data in a senseful manner and finally to derive reasonable suggestions of further activities, as roughly delineated in Fig. 5.2.

Apparently plausible and easily implementable, this concept is still far away from being mature for clinical practice, since many elementary preconditions are not yet realized. One basic precondition is systems integration in the OR.

5.2.2 Systems Integration and Data Capturing

5.2.2.1 Systems Integration

An essential precondition of any approach to make the OR "intelligent" is the integration of all systems and devices used during surgery into a comprehensive surveillance and control system (SCS). The need for systems integration in the OR is well appreciated all over the world, but despite of many national and international efforts, it is still a vision today that all machines, devices and instruments are incorporated and interconnected (Fig. 5.3).

The process of systems integration is by far more difficult than initially expected. By nature, the problems are less technical rather than legal. The main question is to find a solution for liability. Few manufacturers are particularly interested in taking

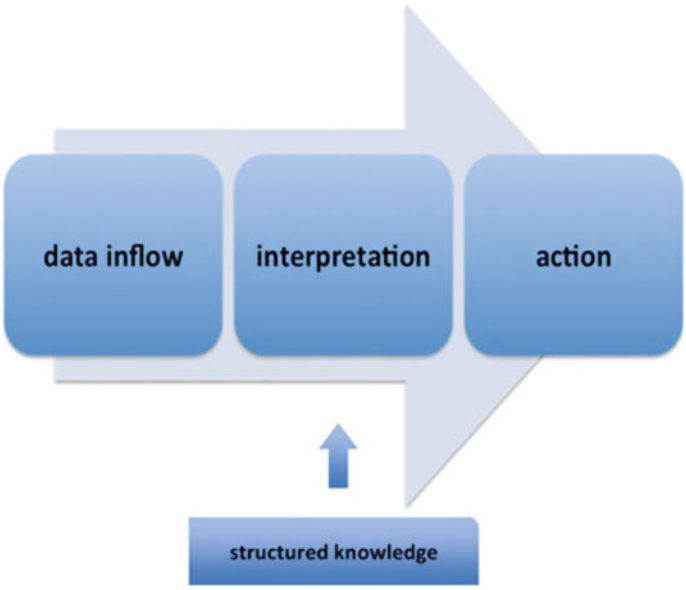

Fig. 5.2 The so-called "collaborative operation room" is based upon 3 pillars: Data capturing, interpretation of comprehensive real-time information ("reasoning") and the prediction of further activities

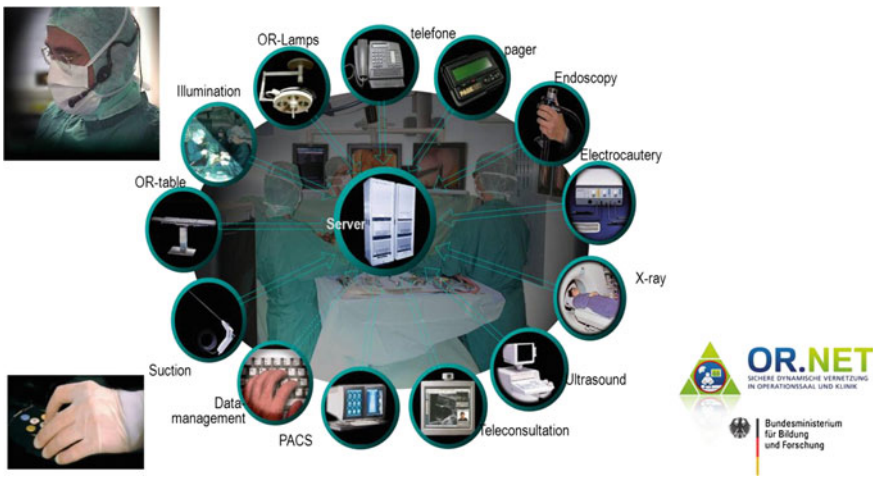

Fig. 5.3 In the surgical OR, a heterogeneous equipment is used coming from various manufacturers. The first step to establish a context-aware system is to develop a central, comprehensive control system capable of information capturing from all devices and additional equipment

over the overall responsibility for a conglomerate of foreign devices. Accordingly, several public commissions have been created internationally to solve the problems of interoperability. One example is the so-called OR.NET group which was sponsored by the German government over a period of 3 years. The project is based on previous work to modular and dynamic networking of medical devices in the OR making use of the paradigm of service-oriented architecture (SOA). The goal is the development of certifiable, dynamic, multi-vendor networking options for existing and future devices as well as for software solutions in the medical environment. The existing approaches will be further developed and improved especially to support plug-and-play networking, capabilities for approval and risk management. At the same time the developed solutions will be implemented as showcases in the commercial medical products of the SMEs project partners. By having a wide variety of consortium members, such as companies, clinics and R&D facilities, the project covers all significant areas like surgical planning, operation monitoring, diagnosis/treatment and documentation. Besides designing and defining new, trans-sectoral standards, the project also considers risk analysis, security, interoperability of exchanged data and developed IT infrastructure, while working on a standardization process with all relevant partners from the very beginning. Together with the involved companies, responsible users and operators operating models are being developed that allow a transfer of the overall functionality. In the development of operating models, the interests and perspectives of the involved groups must be balanced carefully. Moreover, there is a strong dependency between the technical concepts, the conformity assessment procedures to be defined as well as the processes of the operators. This means that the operating models must not only consider technical development and operational processes but also conformity assessment procedures. The participation of leading experts brings up new legal aspects, as well as new validation and testing procedures related to the capability for approval of the sub-components and the entire system. A major goal of the project is to establish a portfolio of methods and tools as well as prototype testing labs and environments that support the certification of new equipment in particular for SMEs.

A similar project is currently under-way in Japan: The “Smart Cyber Operating Theater (SCOT)” was started for networking the operation room. It is based upon ORiN (Open Robot/Resource interface for the Network), a standard network interface for factory automation systems proposed by the Japan Robot Association in 2002.

In the United States, the Medical Device “Plug-and-Play” Interoperability Programme (MDPnP) was established to accelerate the adoption of medical device interoperability to facilitate the development of electronic health records and the cost effective creation of innovative third-party medical “apps”. These apps deal with diagnosis, treatment, research, safety and quality improvements, equipment management, and adverse event detection and reporting when using networked medical devices for clinical care. MDPnP is one aspect of the Open ICE initiative—a community aiming at creating an Integrated Clinical Environment (ICE). Insofar, the MDPnP concept is broader as compared to OR.NET or SCOT which are mainly

focused on the surgical OR. Despite of these intensive international activities, rapid advancements of achieving a comprehensive OR integration can reasonably not be expected short term.

Context-aware systems rely on the acquisition of data/context about the actual situation in which the system is operating and about the activities of the user who is interacting with the system.

Nonetheless, systems integration is an essential precondition for “Surgery 4.0”.

5.2.2.2 Capturing of Raw Data

As compared to systems integration in the surgical OR, data acquisition is primarily a technical issue. Accordingly, it may be expected that information retrieval can soon be managed successfully.

The main pillars are:

Information upon objects:	**Instrument in use**
	Working state of devices
	Consumption of disposables
Information upon persons:	Presence of surgical team
	Position of the team members

Information upon objects

Peripheral and installed devices may provide valuable information about the context.

An example is given in Fig. 5.4.

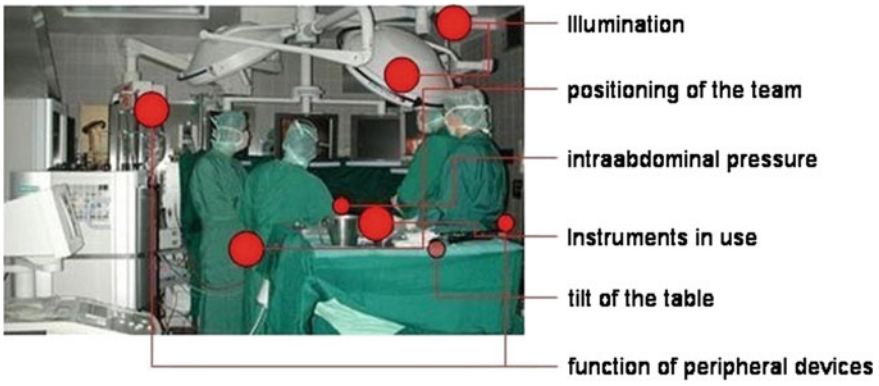

Fig. 5.4 Sensor information retrieval in an integrated laparoscopic OR suite. Comprehensive sensor information is fundamental for the development of cognitive systems

The actual functional state of the various systems gives a hint upon which steps of the operation are currently performed. This is an easy task if all rules and interdependencies are known and well defined.

It is assumed that about 2/3 of all so-called "high-level tasks" during a lap CHE can be identified with the information inflow as shown in Fig. 5.4 [8]. This is certainly not sufficient, but a strong base for improving the situation analysis by complimentary data such as staff tracking as mentioned below.

The data acquisition framework has to be integrated as perfectly as possible into the OR setup. It must, under no circumstances, disturb the regular surgical workflow and should not interfere with the system operability. The sensors should be as invisible as possible—additional wires or cables have to be avoided. Speed of data delivery is crucial, since the cognitive system in the surgical OR has to react in real time.

Up to now, only quite a few devices provide functional data and information via an open interface despite of the above mentioned approaches like OR.NET, SCOT and MDPnP.

As has been demonstrated by several papers [9, 10], information can also be gained by external sensors attached to "foreign" devices to analyze the display image or acoustical signals. Direct delivery would of course always be preferable, but it is not an absolute precondition.

Information about the staff

The presence and the activities of the individual members of the surgical team are invaluable clues to interpret the actual situation in the OR correctly and reliably.

Once the team is positioned at the OR table (according to strict rules), the individuals remain at their place till the procedure is finished. If they change their respective places, it is a sign that something particular is going on. The meaning depends on the context. If the surgeon is still in training/education, he is usually assisted by an experienced surgeon (first assistant). If the experienced assisting surgeon is forced to take over the operation, he has to change his place with the surgeon who now takes over the role of the assistant. This is a clear sign that the procedure is significantly more difficult than initially expected [11].

In another context, however, this change of roles could mean just the contrary: If the OR was originally begun by an experienced surgeon assisted by a less experienced surgical assistant, it may turn out intraoperatively that it is easier to perform than originally assumed. The surgeon decides now to leave it over to the assistant.

Moreover, assigning an instrument or device to one of the surgeons could generate another level of data capturing and would provide information upon the active and passive part independent from the position at the OR table.

All persons involved have to be equipped with a suitable identification tool as soon as they are entering the OR tract. Hence, they can be identified (and their respective role: anaesthesist, scrub nurse, circulating nurse, first assistant, second assistant, surgeon, etc.) as soon as they arrive in the OR.

A suitable real-time locating system (RTLS) is required to locate the players reliably.

There is a variety of technologies applicable for real-time location tracking, differing in metrics, such as position accuracy, energy consumption and costs. Those systems usually comprise two functionalities: on the one hand, a unique identifiable tag can be located in a certain range (depending on the amount of antennas and the signal strength) via triangulation. On the other hand, those systems usually allow the wireless transmission of sensor data connected to the tags. Modern tags often include sensors for temperature, humidity, acceleration, brightness and many more. Hence, it is possible to transmit wirelessly sensor data and simultaneously to track the location where the corresponding data was assessed. Such systems open a broad field of applications not only in the OR but the whole hospital, including patient safety, logistics and asset tracking.

An example of how a centralized data acquisition framework for operating theatres could be implemented is given in Fig. 5.5.

Since sensor data is known to be noisy, a filtering process is required in many instances. A hidden process is required to determine the true value of the sensors, such as presence of a tag in case of RFID, from a noisy and uncompleted set of features.

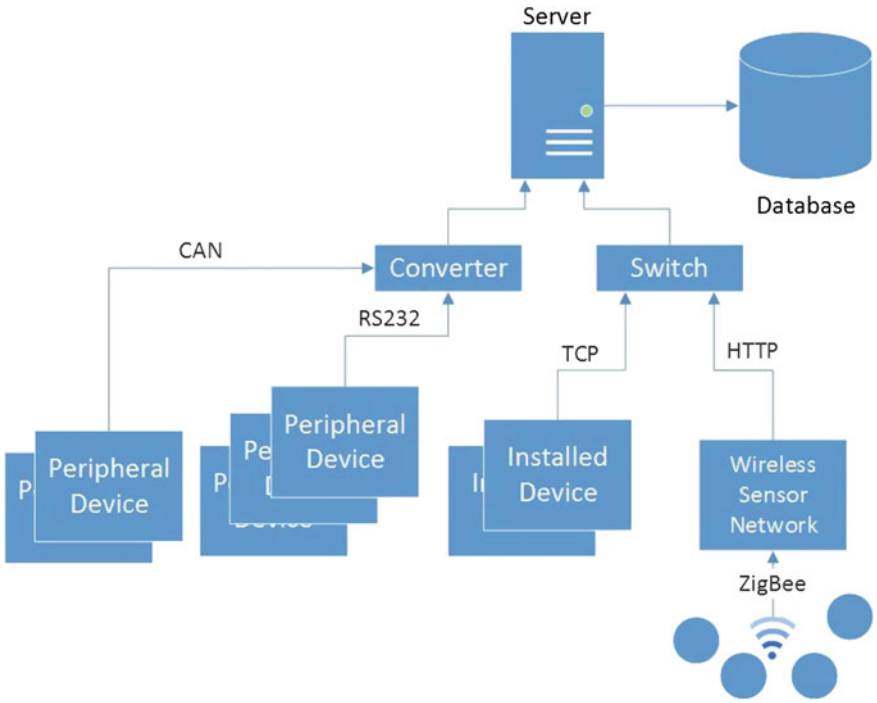

Fig. 5.5 Network scheme of the data acquisition framework. The different peripherals are connected via dedicated interfaces to the server with an attached storage database. In this particular case, ZigBee is used as one example for the RTLS implementation for localization of the staff members

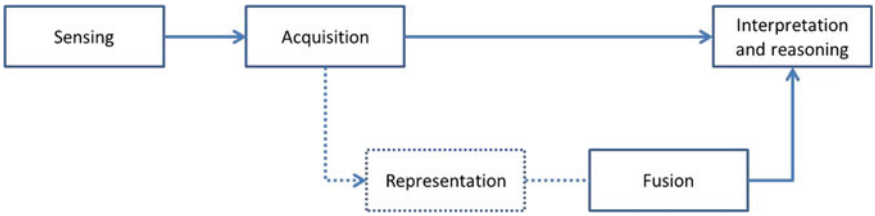

Fig. 5.6 Some data may be used directly for the analysis of the actual situation. In the majority of cases, a "fine-tuning" is required beforehand (context representation and context fusion (*dotted line*))

To cope with the incomplete set of sensor signals, Bouarfa et al. [8] propose to use Bayesian networks to define the structure of the sensor signals that occur in a certain action. In case of RFID, features usually describe one or more characteristics of the tag detected: the item to which the tag is attached, the location where the reading took place or the reader of the tag is placed.

However, in most cases additional steps have to be considered as shown in Fig. 5.6.

Context representation means the formal representation of the acquired contextual information, whereas context fusion focuses on the integration of information from different sources in order to merge overlapping aspects.

Context representation and fusion facilitate detecting and recognizing the dependency or relationship of one data source on another to infer user context. This problem becomes even more critical when context information is emerging from very heterogeneous sources like sensors, patient data and user profiles.

5.2.3 Data Analysis and Interpretation

Sensing and data capturing is the first step prior to data analysis and interpretation.

If this is provided, the "intelligence" behind the system must "interpret" these data, derive what is actually going on and foresee, in the third and last step, what should come next [12].

Like in human decision making, this is only feasible if he/she knows what he/she is dealing with and what has to be done.

She/he must understand the situation and must have a clear plan what has to be done why and how.

When entering an OR an experienced surgeon and a well-trained nurse will immediately understand the actual state of an ongoing operation and will be able to precisely predict the next steps on the base of their sound empirical knowledge. If a machine is supposed to do the same, this copious wealth of professional knowledge (about the procedure, the stage of the disease, the training level of the OR team, etc.) has to be formalized in a way that it may be understood by the computer.

Hundreds and thousands of rules, interdependencies have to be defined beyond of providing simple fact. So-called "models" are required!

In our context, at least two models are a precondition of data analysis and interpretation: The patient model and the surgical model.

5.2.3.1 Patient Model

Each single patient is unique and the actual course of surgery may vary—and this matters even if a standardized surgical procedure is considered. A normal cholecystectomy may be extremely simple and fast in case of a young lady with a reasonable Body Mass Index but extraordinarily time-consuming and challenging in a male patient with 75 years of age with a long history of chronic cholecystitis. In other words, individual features have a considerable influence upon the course of an operation and the outcome. Self-evidently, this has to be regarded if a context-aware system is to be developed (Fig. 5.7).

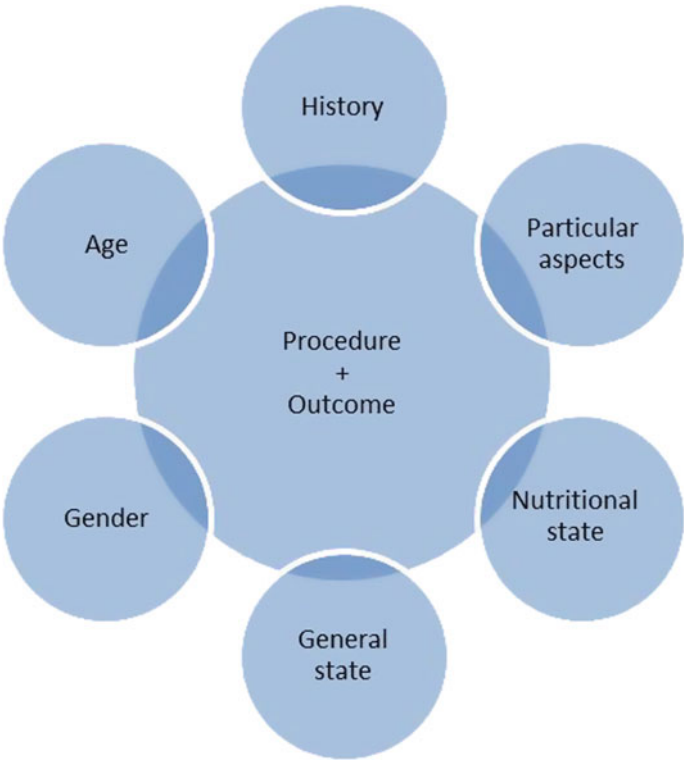

Fig. 5.7 Multiple factors contribute to the healthcare providing process and the surgical workflow. Many aspects like age, history, etc. are generic. Particular aspects are related to the individual surgical procedure

A patient model is required. This could be defined as a comprehensive robust model of the patient making all data available that is relevant for the operation. To create a patient model, all achievable information have to be collected (personal data, laboratory findings, results of imaging procedures, etc.), which is the first step. In the second step, the impact of each single information onto the expected course of the procedure has to be quantified.

Above, the impact of BMI on the workflow has already been mentioned. Another example is the number, size and quality of gallstones if cholecystectomy is considered. The experienced surgeons know that it is comparatively easy to retrieve a gallbladder if only a few, small and soft stones are present. Conversely, large, hard stones need more effort and time than the average.

In a patient specific model, it must be documented how many stones are present, and how large they are. In addition, the consistency of the gallstones should be known. As with gallstones for cholecystectomy any intervention has operation specific data that have to be included in the patient model.

Surgeons possess the domain knowledge to help create a patient specific model. This could already be shown in case of laparoscopic cholecystectomy, but much has still to be done to provide appropriate patient models for a broader range of surgical interventions till "Surgery 4.0" comes to reality.

5.2.3.2 Surgical Model

To understand what is currently going on is necessarily based upon a comprehensive understanding of the entire process. If a particular scenario of a surgical operation is evaluated, one needs to know what has happened before. In order to predict the next steps, it has to be known how the procedure is normally continued. A model of the procedure is required. In our case, a surgical model has to be created. Modelling a simple procedure is relatively easy: "Go from A to B; if B is reached, go to C". It soon becomes less trivial, if more than one option may exist, if some steps could be repeated.

The idea to break down a surgical operation into clearly defined segments still today is seen as an academic exercise, but is a prerequisite to make the machine to understand what is happening.

The surgeons have to define clearly step by step the normal course of the operation, and, concomitantly, potentially deviating actions.

Using an appropriate modelling language, a workflow description can now be designed. Today, numerous languages are in use with specific advantages and drawbacks. Mainly three of them are considered for surgical workflow modelling [13]:

1. **E**vent-driven **P**rocess **C**hains (**EPC**)
2. **B**usiness **P**rocess **M**odel and **N**otation (**BPMN 2.0**)
3. **Y**et **A**nother **W**orkflow **L**anguage (**YAWL**)

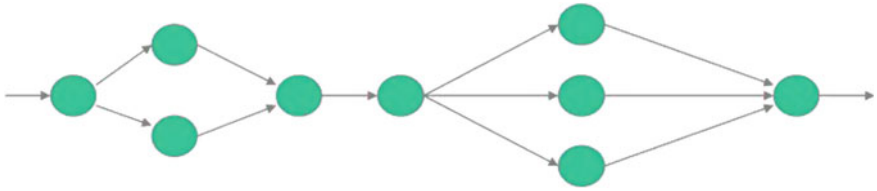

Fig. 5.8 Exemplary workflow model

If a workflow description is available (including all conceivable modifications), a fundament is laid to predict the next steps.

Workflow prediction by combining data and model

In a model, transitions are based on probabilities or abstract triggers. Hence, it is not possible to predict the duration spent in a particular state. In case of multiple subsequent parallel transitions, external signals are required to define the actual path. Specific transition triggers usually consist of non-obvious combinations of multiple external signals and events. In order to identify such combinations, it is common to utilize machine learning algorithms. In this case, the set of current measurements is classified as one of the possible model states (Fig. 5.8).

So far methods like hidden Markov models (HMM), random forests (RF) and support vector machines (SVM) have preferentially been investigated for their applicability for this task.

HMMs build an internal sequence model during the training process that is based on the provided data. This internal model has no direct connection to any manually created workflow model; however, both models ideally show the same or a very similar structure.

RFs are a collection of a plurality of generated decision trees, influenced by randomness during the training process. This introduced randomness provides increased robustness for uncommon input data, although it requires slightly larger datasets for training than other classification methods.

SVM try to form an optimal separation between representatives of different classes. Those representatives are called support vectors and define the borders of their respective classes within a multi-dimensional hyper space.

A method currently under active research is the so-called deep-learning method, in which huge amounts of unlabelled data are analyzed without manual supervision. Currently, this method is not yet applicable to surgical workflow analysis, since, up to now, no sufficiently large datasets exist.

For all presented methods, an exhaustive collection of relevant surgical data is of utmost importance.

5.2.3.3 Self-learning Systems

As already pointed out above, it is simply impossible to provide sufficiently granulated surgical models for the large variety of surgical procedures. Workflow analysis and prediction is only feasible if the computer has gained the ability to without being explicitly programmed. Using both declarative surgical knowledge (from textbooks, formal description, etc.) and the information gained by analyzing numerous procedures of the same kind, the machine should learn to understand the details of a standard procedure and to recognize anomalies.

At least in the beginning, self-learning systems in surgery will be dependent upon "supervised learning". The surgeon will present "example inputs" and should define the desired outputs to make it easier (and safer) for the computer system to identify the general rules. In the long run, unsupervised learning has to be the goal.

5.2.4 "Intelligent" Man–Machine Interfaces

Though a direct communication between the devices and systems (internet of things) and some autonomous actions are key elements of "Surgery 4.0", the surgeon must always be part of the loop. A continuous dialogue is essential. Up to now, the tools to interact with machines is still rather primitive. Foot switches and buttons are dominating. Much was expected from voice control, but under clinical conditions it did not find acceptance. What is really needed is an intuitive virtual assistant which enables to communicate in forms of a dialogue. This requires some degree of "intelligence" of the system including reliable speech recognition and interpretation, but also safety checks. Finally, this system should translate the verbal command into the respective action. In case of insecurity, it should even be capable to pose a question or to demand more information. Self-evidently, the system has to have fast access to a very large database and the surgical domain knowledge.

5.3 Surgical Telematics

Surgery of the future will become increasingly more transparent and open-label. Laparoscopic surgery is video-based per nature, and in most OR lights for open surgery video cameras are integrated. Accordingly, the surgical procedure becomes visible not only to the OR team but also to—at least in theory—an unlimited number of spectators. This offers new opportunities for quality control, education and training .

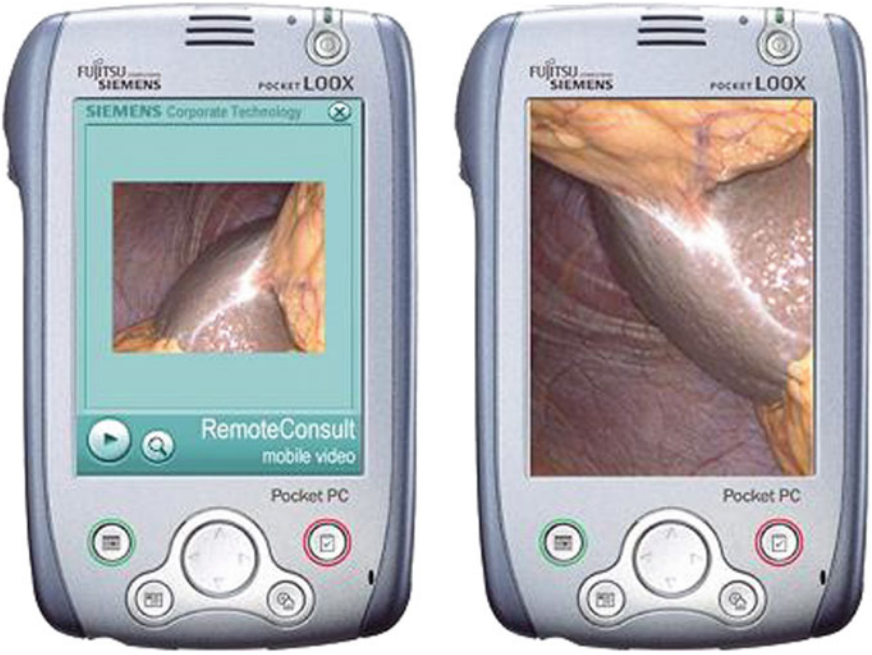

Fig. 5.9 Mobile device with video at original size (*left*) and zoomed to full screen (*right*) [16]

5.3.1 Teleconsultation

In case of difficult intraoperative decision making, external consultants are sometimes required—e.g. a senior expert or a specialist from other disciplines.

This is time-consuming and tedious both for the OR team (waiting) and the consultant who is forced to walk to the OR, change clothes, etc. To avoid physical presence of the consultant, teleconsultation could be an answer. The first attempts to use teleconsultation in surgery were made more than 20 years ago [14]. However, consultants needed appropriate equipment in their office or had to go to a room equipped with telemedicine facilities. In daily routine, this was too impractical to make teleconsultation popular [15].

To overcome these limitations, and to allow spontaneous video communication during routine clinical activities, mobile video consultation systems could be better. The first attempts were made about 10 years ago ([16], Fig. 5.9).

It took another 10 years till it is now mature for routine clinical use. Experts are now able to attend virtually to any operation. They are able to communicate with the surgeon at the point of care, give advice, etc.

5.3.2 Telepresence

Telepresence is a more sophisticated version of teleconsultation. Whereas the latter is merely based upon visual and oral information, in telepresence the consultant is enable to take actively part in the process at the point of care.

If an active camera holder is used during a laparoscopic surgery, he is able to control the camera. In case of open surgery, he can move the OR camera mounted in the OR lap to get optimal insight into the surgical field. In addition, he can clearly indicate at the surgical site what he/she is speaking about: By using a cursor on the monitor in video-based surgery or a "telestrator" in open surgery [17].

The next step would be telesurgery, i.e. the surgery is performed by the remote expert.

5.3.3 Telesurgery

The idea of teleoperation came up about 16 years ago, when the first two master-slave units (DaVinci, ZEUS) appeared on the market. In this type of surgical robots, the surgeon in his/her "cockpit" is separated from the OR table and the patient. Thus, the surgeon may be located in the US, and the operation is going on in Europe which has already been demonstrated in a pioneer application in 2001 [18].

However, telesurgery still is by far too expensive up to now to gain a role in practical care. What weighs even more are the technical shortcomings like the high end-to-end latency and the limited availability.

It is expected from the oncoming 5G programme that the specific requirements of telesurgery will be met: Guaranteed and reliable availability of information from back and data bases and real-time data streams from a large variety of sources (Fig. 5.10).

However, telesurgery is not only meant to be performed over large distances but even within an OR theater. Thinking of master-slave telemanipulators the surgeon will be separated from the patient only by meters while the operation is mechanically performed by a machine. In the future application of uncoupled robots and micro-systems require further development of telesurgical systems that will need provide a comprehensive sensorial input.

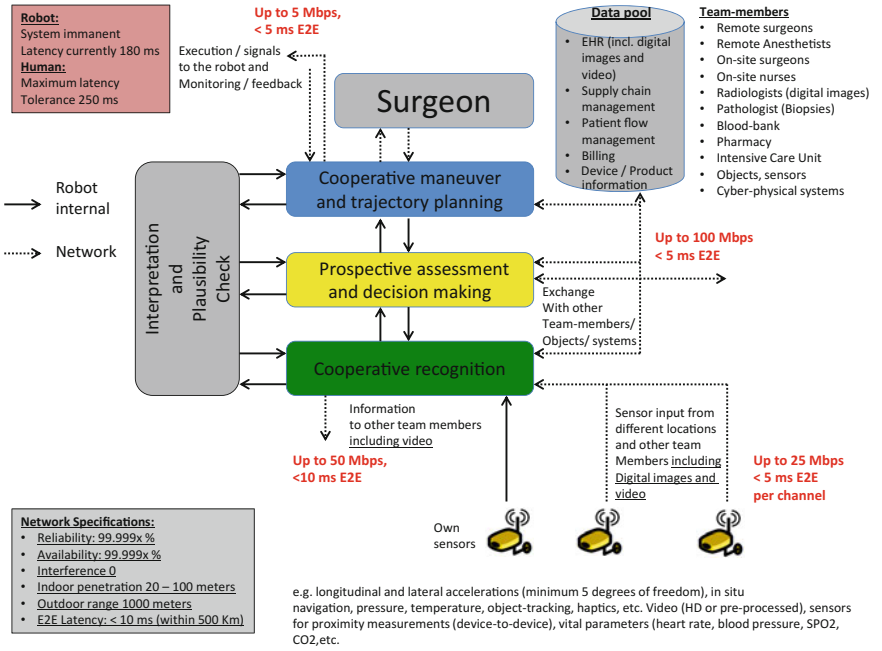

Fig. 5.10 Telesurgery is a complex process: Players, functionality and technical requirement of data streaming

5.4 Data Mining

Each single case produces a vast amount of data: Individual state of the patient and medical history, preoperative imaging, intraoperative findings, surgical care including the specific type of intervention and the final outcome. These data will be easily accessible in the future since all of them are stored in a digitalized manner. Self-evidently, these comprehensive databases are too large-sized and complex for manual knowledge extraction, but computer science offers now sophisticated methods of automatic analysis of large quantities of data that will also allow to extract previously unknown information. The hidden treasure of information from a vast number of cases is now accessible to identify the most adequate therapy for each individual patient and to bring surgery to a new level of quality.

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Chapter 6
#FocusOnTheEndUser: The Approach to Consumer-Centered Healthcare

Matthias Mettler

The fight for supremacy in the market is strong in many different industries. Taxi drivers go on strike and drive through capitals of the world in a honking convoy. By doing so, they demonstrate against the aspiring transportation network company *Uber*. Restaurant owners fight against online customer reviews on *TripAdvisor*, and hotel owners are taking the online accommodation facilitator *Airbnb* to court. Digitalization allows for new and industry-changing business models and simplifies the market entry for new competitors. Established industry players are trying to fight against these changes but, simultaneously, find themselves performing a balancing act. Why do they encounter these issues? Because, along with these newly digitized business models often follow a completely new product and service awareness for the consumer, as well as maximum customer orientation. The consumers are the center of attention, more than ever before: Never has a ride been so easy and comfortable as it has been since *Uber*. Never has the service quality in restaurants and hotels been as transparent as they are today thanks to *TripAdvisor*. A fight against new digital business models is therefore also always a fight against the consumer, as well as any potential threats for the entire company.

Powered by the increased consumer focus in other industries, the discussions about a user-centric, consumer-oriented healthcare in politics and medical circles has increasingly become the center of focus. From the *Harvard Business Review* to the *World Economic Forum* in Davos, from web communities and YouTube to professional journals, everyone is discussing the new digital business models and their impact on the healthcare system. The focus of these discussions is specifically the intensification of the competition and the entry of marketers new to the industry: When will the first doctors stand up against the rating platforms such as *DocApp* or *Jameda*, or new treatment models such as *Pager*? When will health insurances go

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on strike against the online insurance *Oscar*? When will physiotherapists start the fight against new digital therapy options such as *Hinge Health*?

Because the discussions about digitalization and new digital business models in the healthcare industry are held so intensively, the orientation toward the needs of the consumer (e.g., the patient and his or her relatives) do not yet have the same significance for the market players as in other service-oriented industries [1, 2]. However, as digitalization becomes increasingly significant in the healthcare industry, so does the focus on both consumer and public interest [1–3]. Key words such as digital networking, mobile health, health wearables, or telemedicine are part of many political and public debates, have become part of the healthcare industry, and are necessary for the continued growth of the industry [3, 4]. The consumer can access new information sources through various digital tools, e.g., mobile health apps or electronic patient files. Therefore, the consumer develops new ways to control knowledge and data about his or her own personal health. Digitalization empowers the consumer and simplifies the contact with the main players in the health industry, e.g., doctors, hospitals, pharmacies, health insurances, or therapists. The consumer no longer takes on a passive role, and increasingly welcomes information and recommendations of all health related-topics, not only their own. Digitalization makes the consumer an informed, and therefore a more mature stakeholder in the healthcare industry, with a need to codetermine options.

This area of conflict accompanies the demand for more consumer orientation in healthcare is the focus of this report. In order to fulfill the analysis of this area of conflict, this report will develop and present the methodical concept of the *Health Journey*. It will show how consumers move through the healthcare industry and which unmet needs remain for the consumer and where there may be opportunities for disruption. Additionally, this report will introduce three Swiss startups that focus on different unmet needs in the *Health Journey* and that have developed new digital business models.

6.1 Consumer-Centered Healthcare: Reality Check and Exploration in the Market

As mentioned in the previous introduction, there are currently intensive discussions in social media, politics, and professional circles about the omnipresence of a consumer-centric healthcare industry. New business models, perfectly tailored to the consumer, are taking over the healthcare industry and have become the focus of discussion. However, a glimpse into the reality of various healthcare markets depicts that digitalization and the push for more consumer orientation often encounters difficulties and skepticism.

Traditionally, the healthcare market belongs to those markets that are leading in the area of product innovation. Thanks to innovative new medicines, medical

technology products, or research methods, general public health has drastically increased in many nations [5]. However, legal regulations and a fragmented medical service lead to consumers perceiving medical procedures as inconvenient, media disrupting, and misleading with too much red tape [4, 6]. What is often missing is sufficient service quality and process innovation. Healthcare consumers benefit from expansive medical knowledge, new medicines or medical products. However, these same consumers face timely and bureaucratic expenses, media disruption in the treatment process, information disadvantages, as well as a shortage of service quality, [4–6]. For example, *PwC* recently published a *Healthcare-Barometer 2016* in Germany, which displays consumer's discontent [7]. About 45 % of the people asked are bothered by the fact that the doctor does not spend enough time with them, and that the office hours do not meet the patient's needs [7].

Looking at the above-mentioned process innovation in healthcare, it is evident that the differences between the various countries are immense. While the American healthcare system is seen as innovative and startup friendly, this system highlights how other countries struggle more with the advancement of digitalization, new technologies, and innovation. A survey in the innovation and startup hotspots outside of the USA, such as Berlin, Stockholm, or London, shows a very positive outcome and brings certainty that innovation and the urge for change in the various healthcare markets is not lacking. The challenge is, however, mostly systematic: multi-rationality and conflicting interests of the main players in healthcare, concerns about data security in politics and associations, insufficient financial resources for investments, fear of new technologies or difficult legal frameworks often prevent or complicate process oriented innovation in the healthcare industry [3, 5].

When reviewing the numerous debates and discussions about digitalization in healthcare, it is noticeable that the consumer is not fully aware of the strengths of digital transformation [7]. Healthcare politics as well as established players in the healthcare industry are part of this challenge. Instead of highlighting the potential of digitalization reducing merit costs, or improving the monitoring of health and insurance processes, the focus often remains on the weaknesses of the digital transformation in healthcare. For example, it is often argued that, there is insufficient evidence for the benefits of digital tools such as electronic patient files or mobile health apps. Instead, the focus is on gaps in information security and in the protection of Personality Rights, or simply that digital tools lead to administrative costs and competitive disadvantages. It is disregarded that digitalization offers an essential contribution to cost reduction, simplifies medicinal treatments, and allows for a more transparent and service-oriented treatment process of consumers. These developments are ultimately in the minds of the consumer. Just as *PwC*'s *Healthcare Barometer 2016* shows, the public is still averse to certain aspects of digitalization [7]. However, process innovation and service orientation, as well as supporting digital tools in healthcare are still called for [1, 3, 7]. Established market players such as doctors, pharmacists, therapists, hospitals, caregivers, and health insurances, as established market players, should not forget that, foremost, they act

as service providers in the healthcare industry. They should orient themselves on the needs of the consumer, focus on the consumer's health, and perform first class service on the person.

6.2 Consumers Transfer Their Expectations from Other Industries to the Healthcare Industry

The demand for first class service and orientation for the consumer builds the focus of the consumer-centered approach in healthcare [8]. A broad view on the needs of the consumer as well as a constant adjustment of business models should be given in service-oriented industries such as the healthcare industry. Instead of consistently pushing the consumer into the limelight, established healthcare players prefer to hide behind regulating frameworks and lobbyism, or they legitimize their market position with an advance in knowledge over their consumer, as well as a shortness of medicinal professionals. Simultaneously, they show little ambition to focus their medicinal services on the consumer needs and ignore the looming digital change in the healthcare industry. This behavior surprises and should motivate a comparison with other service related industries. Digitalization, new digital business models, and new technologies have led to profound and lasting changes in various industries. There are well-known examples of businesses that have used old technologies and thought processes, and which do not focus on changing consumer needs, and have therefore disappeared from the market. Similar developments could play out in the worldwide healthcare industry as the digitalization wave increasingly swashes over to the healthcare industry. The changes in the product and service landscape are already advanced. For example, patients can utilize offers in the area of digital diagnoses or therapy, or they can communicate with their doctors via telemedicine. The current adjustments to the legal landscape in many healthcare markets are forerunners for a comprehensive digital revolution in the healthcare industry. For example, in Germany and Switzerland laws that regulate the legal framework in regards to dealings with telemedicine, electronic patient files, or healthcare cards are currently under debate [9, 10]. In the USA, the state of New York recently passed a law that obligates all doctors to carry out all prescriptions electronically via e-recipes [11].

These looming changes have various origins but are often powered by the growing discontent of consumers. This discontent originates from the uneven development of various service markets. The main point though is that consumers will project positive experiences in relation to new business models in other industries onto the healthcare industry [1, 2, 12]. The transfer of expectations can be circumscribed by the principle of *liquid expectations*. The thereby emerging direct comparison opportunities, e.g., between the travel industry and the healthcare industry, can be versatile: Today, for example, it is possible to check into a hotel room via *Apple Watch* without contacting the reception desk. You can order a Taxi from the comfort of your home without having to wait in the rain. However, when

visiting the family physician, there are often long waits in the waiting room. From the travel industry, consumers are used to reading ratings and experiential reports as well as comparing services before purchasing one. In healthcare, comparing different doctors or hospitals is only available on a limited scale.

These industry-overlapping comparisons of customer experiences show the consumer, that the service quality and customer orientation in healthcare are often not on the same level as in other industries. The principle of *liquid expectations*, or the transfer of expectations from one industry to the other, does not exclude the healthcare industry. Very few people like to spend time in waiting rooms, hospital entrances, or call queues. Since consumers are used to being the center of attention in other industries, they increasingly want the same experience when dealing with the healthcare industry.

The consumer's highest guiding principle is always personal health. Consumers do not look for the best doctor, the best pharmacist, or the best health insurance. They look for those partners in the healthcare industry, who can offer the best support to maintain or improve their physical and mental health. Besides looking for specialized knowledge, consumers look for customer and service orientation as well as an understanding for their own problems and unmet needs. Doctors, pharmacists, or therapists must fulfill each of these criteria sufficiently if they want to position themselves as a trustworthy, competent partner for the consumer in this time of new digital business models.

6.3 The Healthcare Industry Offers Industry Foreign Businesses Room for Disruption

Since established, traditional healthcare players often show deficits in customer and service orientation, industry foreign technology companies such as *Apple* and *Google*, large retail companies, as well as various startups have attractive ways of filling those gaps. They have all selected the multibillion dollar healthcare industry as a strategic area of growth and are working intensively with strategic initiatives. They specifically exploit those healthcare players who do not have the consumer in focus, and occupy the customer interface with innovative services. This strategy is very successful where there are unmet needs on the consumer side, where there are low market entry barriers, and where there is a low need for assets for a fast construction of a market position.

The service offering and process used for the market cultivation of these players new to the industry is radically oriented on the needs of the healthcare consumer. It is similar to the process of successful disruptors in other industries such as *Uber* in the taxi industry or *Airbnb* in the hotel industry. *Uber* does not own any Taxis and *Airbnb* does not operate any hotels. Both operate in an "asset-light" manner. Nevertheless, both companies have been able to "layer" themselves between the consumer and the established players such as taxi businesses and hotels. By fitting

their services perfectly to the needs of the consumer, they occupy the targeted interface of the consumer and orchestrate the processes in the market.

In summary, the *Uberization* of the healthcare industry is increasingly a threat for established players, as it breaks up the available processes and value chains and allows for new interaction opportunities with the consumer. Simultaneously, established players in healthcare prove to have little ambition to question their own business models, continue to develop them, and to push innovation. So the question emerges; which players will an *Uber in healthcare* attack and possibly replace?

6.4 Consistently Remain Focused on View of the Consumer and Begin with Their Unmet Needs

In order for established players in the healthcare industry to avoid an *Uberization* in the future, they must consistently put the consumer in the center of attention when it comes to service delivery. This calls for a systematic realignment of their own service and product offerings and requires them to know the consumer and understand their needs. The requirements in healthcare are therefore quite convenient as trust and personal connections build the basis for many interactions. Many established players know their customers and the customers' problems and needs from dealing with them for multiple years or even decades: Physicians treat entire families over the course of generations, caregivers do not only know the patient but also the patient's familial surroundings, and pharmacist consults the same customers over years on various medical topics. An inherent understanding of the customer is in place.

However, even when certain traditional industry players have learned to understand their customer and his or her needs over the years, they should consider that requirements can change based on economic or social trends. Digitalization and the resulting new digital business models contribute to a change in the needs and actions of the consumers in the healthcare industry [1–3]. Traditional players in healthcare should realize that the digitalization is not a short-term phenomenon, but rather a sustainable change to the healthcare industry. Therefore, the following applies: if doctors, hospitals, therapists, pharmacists, or health insurances do not want to lose connection and be uberized by industry foreign players, they must consistently align their product and service offerings with the consumer. In order to create a successful realignment, they should understand how the consumer moves through the healthcare industry and what media disruptions and difficulties he or she has to deal with. Helpful here is the *Health Journey* methodology, depicted in the following Fig. 6.1.

Leaning on the generic customer journey, the *Health Journey* shows the stations a consumer must go through to, ideally, reach recovery in an acute medical treatment case. The following steps are part of the *Health Journey*:

Fig. 6.1 The consumer's *Health Journey* in the healthcare industry, for acute treatment cases

- *Prevention*: In this step, all activities that should maintain health are included, e.g., healthy nourishment or sufficient exercise and sport.
- *Awareness*: As soon as the consumer realizes there may be a health issue looming, e.g., an illness, pain, or mental unease, the consumer is in the stage of *Awareness*.
- *Information Search*: *Awareness* is the catalyst that moves the consumer to information search in order to identify the root of the problem. Typically, consumers use the internet, e.g., medical diagnose websites, or mirror their problems in their personal social field for this step.
- *Diagnosis*: If the consumer cannot treat the problem, he or she contacts a medical professional, e.g., a doctor or therapist, and presents them with their medical problem. Subsequently, the consumer receives a medically funded diagnosis.
- *Treatment Selection*: In conjunction with the medical professional and in consideration of all available information, the consumer selects an adequate treatment for the medical problem. Thereby, more digital data, generated for example by mobile health apps or electronic patient files, are used.
- *Therapy*: Therapy will treat the medical problem. At this step, healthcare professionals also use digital tools such as app-based pain and medical journals or electronic patient files.
- *Evaluation*: In relation with *Therapy*, the healthcare professional makes regular evaluations of the treatment process. When needed, the healthcare professionals adjust the therapy or transfer the patient to a different healthcare professional.
- *Result*: As soon as the treatment has successfully ended and the patient is healthy, the *Health Journey* is completed. The consumer finds him or herself back at the first step, *Prevention*.

The *Health Journey* hereby shows the different steps a consumer takes in the course of a medical treatment process. Based on the *Health Journey* various media disruptions and changes of medical professionals can be identified in the treatment process (see following Fig. 6.2). The number of media disruptions and involved professionals varies depending on the medical problem. Fundamentally, media disruptions and an extensive inclusion of healthcare professionals complicates the treatment process and, from the view of the consumer, makes it less transparent. This promotes potential frustration and unmet needs on the consumer side.

Summarized, the *Health Journey* simplifies the thought process of the consumer, as it shows where the consumer meets media disruptions in the treatment process.

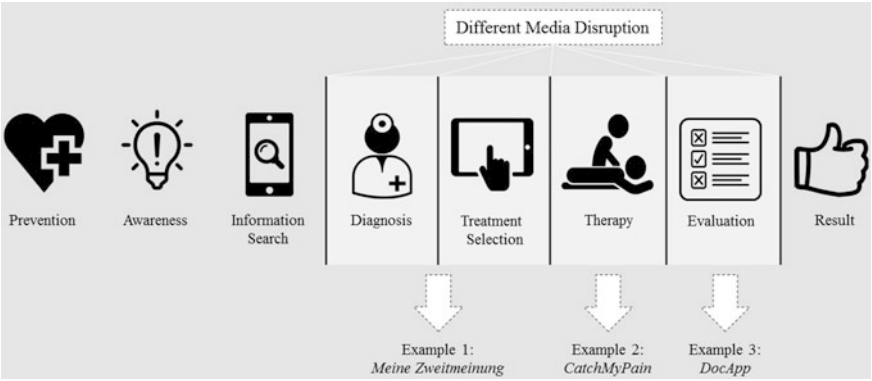

Fig. 6.2 Depiction of points of media disruption and advantage points for new business models within the *Health Journey*

This methodology helps us understand which different healthcare professionals and institutions are relevant within the scope of the personal *Health Journey* of a consumer. It specifically shows where the consumer has to fight with difficulties in the dealings with the healthcare system, as well as where dissatisfaction and unmet needs occur on the consumer side. Following, three examples from the Swiss healthcare industry will show different areas of tension in the *Health Journey*. These examples will specifically highlight which unmet needs the consumer must deal with and how Swiss startups were able to solve issues through their launch of new digital business and interaction models.

Example 1: Diagnosis and Selection of Treatment—*Meine Zweitmeinung* Helps

On their way through the healthcare industry, consumers are often confronted with incomplete information, [6, 13]. Despite various analog and digital information sources, as nonprofessionals, consumers have difficulty determining the severity of various medical problems. Likewise, the professional capability to assess which methodical treatment is adequate and which healthcare professional should be included in the treatment process is nonexistent. Consumers are, in regards to the optimal treatment selection, overwhelmed and suffer under the condition of information asymmetry [6, 13]. In economic teachings, this state and the therewith-occurring side effects, such as abuse of confidence through better-informed market participants, are explained through the *Principal–Agent Theory* [6, 13]. Analogous to this theory, consumers are clearly disadvantaged due to incomplete information in the medical treatment process. They either need to rely on the general opinion of the doctor currently treating the patient, or take considerable time and financial costs into consideration when looking for a second opinion with other doctors. The treatment process as well as the search for a second opinion is based on trust in both the treating doctor as well as the additional medical

consultant. The objectivity and validity of a first and second opinion is difficult for a consumer to comprehend.

To remove the area of tension and to create more transparent evaluation processes, the Swiss health startup *Aware Plus* launched an online platform called *Meine Zweitmeinung* (My Second Opinion). Through this platform, consumers can currently receive a second opinion on two topics, angiopathy and orthopedics [14]. Hereby the focus lies on having the most user-friendly process possible. In the first step, the consumer must fill out a questionnaire and upload or send in the documents. Subsequently, the independent medical specialists create a second opinion and make this available for the consumer. *Aware Plus* currently collaborates with the Swiss health insurance *CSS Versicherung* [14]. Consumers who are insured with *CSS Versicherung* can use the *Meine Zweitmeinung* services without incurring additional costs [14]. All other consumers are billed a standard rate [14].

With this service offering, it becomes simply to seek a second opinion in the medical treatment field. *Meine Zweitmeinung* applies to the consumer's specific unmet need of the missing availability of information of adequate treatment options. Consumers receive the chance to tap into new, independent information sources that were previously not available to them and outside of their current, closed medical evaluation system. Thus, the pressure rises on established doctors to make objective, comprehensible second opinions and to act for the purpose of the consumer. The *Health Journey* becomes more transparent and easier to understand for the consumer in regards to the treatment selection. *Meine Zweitmeinung* seems to support the process in the scope of the *Health Journey*, but does not replace the personal, initial contact with the doctor.

Example 2: Therapy—*CatchMyPain* Makes Pain Tangible

An overaged population and an increase in chronic diseases such as diabetes, asthma, or cancer characterize the societies of many developed countries. The therapy and treatment of these illnesses are the causes of around 80 % of yearly health costs in developed countries [15, 16]. Next to having a strong influence on the health costs, chronic illnesses also have a particular care and orientation requirement on the consumer side. As the illness progresses, the chronically ill are practically always in the care of numerous healthcare professionals. Thereby, the *Health Journey* is especially complex for chronically ill people.

This heightened complexity leads to consumers wanting tools to help both themselves and the relevant healthcare professionals. These tools should help orient both parties within the *Health Journey*, and to simplify the disease management. New digital approaches in the treatment and therapy of chronic illnesses that have simplified the dealings with the illness and have created transparency in the treatment process belong to the classic growth fields of digitalization in the healthcare industry [3]. Many of these digital offerings allow patients and medical professionals a way to monitor the individual treatment and health process over a longer period of time [3].

The Swiss startup *Sanovation* launched such a monitoring tool. *Sanovation* developed the mobile health app *CatchMyPain*, which focuses on the diagnosis and

therapy of pain in conjunction with chronic illnesses [17]. With this solution, patients can capture their individual pain situation as well as the pain character, whereby a digital body model helps localize where the pain is, and define the intensity of the pain [17]. Simultaneously, other involved parties, especially doctors, therapists, and family members can understand and view the patient's pain level. Beyond that, the journal function can also capture soft factors such as satisfaction, stress, or fatigue, as well as treatment-related information such as the ingestion of medication [17]. This journal function allows a long-lived monitoring of various treatment methods and tracking of treatment success. *CatchMyPain* also offers a user community in which those affected can communicate and exchange their experiences with one another. In addition, *Sanovation* engages with other medical partners in pain research and uses anonymized information from the pain journals for scientific evaluations [17].

The service offering *CatchMyPain* allows consumers to have a completely new interaction with their pain. Often even doctors and therapists are overwhelmed with the pain profile of their patients and search for adequate treatment options. Therefore, an experience exchange in the *CatchMyPain* community can be advantageous when discussing various treatment options and their success. Further, *CatchMyPain* can be a useful tool for patients to ease dealings with the illness. This Swiss mobile health app focuses on both the consumer as well as medical professionals and instigates added value for both parties.

Example 3: Evaluation—*DocApp* Leads to Doctors with Increased Service Orientation

As seen in Example 1 regarding *Meine Zweitmeinung*, in the healthcare industry a certain information transparency for the consumer is often lacking. Simultaneously, consumers must rely on the knowledge of medical professionals when it comes to the medical treatment process. As illustrated in Example 1 about *Meine Zweitmeinung*, the tension areas of lacking information transparency and simultaneous dependency on specialty knowledge are large. Especially where there is media disruption in the *Health Journey*, or where inclusion of further experts is necessary. In other service-oriented industries such as the hotel or travel industry, such information asymmetry issues have been solved through publicly accessible digital rating portals such as *TripAdvisor* [18]. These portals make more room for the consumer to express their opinion about the service used. Thus, the quality of the offered service is more transparent for the consumer and he or she can create a better-founded purchase decision [18].

In the healthcare industry, a similar trend is apparent as well as an increased urgency to offer more transparency in doctors', therapists', and hospitals' service quality. The Swiss startup *DocApp* tackles this trend and offers an online booking and rating platform that works analogous to the above-mentioned portals in the travel industry. This system offers an easier search function for consumers to find a fitting doctor or dentist [19]. In the first step, users can specify their grievances, subject, or name through a search field [19]. Following, users can select the fitting contact at the selected treatment location and schedule a meeting directly with said

contact. Analogous to the counterpart in the travel industry, users can rate the service quality of the treating doctor or dentist [19].

The advantages of *DocApp* from the perspective of the consumer are obvious. The search is simplified and more transparent. The over 30,000 doctors and dentists registered on the platform guarantee a comprehensive coverage of the Swiss healthcare system. Due to previous consumer ratings, users can create an objective illustration of the doctors and dentists' service quality and can therefore make informed decisions. Doctors receive direct customer feedback and implications for improvement of their processes and medicinal services. Therefore, rating services in healthcare encourage information transparency as well as higher service orientation for doctors.

In order for the underlying digital business model to work, however, a few success-defining items must be considered. First, the system needs a sufficiently large user base in order to secure a certain dynamic and objectivity of the ratings. A rating system such as *DocApp* lives from the engagement of the doctors and consumers. Second, for the model to be reliable, the system must ensure that consumers can only rate the services of doctors they have actually visited or been helped by. Otherwise, the rating system loses credibility, so that both doctors and consumers interdict their contribution. Finally, a debate that offers topics and categories from an objective perspective for consumers to rate is necessary. As non-professionals in healthcare, consumers can poorly estimate the professional knowledge of a doctor or the fit of a treatment method for a certain medical problem. However, they can answer questions such as "Was the doctor service and customer oriented?" or "Did the treatment help you fight the pain and create a continuously pain free work day?". Here, a system with sufficient creative freedom for both consumers and healthcare professionals is necessary. In addition, both players must receive the chance to reply to ratings and feedback.

6.5 Digitalization and Consumer-Centered Healthcare as a Chance for Established Players

The digitalization in the healthcare industry as well as the development to a more consumer-centered healthcare is not just a threat for established healthcare players. It also offers the opportunity to rethink existing business models and new growth fields, e.g., in the area of chronic illnesses. Hereby, new differentiation opportunities are made available toward competitors. As explained in the following paragraph, established players such as health insurances or pharma companies have specifically started to target these growth fields.

In the course of the developing digitalization, health insurances especially are one of the market players in the healthcare industry that are put under pressure [12, 20, 21]. Due to their function as finance intermediaries between consumers and doctors, hospitals, or therapists, although they have a central position in the market,

the development in the financial industry shows that their services are substitutable. Similar market trends and cutthroat competition can be found both in the financial industry as well as in the healthcare industry. New digital business models and market entries such as fully online health insurance *Oscar* or the health startup *Knip's* brokerage offering lead to established health insurances having to be more innovative and consumer oriented [12, 20, 21]. This follows the need for new opportunities on how to differentiate the service offering in the market. However, there are barriers in regards to performance cost optimization and price competition due to regulatory frameworks [20]. In this area, however, there is plenty of potential for differentiation for the consumer [20, 21]. Health insurances such as the German *Techniker Krankenkasse* or the Swiss *Sanitas* have developed various customer services in the area of health coaching in the past. The coaching offerings include focus topics in the area of prevention, such as healthy nourishment, burnout precaution, and fitness coaching [22, 23]. In addition, they support research activities and various digital health startups that engage in the area of digital therapy of chronic illnesses. The offerings are deliberately formed with new technologies such as mobile health apps or incentives such as gamification [22, 23]. Health insurances are herewith changing their image from being a purely financial service provider to being an innovative healthcare attendant for the consumer. Simultaneously, they achieve increased differentiation opportunities toward the competition and are prepared for new, digital business models and market entries.

The digitalization as well as the constantly increasing costs of the healthcare systems raise the sense of urgency on the pharma industry [24]. New market participants from the startup and technology fields prove that engagement in healthcare and medicinal research can be created with more service and consumer orientation in mind. With the digital service offerings *ResearchKit* and *CareKit*, *Apple* has proven that patient engagement in research projects can be more efficient and smooth than it has been in the past [25–27]. Both new digital interaction opportunities as well as the fact, that a broad group of participants can be part of research projects via *ResearchKit*, have led to an extremely rapid recruitment of participants for ongoing disease research [25–27]. *Google* also follows ambitions in disease research and new treatment methods with their *Smart Lens project* for diabetics. And for example, two digital health startups, *Curebox* from the USA and *healthbank* from Switzerland, have both launched online platforms to participate in clinical trials and research projects. These service offerings create completely new opportunities for consumers, such as how he or she can be part of the research process for illnesses and new medications.

Thus, new market entries from industry foreign players have created urgency in focusing on patient-centric research as well as occupation of customer interfaces [24]. Accordingly, some pharma companies are expanding their market activities and are offering consumers different options on how to manage their health, especially in the area of chronic illnesses [24, 28]. The mobile health apps *HemMobile* by *Pfizer* or *Beat Bleeds* by *Baxter* allow consumers with hemophilia a better handling of their disease. *Bayer* launched a popular app for pollen prediction in England. *GSK* brought an app solution to the market, *MyAsthma*, which offers

asthmatics and their families a digital health journal that should simplify the daily routine. *Novartis* launched a program with their fitness campaign *Mission Schweinehund*, which animates consumers to be more physically active and therefore prevent medical issues. Besides developing their own digital solutions for consumers, many pharma companies collaborate with startups in order to try to take the lead in the market [24, 28].

In summary, in both the healthcare insurance market as well as the pharma market, exciting strategies in the dealings with the topic of digitalization and changing competitive conditions can be observed. These strategies allow for differentiation opportunities in the market competition and can be very successful, as long as the focus remains on the unmet needs of the consumer as well as being able to offer the consumer added value such as life quality.

6.6 Digitalization Will Have a Lasting Impact on Healthcare

Digitalization and new business models that specifically focus on the needs of the consumer will have a lasting impact on the healthcare industry. A part of the existing healthcare infrastructure will be partially replaced or at least relieved. Cost savings and a reduction of complicated health issues can be expected. The worldwide healthcare markets stand at the beginning of a large and extensive wave of digitalization.

As the various examples in this report have shown, digitalization will not replace the personal contact between the consumer and various health industry players such as doctors or therapists. Medical treatment processes in the scope of the *Health Journey* always reach a point, at which direct personal contact is necessary, for example in the context of a medical examination or even an operation. The digitalization, new digital business models, and thus completely new ways to interact with the consumer in healthcare necessarily lead to changes in the traditional processes within the *Health Journey*. On the one hand, the point in time where there is a need for direct physical contact between consumer and doctor is moved back within the *Health Journey*. On the other hand, digitalization allows industry foreign players such as technology firms, retail businesses, or startups to take part in the *Health Journey*. This changes the division of power in the healthcare industry.

In order for established healthcare players not to lose a large portion of market share or even be wiped from the market, these established players must push innovation while continually questioning and developing their existing business models. Analogous to other service-oriented markets, the healthcare industry needs more business models that are oriented alongside the consumers' needs and allow for high service quality. Thereby, it must be noted that digitalization is not a short-term event, but that it will have a lasting impact on healthcare. This digital

revolution includes a tremendous boost toward other players in healthcare and will lead to ensuring that consumers' requests are heard.

Finally, it will be a question of perspective: innovation, disruption, and digitalization in the healthcare industry open up new possibilities for both the consumer as well as established market players. These developments will simultaneously also demand victims and will wipe away those providers that cannot or do not want to orient themselves in a timely manner. A consistent customer focus, agility to a new orientation of their own business models, an increased openness to process innovation as opposed to product innovation, as well as a specific skill to recognize customer needs will decide the success of doctors, therapists, hospitals, pharmacies, and health insurances in the future.

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Chapter 7
Virtualization of Health Care: The Role of Capacity Building

Ai Keow Lim

7.1 Introduction

Rising health care costs, ageing population, shortage of health care workers and equitable of access to health care are some driving forces to the digital health revolution. With advancement in medicine and technologies, people are living longer. Octogenarians are the fastest growing population in many developed countries. The growing elderly population puts a strain on the limited health care resources. Existing health systems and traditional ways of care are no longer viable to meet future health demands [2]. Capacity building through virtualization of health care is the way forward to addressing these challenges. Likewise, supporting capacity building can help people to acquire the skills, knowledge and competency to adopt and use digital health care technologies and applications to self manage their health, wellness and illness.

While Health 3.0 involves firms building consumer-centric business models, Health 4.0 focuses on a consumer's health and wellness lifeline delivered via both on and offline system [3]. Similar to the Internet becoming an essential part of everyday life [4], new virtualised ways of delivering and accessing health care will become the norm, rather than the exception. In a virtualised environment, at Health 4.0 stage, health care will be delivered virtually using mobile devices and remote patient monitoring technologies. Virtual health enables "health care professionals to collaborate with each other and deliver care remotely. This means health care providers can collect patient data and deliver care from a different location, using technologies such as video conferencing, so that patients can receive care from the comfort of their own home or in their local community" [5]. The worldwide network of interconnected objects enables patient data and health information to be shared across platforms. Smart devices, smart phones and wireless sensors are

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linked to create useful content and provide services for both the patients and health care professionals, wherever they are in order to enhance patient outcomes. With advancements in archiving and exchanges using cloud computing, virtually all human activities can be captured, accessed and analysed on a much larger scale. Smart health care such as a virtualised hospital environment can also improve patient experience.

Virtualization of care can help the health care industry to improve efficiencies and reduce health care costs. For instance, teleconsulting and 3D bioprinting are two ways to reduce the rising health care costs while improving medical care and maintaining quality of service [6]. 3D bioprinting of tissues and organs can be used to enhance research, drug discovery and toxicology [7]. Virtual care will also be delivered to the unserved or underserved population such as people with low socio-economic status or living in the rural areas, largely because advances in information technology and telecommunication have enabled an increasing range of health care services to become more affordable. For example, the use of telemedicine and telehealth has been demonstrated as an effective way to bridge the gaps in providing critical care to those who have limited access to physicians due to factors such as geographic limitations or socio-economic conditions [8].

Capacity building can be a means to more efficient health programme delivery or an end in itself [9]. This chapter considers both of these aspects: (1) capacity building as a means to develop a set of relevant capacities to adopt new virtualised health care technologies in order to improve health outcomes, and (2) virtualization of care enables capacity building. Without capacity, even the most innovative virtualised health care technologies will not be effective. Capacity building is about empowerment. Empowering patients by providing them with skills and knowledge of self-management is not only beneficial to the patients but also brings benefit to the society. "Capacity building rests on the notion that change is the norm, because capacity depends on the ability to adapt to change" [10]. In contrast to the traditional model whereby care is provided in hospitals and residential settings, with virtualization patients need to change the way they take control of their health and well-being. They need to adopt new digital health care technologies as well as acquire or build upon existing skills and knowledge to support them in the execution of health improvement.

In contrast to other industries, there is little research in the health care sector on how technology users build capacity in order to adopt and apply new technologies in their daily work process [11]. A reason for the slow adoption of digital health care is because existing services fail to meet patients' needs or because they are of poor quality [12]. Developers often lack understanding of human psychology when designing new digital health care products and services. A person-focused, rather than technology-focused, paradigm in the design and deployment of future health care technologies is more likely to increase capacity for change. This chapter will discuss ways in which psychological models can be used to influence the design and development of digital health care technologies for Health 4.0 which in turn serve to encourage acceptance and uptake of the new technologies, support

individuals in reaching engaging experiences, promoting behavioral change and improving health outcomes.

Blackman et al. [4] identified 10 pairs of principles to guide the future needs for the Internet. As shown in Fig. 7.1, these 10 fundamental principles can also be used to guide the development and implementation of new virtualised health care technologies at all stages of customer-centric care in order to develop appropriate personal change strategies for capacity building and fully realise the potential benefits of virtualization of care. From these fundamental principles, this chapter identifies four key factors that can facilitate capacity building: Individual characteristics, Trust, Motivation and Connectivity. These factors, which will be discussed in more detail later in this chapter, will affect an individual's readiness for change.

The aim of this chapter is to explore ways for nurturing the capacity to adopt new virtualised health care technologies and building capacity through virtualization of care. The second section of this chapter defines capacity building. The third section provides an overview of how virtualization can support capacity building. The fourth section discusses the factors that can facilitate capacity building for adopting of new technologies. Health care consumer psychological factors are related to an individual's acceptance of new digital health care technologies. The

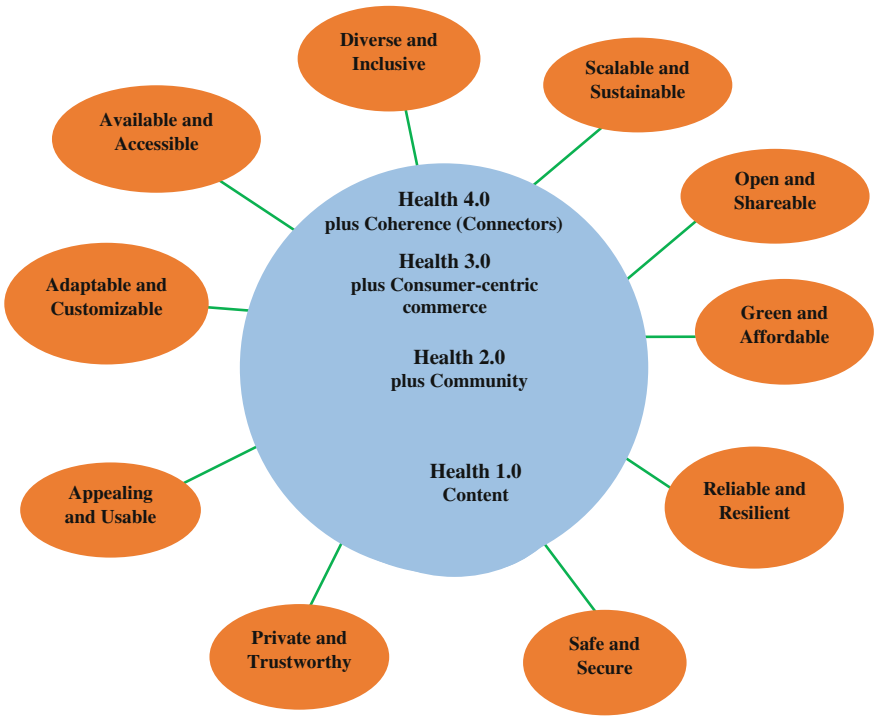

Fig. 7.1 Fundamental principles of a Future Internet and evolution stages of consumer-centric care. *Source*: Concepts from Blackman et al. [4] and McCabe [13]

fifth section considers how health care consumers adopt new technologies. Psychological theories and research can be used to influence the design and development of health care technologies, encourage acceptance and uptake of the new technologies in order to promote behavioral change and improve health outcomes. The sixth section presents three psychological theories in the context of capacity building to foster acceptance, adoption and uptake of digital health care products and services. The chapter concludes with a summary and open research issues.

7.2 Defining Capacity Building

There is no agreed upon single definition for the term "capacity building". Goodman et al. [14] define community capacity as "the cultivation and use of transferable knowledge, skills, systems, and resources that affect community- and individual-level changes consistent with public health-related goals and objectives". Labonte and Laverack [9] define community capacity building as the "increase in community groups' abilities to define, assess, analyze and act on health (or any other) concerns of importance to their members". According to the United Nations Development Programme [15], the aim of capacity building is "to help governments, organizations and people attain a level of self- sufficiency that enables them to effectively manage their own affairs".

This chapter defines capacity building as providing health care professionals, patients and formal and informal carers with the necessary skills, knowledge, opportunities and resources to overcome barriers in the adoption of new health care technologies. In a fully realized Health 4.0, content, community, working commerce models and coherence (connectors) are connected [13, see Fig. 1]. At Health 4.0 stage, "consumer-centric health care system focuses on identifying, facilitating, and integrating online and offline communication and care delivery channels needed to reach and coordinate end goals (value) as defined by disparate customer segments (patient, provider, payer, policymaker, caretaker, etcetera)" [3, p. 1]. Capacities are strengthened through participation by different stakeholders/customer segments. Adopting a multi-stakeholder approach will also reflect the diversity of people. Moreover, this approach will help to create an environment that is conducive to driving healthier behaviors and achieving impact [16]. The different stakeholders can be divided into three broad groups. Following the United Nations Economic and Social Council [17], this chapter will explore capacity building at three inter-related levels: Individual, Institution and Society.

7.2.1 Individual Level

Virtual health care technologies empower patients to take more responsibility for their own health and quality of life. Capacity building through virtualization of care

involves establishing the conditions under which patients are able to embark on a continuous process of self-management of health, wellness and illness. New knowledge and skills are built upon existing ones to guide patients in the new directions of change. This requires a new approach to knowledge enhancement and also points to the importance of patient education as the key for enhanced learning. Interactive technologies that incorporate education programmes can be used to deliver personalised behavior change interventions. Education programmes that take patients' views into account will have higher satisfaction, better compliance and greater continuity of care. Some key components of self-management education programmes include

(a) Initial assessment of patient's knowledge of health conditions and self-management
(b) Identification of target behavior for change or reinforcement. Behavior involves several elements, including the action, the target and the context (Fishbein and Yzer 2003)
(c) Use of medical and community resources such as information on lifestyle (healthy diet, exercise and physical activity)
(d) Set and update or change health goals
(e) Coping with negative emotions such as fear and depression
(f) Taking medication
(g) Monitoring which involves learning to interpret changes in the disease and its consequences
(h) Problem solving
(i) Reducing risks
(j) Reinforce and continuing education.

Although self-management programmes emphasize the role of patients in managing their diseases, effective working relation between patient and health care professions is essential and will help to ensure patients understand and assent to new practices and responsibilities.

7.2.2 Institutional Level

At Health 4.0 stage, the relationship between patient and health care provider will be transformed from an institutional care to a patient-centred holistic-integral care [18]. Capacity building at the institutional level should, therefore, focus on ensuring that health care providers deliver safe, effective and reliable health care at the right place at the right time through developing partnership with the community. Training programmes for health care professionals can help to build capacity and provide an enabling environment for the growth of virtualised health care technologies.

7.2.3 *Society Level*

At the society level, policy support is required to support the goal of achieving a regulated trustworthy health care delivery system. If policy markers are serious about virtualisation of care in improving health outcomes and quality of lives, steps should be taken to facilitate capacity building. Developing national policies and standards are some mechanisms through which the government can help to provide a facilitating environment for the growth of virtualised health care technologies. "Involvement of the governmental health sector is expected to increase awareness and contribute to the development of sustainable health programmes at the country level. Such systematic approach will also pave the way for a multisectorial acceptance of health changes that are needed" [19].

7.3 Enabling Capacity Building Through Virtualization of Care

Virtualised health care technologies will play an increasing role as a means in building capacity at the Health 4.0 stage. Growth of health and medical technologies and applications, wearable devices, sensor-rich Internet of Things (IoT), big data, artificial intelligence and robotic technology will strengthen capacity and empower people to self-manage their health, wellness and illnesses. The World Health Organization (1998) defines empowerment as a "process through which people gain greater control over decisions and actions affecting their health". Patient empowerment can be supported by allowing them to control the process of their interactions with their health care providers [20, 21], supported by virtualised health care innovations such as health information technologies, wearable and implantable devices, Artificial Intelligence (AI) and robotic technology.

Health information technologies will deliver essential knowledge for educating and training of patients, enabling them to have better access to health information to make their own health-related decisions and eventually build capacity. By accessing their electronic health records (EHRs), patients can gain a better awareness of their health condition and actively participate in health promotion, prevention and care [20, 21]. The integration of EHRs and medical devices such as stethoscopes, ultrasounds and X-rays will allow health care professionals to access essential medical history to improve the quality of health care delivery. Health care devices and applications will deliver personalized rather than generic experience and adjust according to changes in individual's goals and conditions. Furthermore, given the shortage of health care professionals, capacity building in digital health care technologies can be used to improve access and address capacity shortages such as providing information and training to the rural and underserved communities [22].

Wearables and implantable devices have enabled patient to manage their health remotely while keeping pace with the increasing number of underserved patients with chronic diseases. With remote monitoring using pacemakers and implantable cardioverter defibrillators (ICDs) with wireless technology, diagnostic information and parameters about a patient's heart failure status can be accessed and followed-up by health care professionals remotely without the need for face-to-face evaluations [23]. Through virtual counselling, health care professionals can mentor and communicate with patients any place any time, thereby increasing support for capacity building. If health care technologies are attractive, people will want to continue to use them to strengthen their capacity in self-management of health, wellness and illness. Therefore, the design of future medical and health care wearable technologies should have appealing features, be seamlessly integrated with the wearer's clothing and body or linked to a mobile device, be suitable for the user's physical and mental ability, be low cost relative to the derived benefit and be simple for the user to set up and use [24].

Virtualised health care technologies and applications can also strengthen the capacities of institutions and governments to address patients' needs. The use of EHRs, wide range of sensors, wearable and implantable medical devices will bring new opportunities for observation, data collection and data mining in different situations and contexts, contributing to a better understanding of human body and disease, quality of life and lifespan. Powerful computer will build predictive models and incorporate big data analysis tools so that big data can be transformed into smart data that offer valuable information. Governments and institutions can use the big data to identify lifestyle patterns and promote behavior changes thus building a national e-Health capacity. Health indices can also be compared across countries and cultures. Moreover, pharmaceutical companies and researchers can mine the big data to design preventative treatments that are most effective for particular conditions. Insurance companies can use the big data to conduct more detailed analysis of insurance risk, increase the accuracy of valuation of policy claims and design tailored products [25].

Harnessing AI can help to address the lack of capacity in reaching the unserved or underserved population. With advancement in technology and AI, patients will receive remote medical care anytime without visiting a physician in person. The virtual world provides a wider range of tools than email, including building new customised environments, creating avatars, interacting with others without revealing one's real identity and person-to-person communication that more closely resembles face-to-face interactions [26]. Speech recognition and virtual assistants such as Sense.ly enables patients to be diagnosed by a digital avatar [27]. Developed by the University of Southern California [28], SimSensei provides real time tracking and analysis of non-verbal behaviors, including facial expressions, eye gaze, body posture and voice intonation. Medical avatar mobile applications such as Oakwood medical avatar mobile application provides a 3-dimension

animation of an individual's exact body measurements, enabling the individual to track symptoms, monitor EHR and wearables data and communicate changes in health conditions, and adhere to evidence-based interventions [29].

Improvement in robotic technology will help to build one's capacity (i.e. confidence, knowledge and skills) for self-management while reducing the burden on health care professionals. For example, Japanese researchers are developing motorized assistants such as the Cyberdyne that could help the elderly perform daily tasks [30]. Due to the rapid decline in fertility rate, many countries face the problem of changes in workforce participation rate, especially in the health care workforce. To solve the issue of shortage of nurses, Japanese believe robots is a cheap form of labour which can reduce the workload on nurses and enrich the quality of life for elderly patients [30]. In the future, robots will become popular at home and in hospice to support long-term care for the elderly population and end-of-life care.

7.4 Capacity Building Factors for Success in Virtualization of Care

The goal of capacity building using virtualization technologies is to help patients; their formal and informal carers attain a level of self-sufficiency which includes acquiring the necessary skills, knowledge, opportunities and resources in order to effectively self-manage their health, well-being and illness and to support health care professionals deliver health care services effectively and efficiently. This is accomplished by examining four factors that can facilitate capability building, namely *individual characteristics*, *trust*, *motivation* and *connectivity* (see Fig. 7.2).

Individual characteristics such as age, gender, socio-economic status, user strategy and personality are likely to affect the adoption and acceptance of digital health care technologies. With growth in dependence on technologies in the

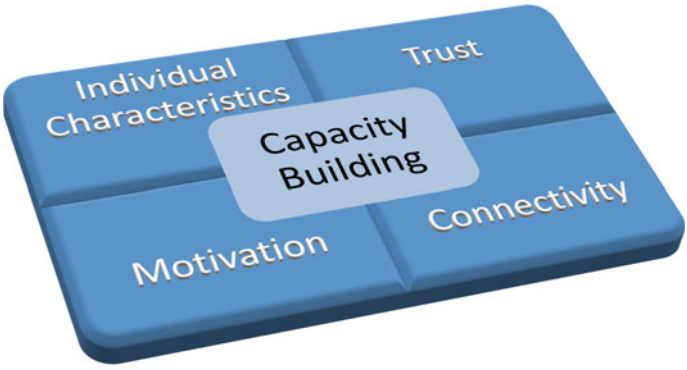

Fig. 7.2 Factors that contribute to capacity building in virtualization of care

digitally pervasive world, users demand for *trust* will increase enormously [4, 31]. Users' acceptance of future digital health care technologies will also depend on the degree of *motivation* that varies according to the extent to which benefits outweigh the costs and risks and the new technologies can make a significant difference in improving the quality of life. The *connected* digital health care market presents new ways for users to communicate, socialize, obtain information in real time, exchange health information and make informed health decisions. The connected health care landscape is also a driving force influencing the ways users accept future digital health care technologies in monitoring their health, approach diagnostics and comply with medication and therapy. The following sections will discuss these factors in details.

7.4.1 Individual Characteristics

Health care consumers come from different stakeholder groups, including patients, carers, medical and health care professionals and pharmaceutical companies. Insight from behavioral sciences will help us understand various aspects of health care consumers' behavior, including what they want and how they use the products and services. A needs analysis that involves considering the biological, psychological and cultural needs of different stakeholder groups is necessary in order to design appropriate health care products, services and interventions. This will require coordinated approaches to create the conducive conditions in the ecosystem that influence and support adoption of digital health care technologies and solutions. In the hospital environments, this will involve considering the needs and preferences of users and analysing the product's impact on work activities and the organization [32].

Individual characteristic variables such as age and education are the most significant predictors of Internet access for health information [33, 34]. Older adults are more likely than younger ones to track their weight, diet or exercise routine: 71% of adults aged 65 years and older compared with 61% of adults aged 18–29 years [34]. A survey conducted by McKinsey and Company revealed that patients above 50 years of age in the United Kingdom, Germany and Singapore want to use digital health care services but prefer traditional digital channels such as web sites and email whereas younger patients are more open to new channels such as social media [12]. This shows that younger generation are more confident in adopting new technologies but might have different expectations about how the technologies should be designed and used.

Gender differences were observed in the use of Internet for health-related activities. Women were more likely than men to engage in the search for health-related information [35]. In the survey of European citizens in 14 European countries, more women perceived the Internet as a main channel for health interaction use than men [36]. Moreover, the perceived importance of ICTs for the health or wellness is more positive for women than men [36]. However, men and

women were equally likely to participate in online support groups and to purchase medications and vitamins online [35] or to track health indicators and symptoms [34]. "In broad terms, people with higher education enjoy better health through a variety of pathways: more affluence or material security (whether or not through more competitive labour market participation), healthier personal behaviors, better self-/social esteem and efficacy, greater social network access, more experience of control; and perhaps through improved sense of coherence, less self-blame, and a greater ability to influence decision markers and mobilise personal and extrinsic resources" [9].

User strategy is normally applied to their choice of media [37]. For example, a patient who lives in a remote area can choose from a wide array of digital, Internet-connected health devices and application such as telemonitoring and mobile phone health interventions to monitor their symptoms and receive reminders. People will not only choose tools and services they wish to use and will pay for but also best suit them based on their psychological requirements [37]. Compared to 21% of the general population that use some forms of technology such as a medical device, a mobile app, a spreadsheet or an online tool to track their health data, half of the trackers in the general population (49%) prefer to track their health indicators in their heads [34]. Hence, a challenge for technology developers is to create tools or interventions that is as seamless as keeping track of health indicators in their heads. Digital health interventions should also incorporate different media such as video, audio, graphics and animations and tailor according to age, gender and socio-economic status.

Besides the strategic aspects of medical selection, users' personal characteristics such as personality can also affect both media choice and usage [37]. According to a research conducted by Pew Internet Centre [34], Internet users living with one or more chronic conditions are more likely to search for health commentary online, watch a health video online and sign up to receive email updates about certain health topics. Likewise, Internet users who have a recent medical emergency and experienced a significant change in their physical health are more likely than other Internet users to have search online to find someone who shares their situation or track their weight, diet or exercise routine. Carers of an adult relative, friend or a child with health condition or disability are also more likely than other adults to use social networking sites to gather and share health information and support. While social networking sites are not a major source where people can gather health information, they can be a source of encouragement and care.

As health care consumers of the future will have relatively high levels of household income and education attainment, they will want to take an active role in making decision about their health care and expect high levels of control, choice, customer service and interaction with their health care providers [38]. Patients will feel encouraged and motivated in improving their overall health when they take an active role in setting goals and making informed and individualized choices about their treatment and care.

An important influence in the design, adoption and usage of future health care solutions is human interface. Lack of user engagement in design and implementation is a major barrier to digital health adoption [39]. The interface has to be adapted to the capabilities of each device and application in a way that is sensitive to the user's needs [40]. User-needs driven design focuses on user motivation, degree of digital literacy, types of signalling, different cultural models (e.g. multilingualism), diversity and inclusiveness (e.g. for older people, for the less educated or those in poverty) [4]. Apple's rise and dominance in the mobile devices is not surprising. One key principle to Apple's success is that all Apple products must be intuitive and easy to understand and learn [41]. Apple's Human Interface Guidelines [42] suggest that app developers should focus on elevating functionality and defer to the user's content, providing clear and easy to interact content, and using visual layers and realistic motion to help users understand the relationships among onscreen objects.

According to a review of the impact of new technologies on workforce organization conducted by the UK Skills for Health [43], there is no standard lifecycle by which new technologies are adopted by staff. However, organizational and clinical leadership in terms of promotion of culture of innovation and other incentives are important influence. If health care professionals do not understand digital health or actively uses mobile medical devices or digital health care technologies, the disconnection between them and the patient is broadened. Health care professionals need to live in the context of digital health to appreciate it as an important tool rather than a novelty [43].

7.4.2 Trust

Similar to the Future Internet being built based on a psychology of trust [4, 31], the same condition also applies for virtualised health care technologies. The core features of user trust are security, privacy and ethics. As sensors and wearables such as health monitors enables personal health data and activities to be tracked and monitored, security and privacy are major areas of concern. Health care providers are concerned with the transmission, storage and retrieval of personal health data. Big data may be misused or manipulated by people and institutions in several ways. As more data traces are left online, sensitive information become publicly available and it becomes easier to identify individuals. Hence, security measurements in terms of authentication, authorization, confidentiality and integrity need to be revised periodically so that improvements can be implemented. In addition, health care providers are worried that given the amount of data collected across multiple sources and devices, there is a strong heterogeneity in the data collected. There is also the likelihood that rather than being rewarded for positive behavioral change, people with unhealthy lifestyles are likely to be penalized. For example, health insurance companies can use the health and medical data to set premiums.

When it comes to managing our health, research has indicated that the Internet plays a supplemental role. Despite abundance opportunities to access mobile and online health information, most adults prefer to seek help from health professional, friend or family member when they have a question [33]. The majority of the interactions occurred offline and only 5% of adults received online information, care or support from a health professional, 13% received online contact with friends and family and 5% interacted online with fellow patients. The supplemental role played by the Internet might be explained by the lower level of trust with online companies and web sites as compared with medical and health institutions. Fear of information overload and concern about the quality of medical information remain barriers preventing people from using online health information and services. Even though the Internet is an important empowering tool for health, European citizens consider direct interaction with doctors and nurses to be most relevant [36]. With respect to the health information available to European citizens, 26% of participants fully trust medical and health institutions. In contrast, only 4% of the participants trust online companies [36]. Level of trust in Internet-based health also varies across European countries. The level of trust in Internet-based health companies is higher for Italy (48% of all participants) and Denmark (43%) compared to Finland (23%) and Sweden (24%) [36]. As shown in Fig. 7.3, several factors were identified as facilitators that motivate European citizens to use the Internet for health [36]. In order to build and strengthen capacity, developers of new digital health care products and services should consider these facilitators in the design, development and deployment of new technologies.

Data privacy is another major challenge in digital health care. Health care providers are concerned with issues of consent and confidentiality. Health care providers must ensure that the right type of consents are obtained from patients up

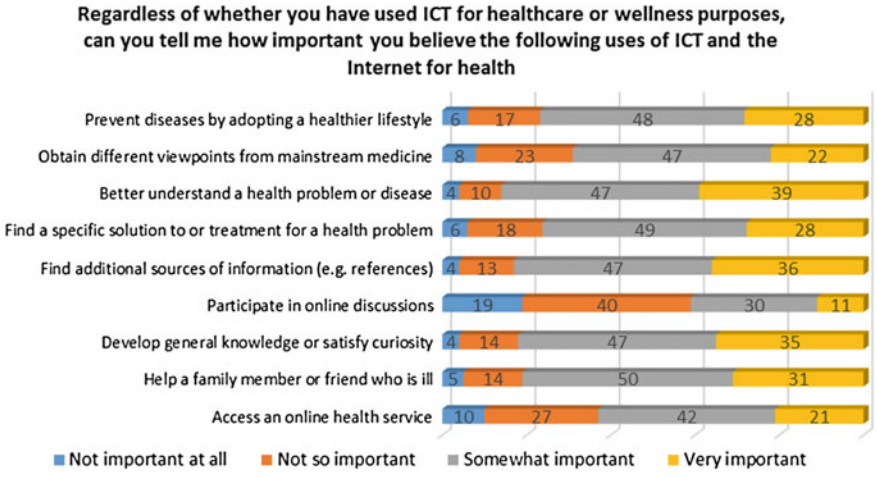

Fig. 7.3 ICT for health motivators and triggers. *Source* Lupiañez et al. [36]

front and data are used in the confidential manner and for the purposes in question. Control over EHRs and privacy assurance are two major concerns for consumers [44]. It is important that the law that governs the security and privacy of health data from sensors and wearable stay relevant as technology advances.

Fears of intrusion and harm drive the need for privacy which is an important issue that the Internet cannot offer today [4]. Health care consumers and patients are fearful of misuses and unauthorized access of their personal health information by anyone other than their physicians. They are also concerned whether personal health information is securely and accurately transmitted across the network. In order to alleviate these fears, digital health market must be regulated by legislation and ethical guidelines. A study of the global m-Health market revealed that regulation is not perceived as a barrier to the m-Health market's growth [45].

There is currently a lack of evidence showing the efficacy or effectiveness of apps aim at improving adherence or clinically relevant outcomes [46]. Depending on the type of mobile medical devices, the type of data collected and how the data is used, these devices can be seen as empowering and threatening. While mobile medical devices can aid people to live independently, they might reduce the need for support from health care professionals and can potentially lead to social isolation. Social isolation can have a detrimental effect on psychological and physical health and well-being. Another significant issue related to the increasing reliance on mobile medical devices is non-adherence to treatment plan. For example, a patient's failure to take medications as instructed and not following recommended lifestyle changes can have profound effect on the patient's health outcome. Building capacity through accountable partnership between patients and health care professionals is the way forward to supporting the delivery of citizen-centred holistic-integral care.

While the health care sector is highly regulated, many of the m-Health apps and consumer electronics such as smart watches remain largely unregulated. However, the United States Food and Drug Administration [47] publishes a set of guidelines on the design, testing and use of radio-frequency (RF) wireless medical devices that is intended to guide both device manufacturers and health care provides towards the safe and secure use of wireless medical device. The FDA [48] has also issued final guidance on mobile medical apps. The FDA focuses its regulatory oversight on a subset of mobile medical apps that pose greater risk to patients if they do not work as intended. This includes mobile medical apps that are intended to be used as an accessory, a regulated medical device (e.g. an app that allows a health care professional to make a specific diagnosis by viewing a medical image from a picture archiving and communication system (PACS) on a smartphone) or transform a mobile platform into a regulated medical device (e.g. an app that turns a smartphone into an electrocardiography (ECG) machine to detect abnormal heart rhythms).

Given that m-Health apps and devices provide wellness, fitness and dietary advice and constantly measure and collect vital signs, there is a need to address the social, behavior and legal challenges. For example, since the wearables market in the UK is dominated by US-based companies [49], personal data might be transferred across borders. There is the potential that national and international data

transfer regulations and privacy laws are being violated. The EU has forbid cross-border data transfers unless certain conditions are met. It is important to note that there is currently lack of international standards and guidelines governing the development of virtual environment for health and social care in order to guarantee appropriate levels of security and privacy. Enforcing a common data legislation across different countries, such as within Europe, and between Europe and other states) is complex. With the EU data protection legislation being delayed, institutions and business must comply with existing framework while ensuring that their business models is future-proof to meet the challenges proposed by the new EU regulation [25]. The issue of security versus privacy has gained prominence in Europe and the United States after the London and Madrid bombing and the 9/11 terrorist acts. In April 2014, the European Court of Justice ruled that communications service providers did not have to adhere to the 2006 Data Retention Directive [50]. In response to this ruling, the UK government pushed through an emergency law that outlines the legal obligations of companies that provide telephone and internet connections to retain "communications data" on their customers [51, 52]. A landmark decision from the Canadian Supreme Court, on the other hand, ruled that Internet service providers are barred disclosing the names, addresses and phone numbers of their customers to law enforcement officials voluntarily [53]. The conflicting data protection laws and court ruling in different countries present significant challenges in achieving the right balance between security and privacy, especially in cross-border data transfer.

Another major challenge in virtual environment is the modelling of human capabilities. Extensive human factors such as perceptual, cognitive and social issues have to be considered in the design of a virtual medical environment [40]. Individual assessment of trust in the virtual environment may differ from face-to-face interaction. For instance, in contrast to a video conference with a physician, it is difficult to establish mutual trust and awareness with a medical avatar in the virtual environment. Moreover, it might be difficult to detect and respond to an individual's non-verbal behavior such as gestures, postures and gaze in real time. Furthermore, even though the virtual world offers unique capabilities such as anonymous interaction, it is a complex and unregulated environment. For instance, there is no guarantee that the person on the other side of the screen is the therapist whom the patient expects since anyone can enter the virtual environment and interact with the patients [26]. However, virtual therapy is most effective when it is used together with traditional therapy or as part of an aftercare plan [26].

In recent years, there has been a predominant focus on gamification of health and fitness apps [54]. "Gamification is the use of game design elements in non-game contexts" [55]. In health care, gamification involves the use of game design and game mechanics to engage a consumer to change a target set of behaviors, develop new skills and engage in innovation [56]. However, Gartner [56] estimates that 80% of gamified solutions will be off the market by 2014 due to poor design. This might be due to the lack of integration of industry standard of effective gaming,

gamification and important elements of behavioral theory in health and fitness apps [54].

With regard to ethics, several medical councils and associations have published code of ethics for the use of the Internet and social media. The Ethics Committee of the American Psychological Association [57] has published a statement on services by telephone, teleconferencing and Internet. This statement stipulates that psychologists must take reasonable steps to ensure competence of their work and to protect patients, clients, students and research participants from harm. In the British General Medical Council's [58] practical and ethical guidance, doctors and medical students have the ethical and legal duty to protect patient confidentiality on the Internet and other media. Doctors and medical students are advised to adopt conservative privacy settings and be aware that not all information can be protected on the web.

7.4.3 Motivation

The self-determination theory (SDT) provides a useful framework for understanding human motivation in the acceptance and adoption of new health care technologies. SDT is a micro-theory that focuses on human motivation, personal development and well-being [59]. The three basic psychological elements of the self-determination theory, as discussed below, could be employed in the design of new medical technologies and applications. Fulfilment of these basic psychological needs within a social context are essential and necessary for psychological growth [59]. An analysis of health and fitness apps related to physical activity and diet showed that apps that use gamification are trying to influence the motivation of users to engage in a desired behavior without considering the ability of an individual to perform the behavior and the triggers to engage in a behavior [54]. Therefore, in addition to motivation, increasing an individual's self-efficacy is crucial to achieving long-term behavior change [54].

(a) Autonomy: Patients want to feel in charge of their own health and take active role in their own care. Health care devices and applications should make patients feel more empowered by linking lifestyles and dietary changes to the goals set by the patients.
(b) Competence: Patients need to feel confident and realize they are capable of learning and achieving success. Self-management health care devices and applications should provide clear step-to-step procedures to support patients in managing their health, especially for patients with multiple chronic conditions.
(c) Relatedness: Social connection is a fundamental human need. Humans live as members of groups from early in life. Patients want emotional support and to feel connected to other people. Health care devices and applications should provide a platform for patients to share, learn, interact and build relationships.

Digital divide can create psychological barriers that may inhibit an individual's motivation to accept and adopt a new health care technology. The Global Information Technology Report (GITR) published by the World Economic Forum and INSEAD showed that despite some positive trends showing growing availability of technology in empowering citizens in both developed and developing countries, there is a sharp digital divide between impoverished nations and richer economies [60]. Greater perception of empowerment with respect to health appears to be linked with countries where the digital divide among citizens is more marked, in particular Estonia, Slovenia and Slovakia [36]. Individual's literacy level with the technology used can also affect the level of engagement in digital health care technologies. The issue of technology and health literacy among different ages and abilities has also not being fully addressed. Some elderly people are apprehensive about the impact of telemedicine due to fear of new technology [61]. Hence, significant effort should be made to motivate elderly and people with disabilities to participate in digital health through the improvement of human–computer interaction design, reduction of language and literacy-related barriers by translating site contents into different languages, and reduction of age-related barriers to participation by effectively engaging elderly population [61].

7.4.4 Connectivity

Connectivity is a necessity to capacity building. As Nosta [62] has argued, the shift in focus from "fashion of the device" to connectivity will lead to better health outcomes. Connectivity refers not only to people-to-people but also human-to-machine and machine-to machine communications.

7.4.4.1 People to People (P2P)

Capacity building involves a collaborative process of sharing knowledge, resources and experiences. The vast knowledge and experience of patients and caregivers must be tapped by researchers. Future models of connectivity in health care devices should not only enable health care researchers to connect with physicians but also facilitate effective and efficient communication among researchers, patients and their caregivers. For example, the primary focus of EHR systems is to support clinical decision, but it can also be redesigned to encourage engagement among health care professionals, researchers, patients, and caregivers.

Building capacity involves strengthening of social networks. Large and densely layered social networks have "health enhancing effects" [9]. Only by engaging with health care professions, their formal and informal carers and other patients can the patients better identify the gaps in their knowledge, skills and resources. Interaction

between patients acts as a form of social empowerment enabling patients to share and discuss information with other patients who have similar conditions [21]. Moreover, social networking can improve patients' self-esteem and decrease isolation.

7.4.4.2 Human to Machine (H2M)

Another approach to build capacity is to design future medical devices and applications to act "more human". That is, be more human-like and more empathetic in order to understand human mind and communicate with humans in more natural ways. As Douglas Hofstadter (1979 in [63]) has argued in his book titled "Gödel, Escher, Bach: an eternal golden braid", AI should be concerned more with understanding human intelligence rather than solving human problems intelligently.

Mobile applications such as iPhone's Siri, Anroid's Google Now and Window Phone's Cortana have changed the relationship between human and machine. Microsoft's Cortana is an intelligent personal digital assistant that will be built into Windows 10 devices. Cortana includes some smart features such as learning about an individual's habits, voice recognition, customized reply in audio or text and performing approved search tasks [64]. In addition, developers have started to employ machine-learning algorithms to build machine that can understand and express emotions and analyse the psychological state of the patients. For example, speech recognition and virtual assistants such as Sense.ly [27] can identify patients' extremities and measures their movement so as to gauge symptoms. Medical avatar mobile application enables patients to use their avatars to track symptoms, monitor EHRs and wearables data, and communicate changes in health conditions [29]. In the future, medical technologies might be able to assist physicians in detecting diseases.

7.4.4.3 Machine to Machine (M2M)

As highlighted earlier, there are several factors contributing to the rise in machine-to-machine connectivity in health care technologies. An ageing population, an increasing number of patients with chronic diseases who need to be monitored at home, an escalation of health care costs and a critical shortage of health care professionals all present great challenges. Wireless technologies offer opportunities to support capacity building by enabling care to be extended beyond the hospital. High quality care can be delivered to patients at home and in remote areas at lower costs. In the event of emergencies or urgent situations, notification can be sent promptly using wired or wireless connectivity between connected devices without the need for human intervention.

7.5 Understanding How Health Care Consumers Adopt New Health Care Technologies

Introducing technologies to support self-management of health, wellness and disease requires significant changes in habits, work practices and communication methods. Individual adoption of new technologies is influenced by psychological factors such as perceived usefulness, ease of use, conscious and unconscious motivation, compatibility, cost-benefit comparison, credibility and trust. As discussed earlier, variations in individual adoption and sustained use of technology are also influenced by biological or individual-difference factors (e.g. age and gender), cultural factors (e.g. race and ethnicity) and socio-demographic variables (e.g. education, occupation and income). Social factors that influence the adoption and use of new technologies include subjective norms, voluntariness and image [65].

Many Internet interventions have not been grounded in theory or derived from behavior change models [66]. The key to patients' and health care professionals' acceptance and sustained use of new digital health care technologies is to incorporate theories across multiple disciplines in the development of digital health care technologies [39]. Psychological theories will help developers and health care providers identify barriers and incentives that influence people's adoption of new digital health care technologies and inform them about factors that affect people's lifestyles and health-related behaviors. Moreover, health care providers can apply evidence-based digital health care interventions to assist people in changing their lifestyles and tailor individualized care according to people's needs.

7.5.1 Psychological Models

There are many competing psychological models in explaining behavior change, including the Biopsychosocial Health Model [67], Health Belief Model HBM [68, 69], Theory of Reasoned Theory TRA [70], Theory of Planned Behavior TPB [71], Social Cognitive Theory SCT [72], Stages of Change or Transtheoretical Model TTM [73], Prochaska et al. [74], Self-determination Theory SDT [59], Precaution Adoption Process Model PAPM [75] and Integrated Theoretical Model ITM [59]. The list is by no means exhaustive. An in-depth discussion of these theories is beyond the scope of this chapter. In addition to SDT described in Sect. 7.4.3, this chapter will briefly discuss three other psychological models that are applicable in the bidirectional relationship between capacity building and virtualization of care. Although many of these behavioral change models do not place an emphasis on capacity building, we can use these behavior change theories for purposeful capacity building which will ultimately leads to acceptance and adoption of new digital health care technologies and applications. Moreover, understanding these health behavior theories can provide useful insights into the affective, cognitive and behavioral reactions to the acceptance and adoption of new digital health

care technologies and applications and factors that influence these reactions [76] as well as improve our understanding of multiple behavior change [77].

7.5.1.1 Biopsychosocial Health Model

There has been in a shift in focus from a biomedical or disease-based model of illness to a biopsychosocial model in the treatment of chronic disease [78, 79]. The biopsychosocial model, as proposed by Engel 67,

> provide a basis for understanding the determinants of disease and arriving at rational treatments and patterns of health care, a medical model must also take into account the patient, the social context in which he lives, and the complementary system devised by society to deal with the disruptive effects of illness, that is, the physician role and the health care system.

The biopsychosocial model integrates biological science with the psychological (thoughts, behaviors and feelings) and the social and cultural dimensions of individual's experience. While biomedical interventions focus on healing, prevention of disease-related complications and improvement in quality of life (QoL), psychosocial interventions aim to initiate behavioral changes (e.g. reduction in stress, weight loss) to improve disease profile [79]. On the one hand, focusing on the psychological (e.g. motivation, self-esteem, personality), social (e.g. socioeconomic status, culture, religion) and biological (e.g. genetics, mental and physical health, chronic diseases) dimensions when designing new digital health care technologies and applications will take in consideration factors that can influence capacity building (see Fig. 7.4). On the other hand, building an individual's capacity by focusing on the three dimensions can improve the uptake of digital health care technologies. Technology advances have enabled patient-centred care. In light of challenges such as greater patient autonomy and participation in care and increased access to information, Engel's biopsychological model can be realised through building the capacities of health care professionals to become more self-aware and resilient and engage in compassionate action [80]. With the newly acquired knowledge, skills and resources, health care professionals will be able to adopt new digital health care technologies to support their work.

7.5.1.2 Health Belief Model

The Health Belief Model (HBM) maintains that preventive behaviors are a function of one's perceptions about susceptibility to the health problem, the severity of the health problem, the benefits versus barriers of adopting a preventive behavior, and cue to action [81]. The key concepts and modifying factors of the HBM is presented in Fig. 7.5. The definitions of the key concepts and examples of applications of digital health care technologies are shown in Table 7.1. A person will change a health behavior if he/she feels that a negative health condition can be avoided, has a

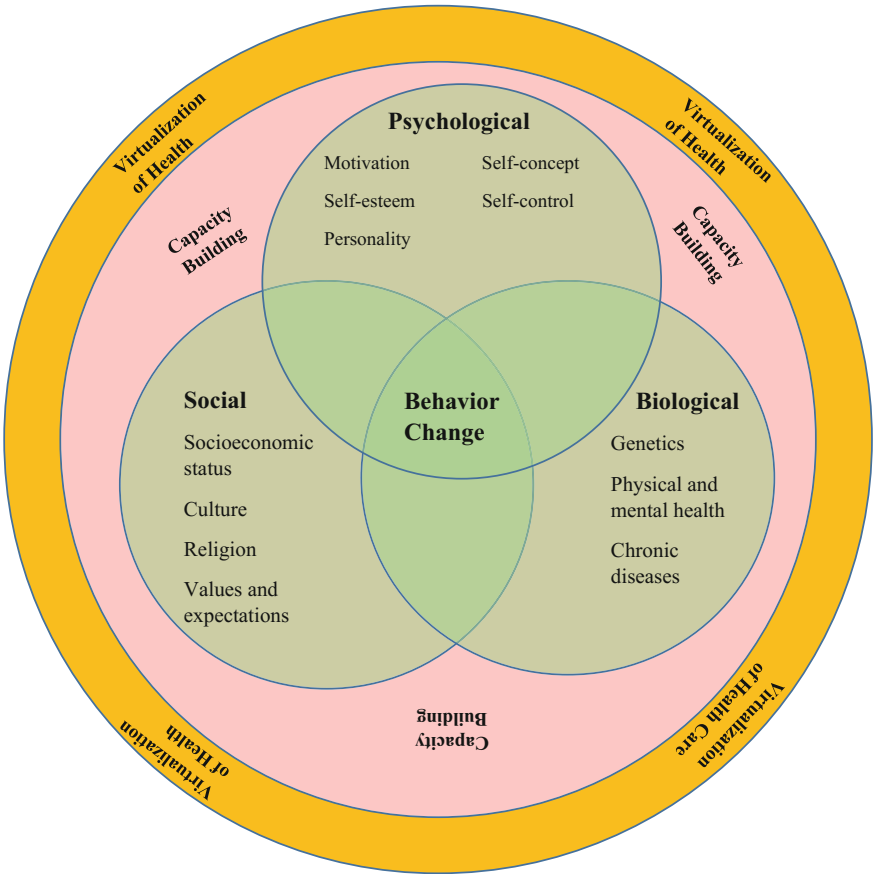

Fig. 7.4 Bidirectional relationship between capacity building and virtualization of health care using biopsychosocial health model

positive expectation that the health action taken will help to avoid a negative health condition and believes that he/she can successfully undertake the recommended health action. HBM has been applied to a wide range of health behaviors and subject population, including preventive health behaviors such as health promotion behaviors (e.g. diet and exercise) and health risk behaviors (e.g. smoking and alcohol) [82].

7.5.1.3 Stages of Change or Transtheoretical Model

The Stages of Change or Transtheoretical Model (TTM) [73, 74] describes behavior change as a dynamic rather than static process, acknowledging that individuals

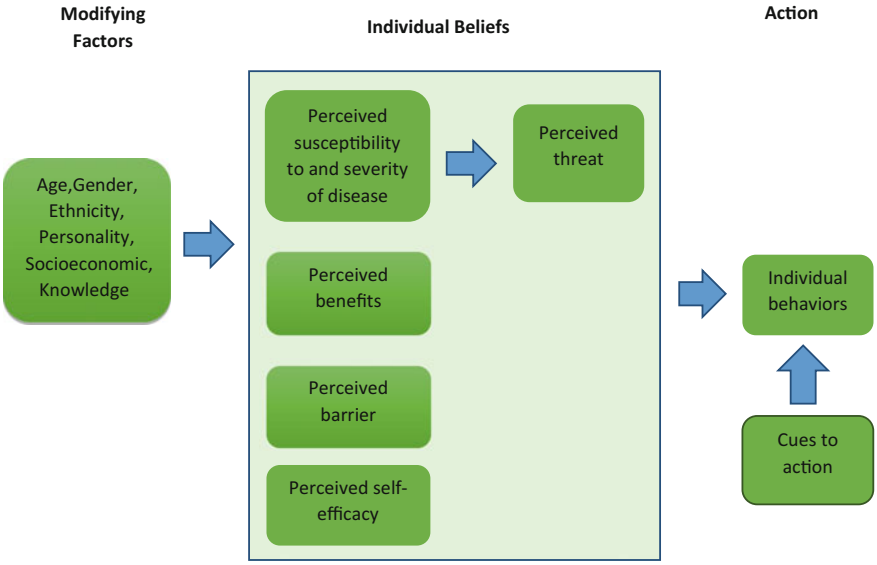

Fig. 7.5 The Health Belief Model (with permission from Champion and Skinner [83])

differ in their readiness to change a behavior and that these changes occur in discrete steps over time. The six stages in this model are:

(1) Precontemplative: not considering change, process less information, spend less time evaluating themselves, experience fewer emotional reactions to the negative aspects of behavior, do little to shift their attention or their environment away from behavior.
(2) Contemplative: aware and thinking about changing, most likely to respond to feedback and education as sources of information, feel and think more about themselves in relationship to their problem behavior, the combination of affective and cognitive self-reevaluation process that carries over from contemplation into action.
(3) Preparation: some experience with change and taking steps necessary for changing in the next 6 months.
(4) Action: practice new behavior for a short period of time, use both counter-condition and stimulus-control procedures for actively changing their behavior and environment, more self- and social reinforcement for their changes, rely more on helping relationships for support and understanding, self-liberating process is emphasized most during this stage, and counterconditioning and stimulus-control processes appear to bridge the gap between action and maintenance.

Table 7.1 Key concepts and definitions of the Health Belief Model and examples of applications of digital health care technologies

Concept	Definition	Examples
Perceived susceptibility	Belief about the chances of experiencing a risk or getting a condition or disease	According Pew Research Centre, people who live with a disability or chronic disease are more likely than other people to engage intensely with online resources [84]. Majority of the research participants (75%) made a decision about their treatment based on their health search [84]
Perceived severity	Belief about how serious a condition and its sequel are	
Perceived benefits	Belief in efficacy of the advised action to reduce risk or seriousness of impact	The results of a study that used HBM to predict the intention to use telecare in patients with chronic diseases indicated that perceived benefits and cues to action had significant positive effects on the attitude towards using telecare in patients with chronic diseases [85]
Cues to action	Strategies to achieve "readiness"	The screening, brief, intervention and referral to treatment (SBIRT) tool is an online intervention aims at delivering short obesity prevention interventions within 10–20 min periods. The SBIRT was designed to act as a cue to action, in which the interventions would prompt parents to initiate and sustain healthy lifestyle changes for their children [86]
Perceived barriers	Belief about the tangible and psychological costs of the advised action	Findings of a study that assessed a stroke patient's receptivity towards and motivation to engage in consumer health information technology programme suggested that the patient was generally negative about his disease course and the unmet need with technology-assisted tools. Hence, the design should focus on the functionality and friendly interface as well as the barriers to successful adoption of personal health records [87]
Self-efficacy	Confidence in one's ability to take action	The HBM construct of self-efficacy has been shown to predict colorectal cancer screening behavior. Computer-delivered tailored interventions that included messages to overcome or reduce barriers could increase self-efficacy [88]

Concepts and definitions with permission from Champion and Skinner [83]

(5) Maintenance: having successfully changed the behavior, continue to emphasize counterconditioning and stimulus-control process for coping with temptations, gain a greater level of capacity and confidence, an active stage of change rather than an absence of change.

(6) Relapse: resume old behaviors, use consciousness raising, self-reevaluation, helping relationships and stimulus control, may prepare themselves to quit behavior again as they engage in process associated with contemplation, may attempt to prevent complete relapse by using action and maintenance process.

Capacity building takes time. It is necessary to follow from one step to another in order to adopt or modify prevention behaviors. As suggested by Prochaska and DiClemente [73], different processes are used in different stages of change. Rather than assume that patients who come for treatment are ready for behavioral change, they should be grouped according to which stage of change they are in. By identifying an individual's stage of change, the health care professionals can select and apply the most appropriate training, resources and interventions that correspond to that stage. For example, increasing patients' knowledge and awareness of diseases can help them move from precontemplation to the contemplation stage. A patient in the contemplation stage would begin with consciousness raising and self-reevaluation process. Patients who are ready for action could begin to apply more behavior-based processes. In order to move from contemplation to preparation and action stages, access to resources and support from carers are necessary. Resources include digital health care technologies or solutions that provide real time monitoring and self-help web-based manual. The self-help manual can be developed based on self-change model.

In summary, there is no single theoretical approach to capacity building in health behavioural change through virtualization of health care. The varied nature of different health behaviors may necessitate the inclusion of additional constructs to understand the reasons people object to change and their reluctance to adopt innovative technologies. Differences between addictive and non-addictive behaviors, between one-time behaviors and those that are maintained and between adoption and cessation behaviors [77] may necessitate the inclusion of a combination of psychological models in the design and development of health care technologies and applications for successful adoption of technologies and applications. Supporting patients to understand their own health, well-being and illness and to select, accept and adopt health care technologies, and applications that are most appropriate to their needs are ways to build capacity.

7.6 Conclusion

User resistance is a major challenge in virtualization of health care. This challenge can be overcome by supporting capacity building. Capacity building through virtualization of care involves empowering patients to self-manage their own health, wellness and illness and enhancing the knowledge, skills of health care professionals. Although capacity building takes time and effort, it is the most effective and efficient route to adoption and use of digital health care technologies and applications. Psychology, social, cultural and individual-difference factors all play

important roles in influencing the extent to which patients, carers and health care professionals feel comfortable with new health care technologies and applications. Future digital health care technologies that give little regard for these factors are doomed to fail at the outset. Psychological models offer a unique understanding of health, wellness, and illness and human interactions in the digital world. For sustainable capacity building, psychological models should be incorporated in the design and deployment of digital health care technologies in order to increase the likelihood of acceptance, adoption and uptake of these technologies. Virtualization of health care will in turn build up the capacity of people by increasing their knowledge and skills, helping them become active partners in their own health care and achieving improved health outcomes.

Interventions based on capacity building to improve acceptance, adoption and uptake of new health care technologies should be based on evidence. However, there is a lack of evidence-base for monitoring capacity building efforts. Therefore, future research should focus on measuring and evaluating capacity building. The measurement and evaluation methods should be informed by baseline information at individual, institution and societal levels. The establishment of a varied range of measurable impact indicators, both in the immediate and longer term, will help to make comparisons comparable over time. Future research should also focus on investigating whether a single psychology model or a combination of different models contribute towards capacity building.

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Chapter 8
E-Health in China

Chunxue Bai

8.1 Health Status in China

8.1.1 General Treatment Dilemma

With most acute infectious diseases being effectively controlled, there are major changes to the human disease spectrum: chronic non-communicable diseases (referred to as chronic) become the primary threat to human health. This has become a global public health problem and common concern, and in China chronic diseases have become a hazard to public health.

According to the 2008 fourth national health services survey in China, whether in the city or countryside, cancer, heart disease, cerebrovascular disease, and respiratory diseases accounted for the top 10 diseases causing mortality. The mortality rate from these diseases is approximately 78 %. In 2012, the Ministry of Health and 15 other departments jointly issued the "China Chronic Disease Prevention and Control Plan" data in its launch of the "Chronic Diseases Chinese Expert Consensus." It showed that chronic diseases, such as cardiovascular diseases, cancer, diabetes, and chronic respiratory diseases, are by far the most important public health problem in the world and that in China they are the top four causes of death in urban and rural areas. In China, death due to chronic diseases accounted for 85 % of deaths before the age of 70, and 45 % of patients die from chronic diseases. Premature death from chronic diseases nationwide is 75 % of the total

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number of premature death. There are 200 million hypertensive patients, 120 million obese patients, 97 million diabetics, and 33 million patients with hypercholesterolemia, in which more than 65 % of these patients are 18–59 years old, which has serious implications for the work force and thus is also a burden to society.

Chronic diseases have very complex etiology and usually start from some occult causes and have delayed healing. In addition, these diseases are closely related to psychosocial factors and lifestyle. Common chronic diseases include cancer, diabetes, cardiovascular disease, asthma, chronic obstructive pulmonary disease (COPD), arthritis, and acquired immune deficiency syndrome (AIDS). Delayed healing of chronic diseases, poor prognosis, repeated exacerbations, or disease progression accompanied by complications and disability can seriously affect human health for individuals, families, and society, causing heavy economic and social burdens. Chronic diseases and the vicious cycle of poverty make this into a "poverty caused by illness" predicament.

8.1.2 Potential Aging Problem

China has one of the world's fastest aging populations, which is the inevitable result of economic development, but social and cultural developments also have a major impact. The 2010 sixth national census data show that the average life expectancy of China's population has been increasing, extending the life of women faster than men. In addition, China's elderly population (over the age of 60) in 2010 was 178 million and at the end of 2013 it has reached 202 million. China is currently the world's most populous country and it is estimated that the population will grow at an annual rate of 8 million in the future.

Compared with other countries, China's aging population has six salient features:

(1) Absolute number of the elderly population: China is the only country in the world with an elderly population of hundreds of millions. It has the highest degree of aging in developing countries, accounting for approximately half of the elderly population in Asia and one-fifth of the world's elderly population. In 2050, the total elderly population is estimated to be close to 500 million, accounting for two-fifth and one-fourth of the world's and Asia's elderly populations, respectively, which is more than the sum of the elderly populations in developed countries.
(2) Rapid aging population: In 1999, the elderly population was one-tenth of the total population of China. It is currently one-seventh and is estimated to be one-sixth in 2020, one-fourth in 2030, and one-third in 2050. The elderly

population is estimated to remain as one-third of the total population until the end of the century. While it would take approximately 100 years for the level of aging to raise from 10 to 30 % in Britain, France, the United States, and other Western industrialized countries, it is expected to be only 41 years in China.

(3) Significant aging trend: From 2010 to 2049, the Chinese population aged 80 and over will grow from 19 to 100 million. By mid-century, the total number of the oldest old will account for more than a quarter of the world, equivalent to the sum of the oldest old in developed countries. Since 90 years ago to the present century, China had the largest elderly population worldwide.

(4) High degree of family miniaturization: The average Chinese household size fell from 4.6 persons per family during the reform and opening-up period to 3.42 persons per family in 2000, and will reach 2.61 in 2030 and 2.51 in 2050. Continued low fertility will reduce the proportion of the adolescent population, which will decrease the age of the new labor force population.

(5) Huge difference between urban and rural aging: Aging in rural areas is 1.24 % higher than in urban areas. In 2050, it will reach 39.9 % of the total rural population, 7.7 % higher than the city. The proportion of the elderly in rural areas in 28 provinces around the country is 20 % more than the urban areas. The urban and rural inversion situation will continue until 2040.

(6) Prominent problem of getting old before getting rich: People in Western countries generally become rich before or with getting old. The basic per capita gross domestic product (GDP) is approximately $10,000 for a reentry population in an aging society. However, the per capita GDP in 1999, when China became an aging society, was only $840, which is one-sixth of the world's average. Thus, there is an obvious problem of becoming old without accumulating wealth. China's per capita GDP is still currently in the ranks of middle-income countries. The economy is relatively poor, making it difficult to cope with an aging society.

The elderly population is characterized by high prevalence, high disability rate, and high rate of medical needs. Human illness and loss will increase rapidly in the aged people, and health services would be critical and will have a large impact on the China's social and economic development. The burden of the entire healthcare system will gradually increase.

8.1.3 Prevention and Healthcare Problem

China has launched a community healthcare network since the 1950s. There are relatively sound urban and tertiary care networks, and the system can provide health services for area residents, eventually implementing the primary healthcare

organizational guarantee. This system is an advantage of China's primary health care. Each city's general hospitals have set up many health departments, health facilities, and there is medical staff to provide clients with regular services such as regular follow-up, medical consultation, physical examination, perinatal care, and neonatal care.

Due largely to the country's vigorous advocacy, healthcare workers and management have created an ideal first-line medical staff working with a community health model, developed of a number of policies, and defined the function of community health and the general role of physicians in community health care. Through the positive work of doctors and nurses who have many practical experiences, the community health service business is sound in China, such that the incidence of infectious diseases and neonatal mortality have significantly reduced, which is a great achievement. In recent years, community health in China has made a great improvement: the development of a "family bed" to ease the difficulties of getting access to medical treatment and getting a hospital bed and to reduce the burden on patients and society. The provision of health services by the medical staff to permanent residents helps to ensure the continuity of the service of a doctor, which forms a major part in people's lives as well as provides basic health care [1].

However, the current situation and health care throughout the country are far from satisfactory. There is an extreme lack of general practitioners (GPs). Large general hospitals are overcrowded and specialist physicians are overburdened. On the other hand, community hospitals seem deserted.

Lack of general practitioners

Training and deployment of Chinese GPs is still in its infancy, and there is a serious shortage. According to statistics compiled by relevant departments, there is shortage of 10 million GPs in the urban community health service centers, caused by medical resources being distributed to more deficient rural areas.

Abandoned community hospitals

Community hospitals are becoming deserted because it is difficult to attract high-quality medical staff there, resulting in more patients flocking to large hospitals. This situation raises "two difficulties," namely enrolling in well-known hospitals and seeing notable doctors (Fig. 8.1).

Overburdened specialists

Physicians generally have a higher professional level at large hospitals, but because they are busy with daily work and other reasons, they are not able to carry out their duties in prevention, health care, management of chronic diseases and rehabilitation, referred as the "four insufficiencies." Physicians are generally unable to play their intended role in the management of chronic diseases, resulting in poor management of recurrent acute episodes or even loss of lives.

Fig. 8.1 Zhongshan Hospital; pictures taken in May 2011

8.2 How to Improve the Current Situation

As described above, the sharp increase in the scale of chronic diseases is posing a great challenge to current treatments based on the traditional medical model at the health centers. A new model has become the main direction of healthcare reform. In view of the crisis, the World Health Organization emphasized that the medical field should focus on people's health rather than diseases as the main research area, thus transforming the medical model from a disease-based model to a health-focused medical model.

8.2.1 Building a Modern Medical Model

With social development, scientific and technological progress, and the rapid aging of the population, chronic diseases dominate the composition of the Chinese population and the mode of death. Irregardless of whether it is the result of disease or health consequences, the biopsychosocial medical model should be followed. In a report, "Meeting the challenges of the 21st century", the World Health Organization states that "21st century medicine, should not continue with disease as the main object of study, but should be based on human health as the main direction

of medical research". The trend of development of medicine has been the "high-tech medical treatment for the purpose of the endless pursuit" to "prevention of disease and injury, maintain and improve health." This will profoundly change medical theories and practices, from a disease model to a health model giving full consideration to modern medicine and Chinese medicine theories and technological advantages in order to improve patients' health. At the same time, the shift in focus from human diseases to human health and the focus on scientific and technological progress to strengthen the knowledge of integrated care in social and psychological environment are of great importance to unearth human body's own healthy power.

According to the medical model, the mode of medical services should change from achieving prevention first to integrating prevention with treatment so as to prevent and treat simultaneously. Clinicians should focus not only on the treatment of the disease itself, but should make the transition from a purely curative approach to a combination of therapy and clinical disease prevention perspective. Doctors should pass on health knowledge and personal behavior-related disease prevention measures to patients. Prevention staff should change the traditional mode of prevention and prevention contents, from the prevention of infectious diseases to the prevention of infectious and chronic diseases simultaneously, expanding from the traditional, passive means of prevention, which are oriented to the supply side (such as vaccination), to the prevention of individual's health behaviors.

In order to adapt to the new medical model, we need to give support in terms of human and physical resources. Fortunately, China has begun to reform the health system and the personnel system, and the community health service system will eventually comprise of a wide range of specialist medical and allied health professionals. It will also be a win-win situation for the GPs. The establishment of a GP system and the gradual implementation of GPs as the main primary healthcare actors are an important part of the rapid progressive development of primary healthcare services. More importantly, this will help improve people's access to health care.

To solve the problems of an aging society, providing health and medical care to the elderly population are of utmost importance. China is trying to develop community health services and general medicine. General Medicine may need to start from a grassroots level, with a progressive realization of a community first diagnosis system, classification of medical and bidirectional transfer consultation. However, the current status of GP teams is generally not satisfactory, mainly due to the chronic shortage of manpower, and not because of national advocacy, support, and rapid change.

8.2.2 Solving the Contradiction Between Advanced Medical Model and Human Resources

Even if the GP teams are growing and patients are willing to go to the well-known hospitals to see notable doctors, they would rather endure the current state of "three

long, one short" (long registration queue, longer payment time, long time to get the medicine, and short medical treatment time), rather than going to community hospitals. This has resulted in large hospitals being overcrowded with many patients during peak periods and patients and their families queuing for more than three hours in the outpatient halls in order to see the doctor for only three minutes. This is the experience suffered by many patients in many well-known large Chinese hospitals.

The traditional medical model of "visiting large hospitals for outpatient follow-up," is not only increasingly difficult to meet the demand for high-quality health resources, but also is not very effective to detect early warning signs, and early detection, and timely treatment of important vital organ diseases. To solve these problems, we need to change the existing passive mode of treatment where patients "visit the hospital after falling ill" to a modern medical model of "early warning, and early active treatment and management." In addition, we need to first understand why patients would rather endure the suffering of "three long, one short" rather than go to a community hospital in order to develop appropriate solutions. The reasons for this include the imbalance in the allocation and distribution of the current healthcare resource and sub-optimal community hospital conditions caused by the "three lows" (low coverage of high-end equipment, low level of scientific and technical mastery, and low patient acceptance), resulting in the advanced medical mode not being put forward, the sinking of the center of gravity, and unresolved contradiction between the advanced medical model and inadequate manpower and obsolete equipment resources.

Therefore, it is critically imperative that community hospitals solve the "three lows" problem. In developed countries, the "three lows" phenomenon does not exist. GPs in these countries account for more than 30–60 % of the total number of physicians. Family doctors have a basic level of education, a master's degree or higher, can practice independently, can work in a number of medical institutions, can combine to use the facilities of medical centers, earn more than most specialists, and have a high social status. However, it is not an easy task to solve these problems in developing countries. The qualifications of Chinese GPs are generally low. They also cannot use the facilities in hospitals and share clinical results. They have low mastery level of high-end technology. As a result, patients would rather go to large hospitals than going to the community hospitals and face the "two difficulties" of enrolling in well-known hospitals and seeing notable doctors. In large hospitals, patients must face the "four problems" of poor prevention skills of specialists, poor health care, poor management, and poor rehabilitation of chronic diseases. Hence, solving the "three lows" is crucial to solving the "two difficulties and four problems."

8.2.3 Development of New Technology Platforms

The solution for the "three lows, two difficulties and four problems" is to enhance regional, national, or even all levels of health care in developing countries. This is

Table 8.1 Comparison between conventional and mIoT function

Function	Conventional medical model		MIoT medical model	
	Community doctor	Specialist physician	Community doctor	Specialist physician
Disease prevention	2+	1+	4+	4+
Health care	3+	1+	4+	4+
Disease management	3+	1+	4+	4+
Rehabilitation therapy	3+	1+	4+	4+
Improve life quality	Difficult	Difficult	Easy	Easy
Prolong patient life	2+	2+	4+	4+
Decrease outpatient visits	3+	1+	4+	4+
Reduce medical cost	2+	2+	4+	4+

also a problem faced by traditional medicine. The emergence of the Medical Internet of Things (MIoT) and remote medicine has made modern medical model even more powerful, bringing new opportunities while addressing these issues, and helping to solve the contradiction between advanced medical models and inadequate manpower and obsolete equipment resources [2, 3].

A mIoT based model is different from previous conventional medical models of revolutionary medical techniques. MIoT rapidly develops innovative medicine to solve many problems that conventional treatment methods cannot solve, improves the diagnosis and treatment of diseases and promotes the continuous improvement of service levels (Table 8.1). On the one hand, modern medicine is stepping up towards early detection and accurate quantitative development. On the other hand, the transformation process may move from a disease-centered to a health-centered medical model that is grassroots-oriented with family and personal perceptions of health status and early disease warning, health, management, and rehabilitation playing a role. When patients fully embrace health as the main focus, the demand for mIoT services by family units within the new community health services model can produce an even more powerful role for the community and specialist services. MIoT provides community physicians and specialists the opportunity to make up for one's deficiency by learning from others' strong points and unimaginable effect of good technology platforms [4–6].

The application of mIoT technology can solve the contradiction between advanced medical model and inadequate human and obsolete equipment resources and ultimately solve the "three lows, four differences, and two difficulties" issue. Solutions to solve the "three lows" are as follows:

(1) The community doctors employ mIoT technology to check the results of high-end equipment to solve the problem of low coverage [7, 8].
(2) Community physicians will have access to education, as well as regular exchange with specialists anytime, anywhere, in order to rapidly improve their

professional level. This solves the problem of "high-end technology and low mastery level."

(3) Working together with the specialists in the management of patients to overcome the problem of "low patient acceptance." Meanwhile, specialist physicians in large hospital can collaborate with community doctors in the management of patients, and sharing expertise in the implementation of the "prevention, care, rehabilitation, and management of chronic disease," which will naturally solve the "four differences" problem. Finally, patients can use "cloud to connect to renowned experts at home and enjoy the effect of good modern medical service," solving the "two difficulties" of enrolling in well-known hospitals and seeing notable doctors [9–12].

8.3 Current Progress

8.3.1 Application of mIoT in the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a hazard to human health, and seriously affects the quality of life of patients. According to the World Health Organization estimates, COPD is secondary to heart disease, cerebrovascular disease, and acute lung infection and is the world's fourth leading cause of death.

A survey of seven regions in China of 20,245 adults found that people over age 40 had a COPD prevalence rate of 8.2 %, meaning that the number of patients with COPD in this age group is over 43 million. For example, in 2008, acute exacerbation of COPD accounted for 1.6 % of all causes of hospitalization. According to data released by the Ministry of Health of China, COPD ranks as the fourth cause of death in the population of urban areas; in rural areas, it is the third largest cause. In China, the cost of treating COPD is high. A single treatment for a COPD patients may be nearly 40 % of the average household income.

As with all chronic diseases, early prevention, timely diagnosis, and effective management play a very important role in the diagnosis and treatment of chronic diseases. With regard to these aspects, there are major challenges faced by patients or doctors. To standardize the diagnosis and treatment of COPD, in 2001 the global initiative for chronic obstructive lung disease (GOLD) issued the first edition of global strategies for the diagnosis, management, and prevention of COPD that will be updated every 1–2 years. After 10 years of unremitting efforts, the rate of diagnosed COPD in a large hospital and standard of treatment rates are rising, but a large number of communities are still being ignored and misdiagnosed and patients fail to be treated in a timely and reasonable manner.

Currently, large hospitals and the community are completely out of touch. While the diagnosis rate by doctors in large hospitals where patients seeking treatment for symptomatic is high, there is a lack of effective follow-up management and those

patients seeking treatment often have serious conditions. With regard to chronic diseases, we hope that early intervention and standardized management, such as managing lifestyle (e.g., smoking cessation education), and regular medical examinations (e.g., lung function) can be implemented. However, community physicians' lack of awareness of COPD risk factors and lung function and patients do not understand disease management and lack awareness of the importance of inhalation therapy and other aspects of risk factors for COPD. Therefore, there is an urgent need to improve the level of health care and community health management. It is difficult for traditional medicine to find satisfactorily solutions to these problems [13–15].

MIoT is different from the conventional medical model of revolutionary medical management tools, and is best suited for prevention, intervention, treatment, and management of health care. MIoT can be used for COPD management. It allows regular follow-up of the conditions of patients to assess the efficacy, timely adjustment of treatment, changing from patient's "passive treatment" to "early warning and early active treatment" mode. It can maximize the efficiency of medical staff and expand the coverage of patients, realizing the goal of achieving modern management of COPD [16, 17].

COPD screening

COPD pathogenesis is the result of genetic and environmental risk factors working together. COPD is progressive and pathophysiological changes in early stages of respiratory disease result in less damage caused by exhalation. Part of the airflow limitation is reversible by the use of bronchodilators, which can improve obvious clinical symptoms and may prevent progression of the disease. For example, for patients who smoke many years, an exhaled airflow limitation is found by pulmonary function tests, although there may be no cough and sputum symptoms at this time. However, mild COPD may exist and if detected early, quitting smoking combined with drug treatment may control the disease in time [18, 19].

However, in real life early COPD symptoms such as smoking habits, cough, and sputum are often taken lightly or overlooked. Coughing up sputum after smoking is often seen as "clearing the throat." Unknowningly, damage caused by respiratory disease becomes more serious, exhaled airflow limitation is not fully reversible, sputum aggravates asthma symptoms and missed the opportunities for early detection and treatment to prevent the disease from worsening. With further development of COPD, airway obstruction aggravates damaged lung tissue elasticity. When it reaches an irreversible stage, no drug may prove useful in treating the disease, resulting in great loss for health and economy [20]. Therefore, we should actively screen people who are susceptible to COPD:

(1) Long-term active smoking or passive smoking population: approximately 90 % of patients with COPD are smokers, but COPD is not directly related to the length and onset age of smoking. According to statistics, the incidence of COPD smokers was 35.5 %, well above the 7.8 % of nonsmokers [21, 22]. It is noteworthy that passive smoking will also lead to COPD.

(2) People who are regularly exposed to air pollution in daily life and work: Harmful gases in the atmosphere such as sulfur dioxide, nitrogen dioxide, and dust entering the respiratory tract can damage the airway epithelium and increases conditions for bacterial infection. In addition, "bio-fuel" combustion such as wood, and tar release can also cause COPD. Thus, people who live and work long term in a contaminated environment need to be extra vigilant of developing COPD.
(3) People who suffer from specific chronic disease: People with chronic bronchitis, emphysema, and α1-antitrypsin deficiency need to regularly have their lung function periodically checked. Regular examination is not only helpful in determining whether the treatment is effective, but also in adjusting the therapy as needed.

Early diagnosis of COPD

Patients with the following symptoms should actively seek an examination for early diagnosis and treatment, if necessary:

(1) Chronic cough: This is often the first symptom. First it is intermittent, severe in the morning and then exacerbates in the morning and at night or all day. A night cough is often not significant. A small number of patients have no symptoms of cough but their lung function shows significant airflow limitation.
(2) Sputum: A sputum cough produces a small amount of mucus mainly in the morning. During infection, sputum volume increases, and it may be purulent. A small number of patients cough without expectoration.
(3) Shortness of breath or difficulty breathing: This is typical of COPD. Appears after an activity during the early stage and gradually gets worse. As it becomes more serious, shortness of breath may occur at rest.
(4) Wheezing: Symptom may occur in some patients, especially those with severe COPD.
(5) Systemic symptoms: Weight loss, loss of appetite, peripheral muscle atrophy and dysfunction, depression, and/or anxiety may occur.

Prevention of COPD exacerbations

Acute exacerbations in COPD (AECOPD) patients occur approximately 0.5–3.5 times each year. AECOPD is an important cause of death in patients with COPD and the main reason for the high medical costs of COPD patients. It has serious negative impact on the patient's quality of life, lung function, disease process, and results in social and economic burden. Therefore, AECOPD prevention, early detection, and treatment are clinically significant and arduous tasks.

Medical Internet of Things

In applying the concept of mIoT to the diagnosis and treatment of COPD, there are certain requirements in terms of equipment and technology so that information can be sent to open ports or directly to the cloud in order to realize the capabilities of

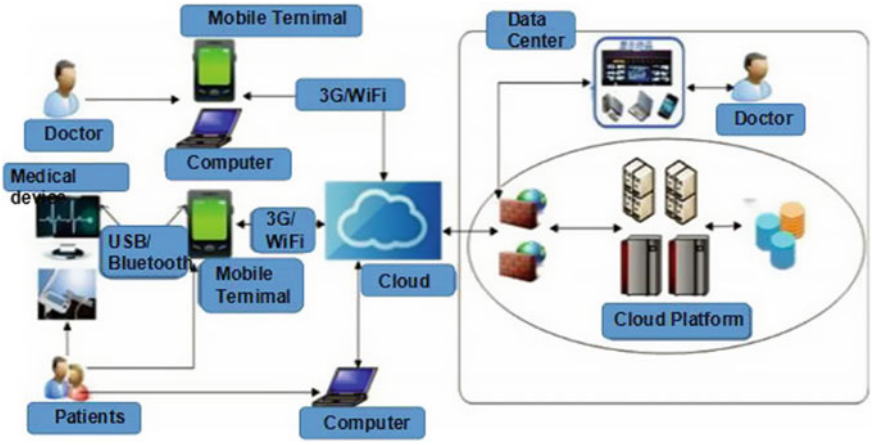

Fig. 8.2 Framework of Medical Internet of Things

massive data mining technology and produce unique effects. The technical architecture is shown in Fig. 8.2.

(1) **Hardware Requirements**

Cloud Devices

Massive information intelligent analysis can be carried out through the "cloud" under the cloud computing framework, not only to retain the "cloud terminal frame, but also to dig deeper in the processing of Big Data." The addition of the mobile function allows medical centers and community physicians to become more sophisticated, dynamic and "wise" with regards to health and early diagnosis and management of disease, improve healthcare resource use, and enhance the level of health care and disease management.

Terminal equipment

Terminals include both wired and wireless transmission of the sensor, as well as mobile IT devices including:

1. Wireless and wired transmission sensors such as spirometry, oximetry sensors, and other medical equipment.
2. Mobile IT devices:
   Can be used to download client software for smart phones, tablet PCs and notebook computers, and television set-top box.

(2) **Software Requirements**

MIoT COPD includes medical management software and medical staff and patient software. The design of the software needs to be taken into consideration for the

various requirements of COPD diagnosis and management, including operational, data security, and privacy protection.

Management software

With regard to the medical center and technical support platform side, the user can authorize access for real-time management clients. Users may at any time trigger an update of their existing management software. Information that has been entered can be easily converted into tabular form for statistical analyses and before-and-after comparisons. Built-in counterparts to the hospital registration green channel, community channels, and 120 emergency doctors have a key speed dial function.

Medical software

Through the establishment of personal accounts, one can view real-time patient information, receive critical early warnings from sensors according to the clinical needs of patients, analyze patient data, and provide medical advice and follow-up. The user interface must be operable; the software is capable to present test results with image data, such as pulmonary function tests that must have a flow volume graph and computed tomography (CT) scans, according to the actual capacity of cloud computing, and provide all or part of a representative image.

Patient Software

A user can create a personal account in real time to allow the sensor to collect information that will be uploaded to the cloud platform. It may support interaction between community physicians and medical center, provide feedback on changes in condition and treatment outcomes, enables health education, and so on. The user interface must be operable, legible, and easy to read for elderly patients. It is recommended to have more multiple choice questions than open questions to collect information and review follow-up information conveniently.

If the information is not updated for a long period, there is a reminder function that prompts patients to use the self-management facility.

(3) **Technicians can check the networking requirements**

For information to be sent to open port or directly to cloud computing equipment or technology, certain requirements need to be met in order to realize massive data mining technology capabilities, including both diagnosis and treatment guidelines and other functionalities. Some examples are as follows:

Pulmonary function room

If the patient end software system comes with a portable spirometer, one can upload the test results to the cloud synchronization server. If the patient end software system portable spirometer plug is not installed, it is recommended to use hospitals' lung function room after examination and upload the images to a cloud server by the relevant medical staff.

CT scan room

After patients completing their chest CT examinations at designated hospitals, results and images are uploaded to a cloud server by relevant medical staff.

Electrocardiogram (ECG)

After patients completing their ECG at designated hospitals, results and images are uploaded to the cloud server by relevant medical staff.

A Typical Case of the Application of mIoT in the Diagnosis of COPD

For example, mobile phone-based cloud terminal mIoT technology for the management of patients with COPD uses the information collection client (remote monitoring portable spirometer) to collect customer lung function physiological parameters. The collected data are uploaded to the cloud computing framework intelligent information analysis systems. Data processing centers analyze the customer survey data to produce the relevant medical information that is then transmitted to the server health. Medical personnel give advice as needed which is feedback to the customer's mobile phone. Not only can this be used in both hospital and family environment for measuring customer pulmonary function, it can also be used for remote regular follow-up according to the condition of patients to assess the efficacy of the treatment plan and make adjustments if necessary.

8.3.2 Application of mIoT in the Diagnosis and Treatment of OSAHS

In recent years, breathing-related sleep disorders have gradually been taken seriously. The incidence rate has gradually increased. The complications risk is huge and brings about a major potential threat to public health. Obstructive sleep apnea hypopnea syndrome (OSAHS) is the most common type of sleep-disordered breathing (SDB). OSAHS is due to repeated complete or incomplete airway obstruction occurring during sleep apnea or hypoventilation [23]. Hypoxemia can lead to the destruction of normal sleep rhythm and is characterized by disease symptoms that can lead to daytime sleepiness and cardiovascular and cerebrovascular complications, metabolic syndrome, or multiple organ damage, seriously affecting the quality of life of patients. According to domestic and international epidemiological surveys, middle-aged men in Western countries have a prevalence rate of 9 % and middle-aged women have a prevalence rate of about 4 %. China's adult prevalence rate is about 3–5 %. The American Academy of Sleep Medicine and Chinese Society of Respiratory Diseases have successively enacted and promulgated adult OSAHS diagnosis and treatment and management guidelines, which emphasize that OSAHS patients should receive early diagnosis, standard treatment, and long-term management [24–28].

However, the current status on the diagnosis and treatment of OSAHS is not satisfactory [29–31]. Compared with Western countries, public awareness of the disease is low. The uneven distribution of medical resources to medical practitioners make OSAHS diagnosis and treatment difficult. In addition to the lack of management experience, the majority of primary healthcare professionals and underdeveloped areas do not have the relevant medical equipment. Medical institutions with the capability in the diagnosis and treatment face huge long-term challenges in terms of patient appointments and outpatient follow-up examination and other problems. In addition, serious illnesses or difficult-to-detect early warnings, such as malignant arrhythmias, and even sudden death accidental may occur. The existing traditional medical model cannot meet the huge demands in the diagnosis and management of OSAHS.

Through real-time collection of information perception layer, network integration transmission, collection and processing of information, and finally combining with sleep apnea monitoring technology, mIoT contributes to early diagnosis, assessment of OSAHS, long-term follow-up, critical value of early warning, emergency treatment, etc. Compared with the traditional medicine medical model, having communication, intelligence, embedded networking features, real-time delivery bring the patient and medical resources closer together in terms of time and space and form an integral part of patients' work and life; thus realizing individual health monitoring, remote management and expert medical assistance, to achieve early detection, early intervention, active management, and change the current medical model concept. At the same time, the integration of "cloud computing," the ultra-large-scale, virtualization, and multiuser computing model, provides many opportunities for more large-scale mIoT. On this basis, the Shanghai Institute of Respiratory Diseases and Zhongshan Hospital, Fudan University, have jointly established the first "cloud terminal mIoT sleep laboratory" and in 2013 released the first "Internet of Things in the diagnosis and treatment of sleep respiratory diseases expert consensus," providing an effective practice, exploration, and summary on the application of mIoT in the management of sleep respiratory disease.

OSAHS screening

MIoT will be used for OSAHS, greatly expanding the scope of disease screening so that screening can be more accurate, direct, convenient, and timely for feedback. It can be widely applied to Internet of Things sleep medicine platform for adults using and operating the client platform, for early detection of risk factors associated with OSAHS, and if necessary, for establishing the detection system based on mIoT test system to carry out medical screening or diagnostic examination, achieving the concept of "treating the disease."

Studies have confirmed that obesity, age, gender, anatomical upper airway abnormalities, family history, long-term alcohol misuse or application of specific drugs, and smoking are the main risk factors for OSAHS. At the same time, OSAHS may also be secondary to hypothyroidism, acromegaly, heart failure, and other diseases. Referring to both local and international guidelines on sleep respiratory diseases, a disease screening questionnaire in the client platform is used to

collect relevant information from different angles of and issues about the client. Its use has now been recognized for collecting and screening sleep-related information. Combined with the characteristics of sleep mIoT, those involved in screening may at anytime, anywhere answer questions. The community physicians can perform a preliminary medical examination and complete the screen, if necessary. The use of a real-time network to upload data to the cloud server and timely access to professional medical guidance are required.

OSAHS early diagnosis

MIoT disease screening can be used preliminary to identify susceptible populations with risk factors or clinical symptoms for OSAHS. The fingertip oxygen saturation or polysomnography system (PSG) on the mIoT platform can be used to carry out fragment or all night diagnostic test. According to the 2011 release of Chinese OSAHS treatment guidelines, a clear diagnosis and assessment of disease severity, comorbidities, and complications can be made. At the same time, the individual data uploaded to the cloud server can be checked and the medicine center or expert can immediately make a complete assessment of the patient's disease, contributing to an early diagnosis of the disease and timely intervention.

OSAHS management

Regarding the diagnosis of patients with OSAHS, mIoT can break the constraints of space and time in the diagnosis and follow-up long-term treatment of disease and effective self-management. It can be used to guide community physicians to develop individualized treatment plan and follow-up plans, including disease, health education, regular behavioral therapy, oral appliance, surgery, or home ventilator treatment; prevent complications and comorbidities; long-term regular follow-up, and regular assessment of efficacy. Patient can carry out assessment of symptoms anytime anywhere. It can provide dynamic monitoring of nocturnal oxygen saturation changes, ventilator parameters, real-time feedback on therapeutic effect, adjustment of treatment. By setting the range of the sensor alarm, patients, community, and medical center can be synchronized to detect critical events, such as arrhythmia so that timely interventions can occur. For troubleshooting, the end user or community center can directly contact, detect, and troubleshoot to resolve problems relating to sensors, medical devices, or instrument software or hardware. In addition, with the massive information storage and extraction function of the Internet of Things, information of patients with OSAHS can be used for data mining analysis, epidemiology, and clinical studies.

mIoT

The application of mIoT in the diagnosis and treatment of OSAHS requires the establishment of a comprehensive end user's medical equipment and devices and cloud computing software support (Fig. 8.3). The formation of the Sleep Medicine Center (expert), community healthcare providers, and patients enables the three stakeholders to be linked in a real-time interaction mode. The patient or the community healthcare provider client platform upload data via sensors and Internet of

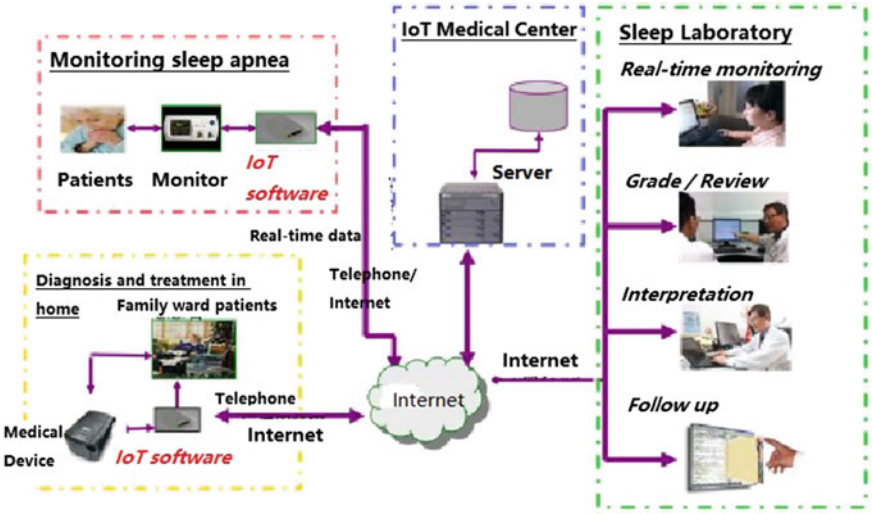

Fig. 8.3 Basic structure of OSAHS mIoT platform

Things in real time to the medical center that then sends report and feedback on the diagnosis and treatment. At the same time, large-scale data storage allows in-depth massive information processing and mining that make the management of OSAHS more sophisticated, dynamic, and intelligent.

(1) Hardware Requirements

1. Cloud devices
   "Cloud" is self-maintenance and self-management of virtual computing resources, usually for a number of large server clusters, including computing servers, storage servers, and broadband resources. In this case, clouds refer to a collection of computers participating in cloud computing, the concept is similar to the client platform. Cloud is the intermediate carrier between software and operating system and can solve previous problems relating to the use of software, software installation, maintenance, efficient use of hardware resources requirements, realizing the potential of a real green software.

   The "cloud" can be used to carry out intelligent big data analysis and extraction of sleep apnea parameters to construct a data model of the subject as well as Internet of Things-based sleep apnea monitoring information exchange and online medical services. The use of the mobile function of the Internet of Things technology for sleep breathing disorders platform not only retains the advantage of "cloud terminal system of cloud computing frame and in-depth processing and extraction of big data" but also the addition of mobile function enables physicians from the sleep center to carry out more sophisticated, dynamic, and "wise" early diagnosis and management of respiratory diseases and improve healthcare resource use.

2. Terminal devices for OSAHS comprise of wired and wireless transmission of sensors, airflow monitoring (including the nose and mouth breathing), ECG, EEG, blood oxygen saturation, abdominal breathing exercise, and other detection signals. The portable wired and wireless transmission of monitoring and treatment signal screening equipment and facilities in the diagnosis and early treatment of sleep apnea include oral appliance therapy and different types of noninvasive home ventilation with input and output signal such as a fixed pressure-type continuous positive airway pressure (CPAP), bi-level positive airway pressure ventilation (BiPAP), automatic type CPAP, BiPAP, or servo breathing machine.
3. A mobile IT device is for downloading the client software such as smart phones, tablets, PCs, notebook computers, television set-top boxes, or removable devices. In view of the differences in configurations and target clients for primary hospitals, the monitoring device configuration can have two sets of high-end and low-end systems. The low-end device can be used for screening and configuring with nose and mouth airflow, chest and abdominal respiratory movement and blood oxygen saturation degree sensor devices. The high-end device is needed to complete PSG additional equipment configurations such as eye movement, electroencephalo-graph (EEG), electromyography (EMG), body position, and other information.

(2) Software requirement includes the sleep mIoT platform management software and medical staff and patients software. In designing the software, there is a need to meet varied requirements including balance screening, diagnosis, treatment, and follow-up management, taking into account the ease of operation, data security, and privacy protection. The software is currently under construction.

Management software is for the medical centers and technical support platform. May be used for real-time management of sensors and client platform; authorize access; data extraction, analysis, and mining; user training; and other troubleshooting.

Healthcare personnel software: Through the establishment of personal accounts, one can view real-time patient flow of information, feedback, and follow-up treatment; set up individualized patient sensor according to clinical need; receive critical warnings from patients; and analyze patient data to assist in clinical or epidemiological studies.

Patient software: After establishing an individual account, the patient can receive real-time data from sensors and upload to the cloud platform; interact with community physicians and medical centers and exchange feedback on condition changes, treatment, and health education.

(3) Networking and project requirements

The networked inspection techniques in Sleep mIoT platforms include screening instruments and PSG monitoring equipment. They can gather a variety of information such as oronasal flow, thoracoabdominal movements,

oxygen saturation, ECG, EEG, eye movements, and electromyography. Patients diagnosed with OSAHS can choose noninvasive ventilation treatment. Ventilator pressure and other parameters can be synchronized through the network to be uploaded to the platform. These technologies and projects require high-quality, accurate physiological signal acquisition and management capabilities, and individual network flow link (achievable by radio frequency identification technology) and easy wear properties, with realistic, credible reflection of changes in patient's physiological conditions.

Examples of application of mIoT in the diagnosis and treatment of OSAHS

With the establishment of cloud terminal mIoT sleep laboratories at Zhongshan Hospital in Fudan Universtity, some patients have joined the platform, enabling community and medical center physicians to use mIoT technology for screening, diagnosis, treatment, and management of OSAHS. We selected some typical cases to illustrate the initial experiences.

Case I

Brief medical history

The patient, Zhou, 52 years old, male. Risk factors: body mass index (BMI) 29.32, smoking history (200–300 cigarettes/year, not quitting), occasional drinking history, history of hypertension for 4 years, Epworth sleepiness scale (ESS) score 12 points, neck circumference 44 cm. Examination showed no abnormal anatomy of the upper respiratory tract.

The above information was collected through mIoT platform. After screening, the patient was identified in the high-risk group and had daytime sleepiness symptoms. The patient was recommended to undergo the PSG diagnostic test overnight in the nearest community hospital. PSG-related sensors, signal receivers, and networks were installed and connected by community physicians in the patient's home to achieve real-time monitoring of PSG data changes in patient by the medical center. Consultation was carried out the following day and a diagnosis feedback report generated and sent to the community hospitals and patients to guide further treatment. As shown in Fig. 8.4, through the client platform, the medical center received real-time monitoring of oxygen saturation of the patient, nose and mouth airflow, chest, and abdominal movement of ECG signal changes and set the heart rate, oxygen saturation alarm range. There would be real-time early warning and intervention if there is an emergency situation. The report generated the next day showed that patients were suffering from severe obstructive sleep apnea (OSA) (Fig. 8.5). The patient was advised to stop smoking, lose weight, undergo noninvasive ventilation (CPAP) therapy, and develop follow-up plan.

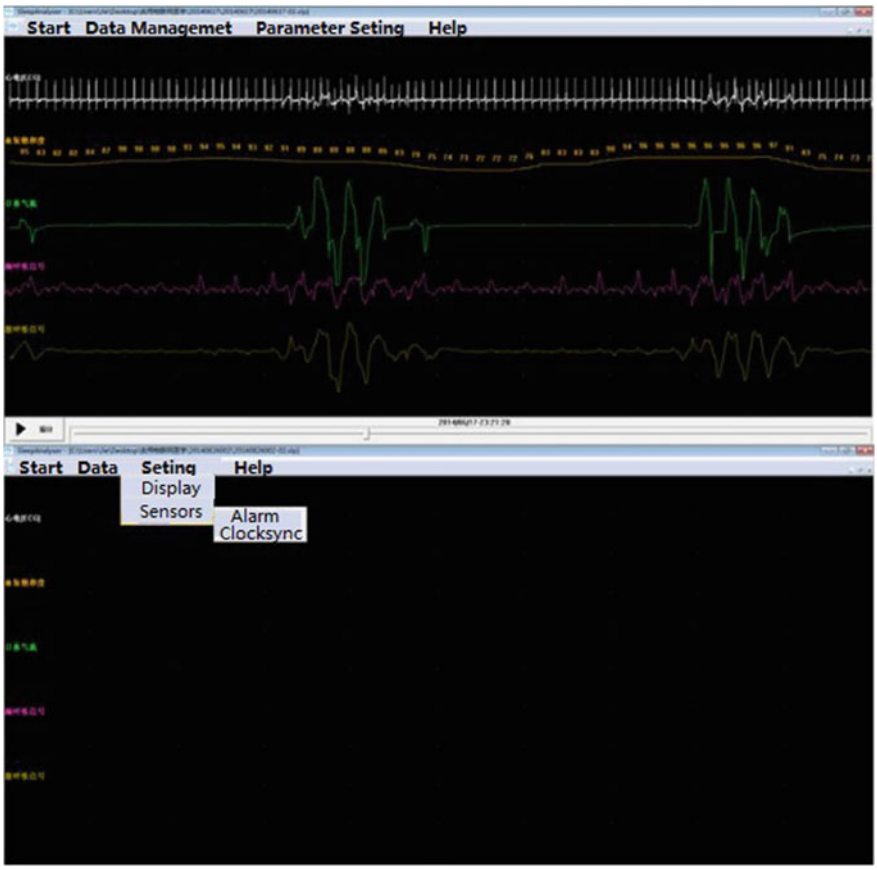

Fig. 8.4 Early diagnosis of OSAHS using mIoT (Real-time monitoring)

Case II

Brief medical history

The patient, Hwang, male, 43 years old. Risk factors: BMI 28.73, smoking history (20 years of support, not quitting), drinking history (300 g white wine/week or 1000 g red wine/week, not quitting), ESS score 10 points, neck circumference 43.5 cm, impaired glucose tolerance. Physical examination did not see any obvious abnormal anatomy of the respiratory tract.

Took advantage of mIoT sleep platform to manage the patient. The patient conducted an overnight PSG monitoring at home and received the main results the following day: Apnea hyponea index (AHI) 71.6, the lowest nocturnal oxygen saturation of 33 %. After consultation with a medical center and analysis of the data, the patient was diagnosed as suffering from severe mixed sleep apnea (Fig. 8.6). It was recommended that the patient quitted drinking alcohol, lost

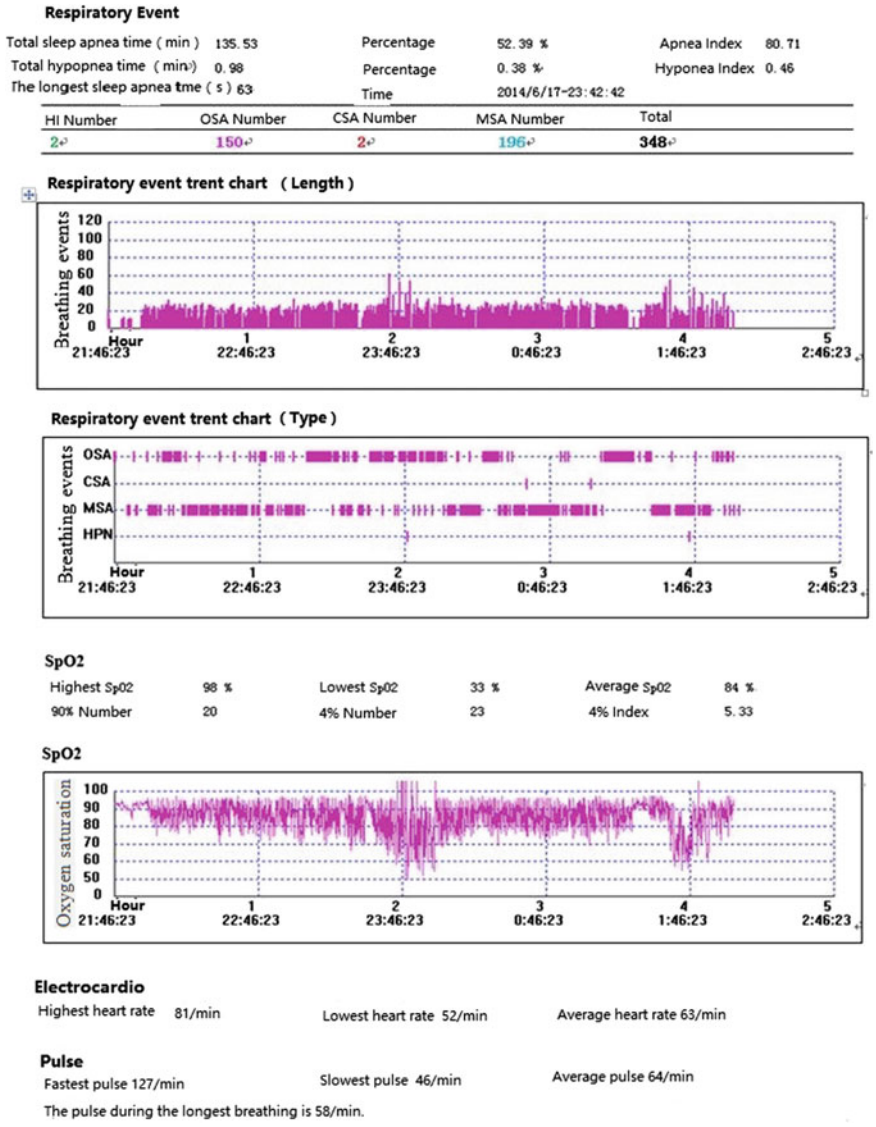

Fig. 8.5 Early diagnosis of OSAHS using mIoT (Feedback)

weight, went a low-fat diet, underwent a noninvasive ventilation treatment, and developed a follow-up plan.

The patient continued on a family noninvasive ventilation treatment and pressure titration. Based on previous missions and client platform, sensors and other devices use the guidance from the community physician to assist the patient to wear and connect to a respirator, fingertip oximetry and other equipment. In the evening at

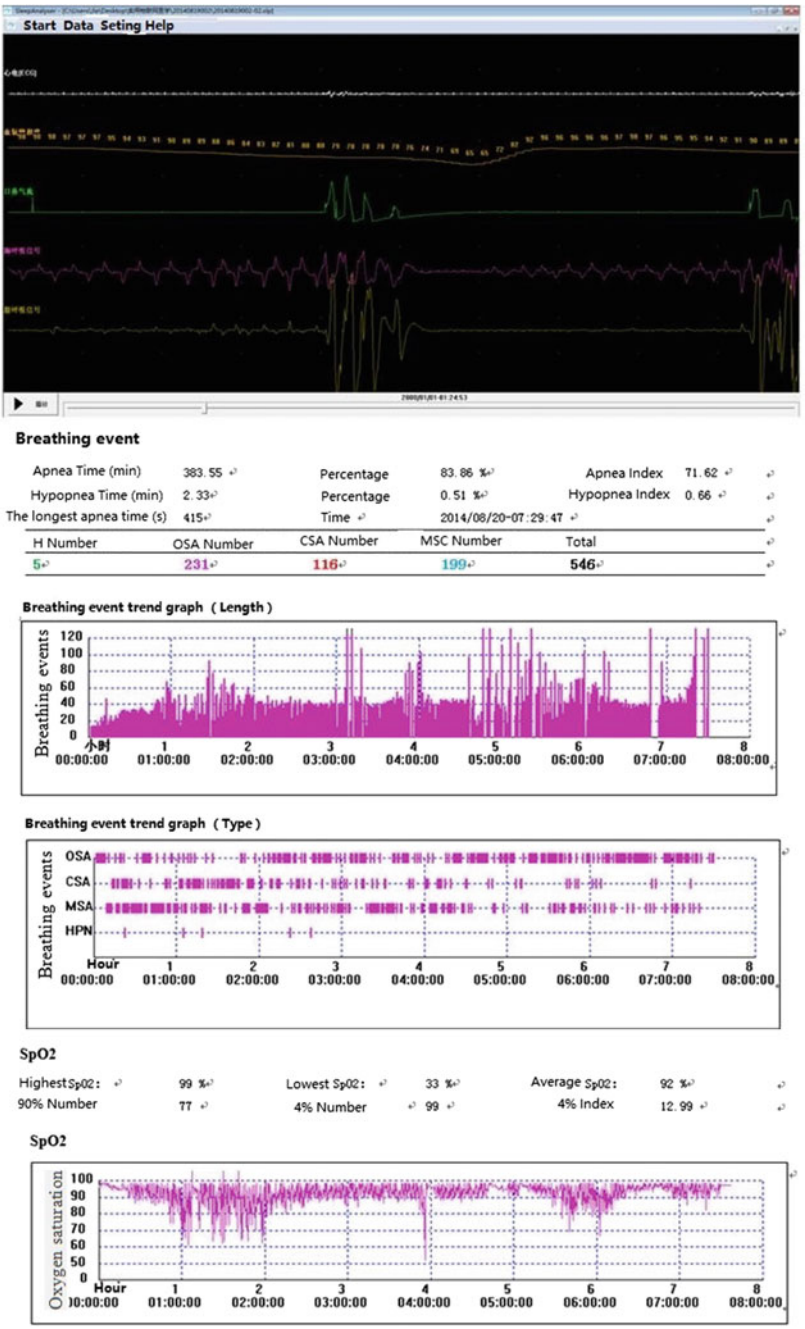

Fig. 8.6 Management of OSAHS using mIoT (real-time monitoring, consultation, and diagnosis)

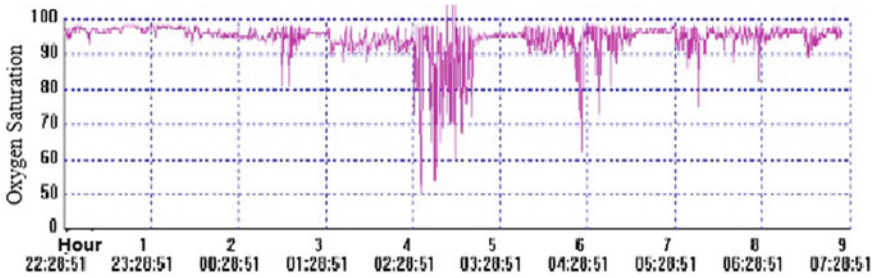

Fig. 8.7 Management of OSAHS using mIoT (treatment monitoring)

around 22.30 pm, the patient used nonsinvasive ventilation therapy, according to the Auto-CPAP mode. At around 2.30 am, the patient self-extracted the ventilator and provided feedback through the platform (discomfort in wearing the nasal mask). Only the oximetry results are shown in Fig. 8.7. The next day, the patient followed up at a community center. The medical center recommended the patient to try other models of nasal mask to increase the ventilator and humidifier functions.

8.3.2.1 Application of mIoT in the Early Detection of Lung Cancer

Pulmonary nodule imaging performance in a single or multiple circular pulmonary opacities, surrounded by whole normal lung tissue, but no lymphadenopathy or atelectasis. Early definition of a nodule was earlier defined as within 6 cm property of the pulmonary nodules, but now that is recognized as within 3 cm to be identified as pulmonary nodules [32–36]. This has great clinical significance regarding the diagnosis and treatment. Chest radiographic examination of a single solitary pulmonary nodule reveals a frequency of about 1–2‰, of which about 90 % was found in the absence of any clinical symptoms during physical examination. The rate of malignant pulmonary nodules is very different in populations in different regions and among different races; the rates are not directly comparable. Before the application of computed tomography, the malignancy rate of calcification or calcified pulmonary nodules was 10–68 %. In 1963 in the United States, findings indicated that malignant pulmonary nodules in half of the 50 years old was 35 %, and the detection rate of infectious granulomatous accounted for 53 %. Subgroup analysis showed that among people over 50 years, the incidence of malignant nodules was 56 and 30 % for granuloma. In subjects younger than 35 years old, only three cases of malignant nodules were detected and in one case for early lung cancer. The probability of benign calcified nodules detected by CT is approximately 56–100 % higher than the detection rate of malignant nodules. In another study in the United States, of the 360 cases, the majority was male smokers about 65 years of age. CT detection of malignant nodules was 79 %, significantly higher than in the early 1980s (60 %), but lower than in the 1990s (100 % detection rate during 1994) [37–40].

The five-year survival rate of lung cancer in China is low, due to the lack of screening, lack of scientific methods for diagnosis, lack of uniform interpretation of standards, and lack of multidisciplinary expert consultations [41–44]. Although it is difficult to solve these problems with the current medical model, mIoT technology can correct these deficiencies and provide the best solution. Since mIoT technology has its unique networking, information mining, and expansion capabilities, it is not only suitable for screening lung nodules and facilitating information collection and storage, but also for collecting and extracting vast amounts of in-depth information, scientific diagnosis of special features while facilitating joint cloud multidisciplinary expert consultation, which will help in diagnosis, differential diagnosis, and follow-up tracking [45–48].

When symptoms of lung nodules are found, the indications are asymptomatic or have medical treatment, in particular solitary pulmonary nodules. Using imaging findings to identify solitary pulmonary nodules has commonly been difficult for clinical diagnosis. The most difficult to determine is whether the nodule is benign or malignant. After the discovery of a solitary pulmonary nodules, the following methods are frequently employed for diagnosis and differential diagnosis: through a series of CT examinations to confirm the nodules; using imaging and/or biopsy diagnosis [49–52]; and surgery [53, 54].

For those nodules that are difficult to characterize, the differential diagnosis further relies on imaging, epidemiology, surgical risk assessment, and the wishes of the individual patient. Early surgical resection of malignant nodules is the best way to cure. On the other hand, mistaking benign for malignant nodules can cause unnecessary surgical resection, increased mortality, and/or increased morbidity due to surgical complications. To address these issues, past experience and regulating the appropriate diagnostic measures are necessary in the differential diagnosis of pulmonary nodules. The system is designed to provide clinicians with diagnosis and differential diagnosis, to avoid mistakenly diagnosing benign as malignant nodules, resulting in unnecessary thoracotomies or missed opportunities for surgery in early lung cancer [55, 56].

MIoT

(1) Hardware Requirements

Cloud devices

By establishing clouds or sub-cloud or renting, cloud computing devices (Fig. 8.8), a hospital can accept information from open ports and perform massive data mining and storage of patient data for diagnostic analysis and follow-up purposes.

The terminal equipment includes CT equipment, mobile IT devices, and wired and wireless transmission sensors. Mobile IT devices that can be used to download the client software include smart phones, tablet PCs, and notebook computers (Fig. 8.9), and can maintain communication with the administrator or healthcare provider.

(2) Software Requirements

The requirements include CT and mIoT platform management software and physician and patient software. In designing the software, attention needs to be paid

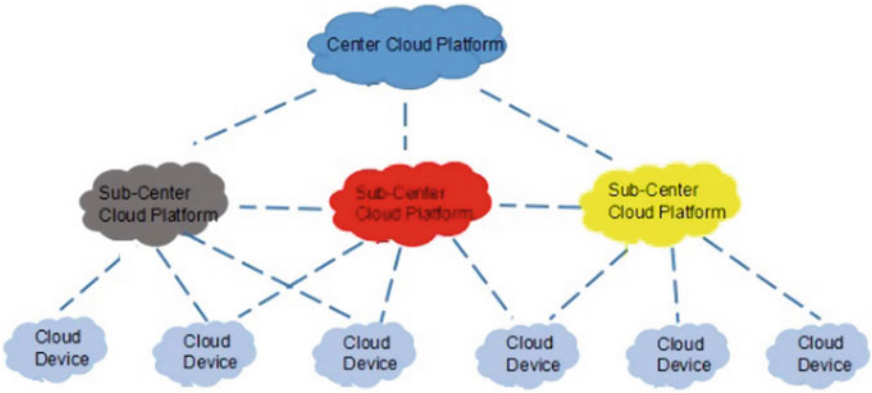

Fig. 8.8 Frame of cloud devices

Fig. 8.9 Schematic drawing of physician and patient terminals of the software interface

to a variety of requirements, including information upload and follow-up management, taking into account the ease of operation, data security, and privacy protection.

Management software: For the medical center or sub-centers, there is a technical support platform. It can also be used for management of CT, real-time management of clients, and authorized access; data extraction, analysis, and mining; user training; and other troubleshooting.

Medical software: After establishing a personal account, the patient can manage real-time information, conduct analysis, feedback, and follow-up. In addition, patient data and clinical information can be analyzed and used for diagnosis and differential diagnosis and proposed treatment.

Patient Software: By creating a personal account, one can enter the relevant information and upload it to the cloud platform to communicate with the administrator and physicians. It can also be used for feedback on condition changes, treatment, and health education.

8.4 "Big Data" in Respiratory Disease

8.4.1 How Patient Information Is Used and Integrated

Big data provide people not just with medical diagnosis and optimal treatment plan, but can be used for mining and filtering data [57, 58]. It can provide the right guidance to change future lifestyles. Deep analytic of big data in health care requires large volume of data to be collected and the collection of big data must be multidimensional [59]. From the trend of digitization of life, the digitization of medical data is the prerequisite [60–62]. Health data that can be quantified will first become an entry point to the collection of big data in health care [63]. The methods of data acquisition are diversified. Under the influence of "mobile Internet," the birth of a new mobile portal is driven by the popularity of wearable devices and smart devices, forming a medical equipment for data collecting that differs from the traditional way. Data can be collected by sensors, wireless communications, multimedia technology and eyewear, watches, bracelets, body weight, clothing and footwear, and wash furniture and other household items. For example, the appearances of shoes that are able to calculate distance and calories, Bluetooth headsets that are capable of detecting oxygen content, and bracelet watches that are capable of measuring heart rate [64, 65].

The diversification of data entry points resulted in big data in health care. The traditional definition of entry point to the collection of big data in health care is often the medical institutions, but in the innovative model "Internet +," the acquisition of big data in health data entry has slowly being centered on people [66, 67]. With regard to physical examination, data that used to be collected in the medical centers can now be carried out by users' at home, such as monitoring of heart rate and testing of blood glucose.

The collection of big data in health care is not merely to record the data related to the medical procedure. The formation of big data requires the following four steps: Through the "Internet of Things + Internet" approach, fragmented data are compiled through a structured method; through the "biological information + cloud computing" approach useful data are transformed into effective information; through the "Internet + social network" approach effective information becomes knowledge repository; and through "AI + Internet" approach knowledge repository is turned into product [68–71].

8.4.2 Precision Medicine Based on mIoT

Present situation of disease treatment

When the patients see a doctor, they hope to receive guidance from the doctor on how to cure the disease to restore or maintain health. However, the treatment or advice given by the doctors is usually based on the average effect obtained from patient population, which is the same for all patients. When an individual is seeking the precise treatment of a disease or to maintain health, existing scientific evidence suggests that this will be affected by the individual's genes, lifestyle habits and environment, individual behavior, and diets that will influence health maintenance and accurate treatment of disease as well as the final effect. Precision Medicine stems from the collection and analysis of big data in disease and health and long-term follow-up tracking. The mIoT platform plays a very important role in the management of chronic disease and long-term follow-up and tracking.

MIoT platform provides technical support for Precision Medicine

The first is the electronic health records system: One can imagine trying to organize and query information on paper health records of 1 million people. This would be a burdensome and disorderly work. Thus, electronic data processing and query greatly improve sorting and retrieval capabilities and incorporate valuable information such as diagnosis, laboratory test results, medications, and enable treatment effectiveness records to be clearly displayed.

Next is laboratory detection technology, in particular, genetic variation detection and identification. Individual whole-genome sequencing is still very expensive, but we already know the fragments that correspond to the disease and have verified the credibility and feasibility of this detection method. For example, if 1 million people volunteered to detect certain individual DNA fragments, the cost of testing is about $50 per person. This is compared with $1000 per person for full genetic testing, which is a significant difference, and the former is affordable.

The final is individual lifestyle and environment. The effect of individual's lifestyle and environmental factors has on health and disease-related information will be collected through a questionnaire. We expect to find correlations between each other. For example, the environmental pollution problems and food safety

issues have become a factor of concern for the population. However, the scientific evidence has not been convincing for disease-specific or health condition changes. This is a core issue of attention for Precision Medicine.

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Chapter 9
Mobile Edge Computing

Swaroop Nunna and Karthikeyan Ganesan

9.1 Introduction

Environment of everything connected everywhere being created by the prompt rise in Internet-of-Things (IoT) has been rapidly permeating from the consumer electronics sector to mission-critical domains such as healthcare. It is currently being estimated that there will be 11.6 billion mobile-connected devices by the end of 2020 [1]. Enabling such a ubiquitous IoT in a wireless environment would definitely imply pushing the ultimate boundaries of our existing IT and communications infrastructure. This situation becomes furthermore complex if we consider the fact that these devices are diverse ranging from simple pedometers to complex surgical robots necessitating the adaption of novel system architectures.

The health sector similar to many others is not impervious to this evolution of the connected world. However due to its immediate impact on human life, the sector in fact poses additional unique technical challenges. Unlike other domains, healthcare often involves employment of several mission-critical services requiring strong Quality of Service (QoS) guarantees. Healthcare data is required to be treated as highly sensitive personal information in terms of its privacy and security. And, context awareness plays a crucial role when it comes to service as well as infrastructure provisioning within the e-Health environment. In other words, health sector is in dire need of a context-aware scalable system architecture capable of supporting mission-critical and ubiquitous IoT.

Mobile Edge Computing (MEC) is a recently proposed network-aware system architecture capable of addressing these ever diverging technical needs of the health

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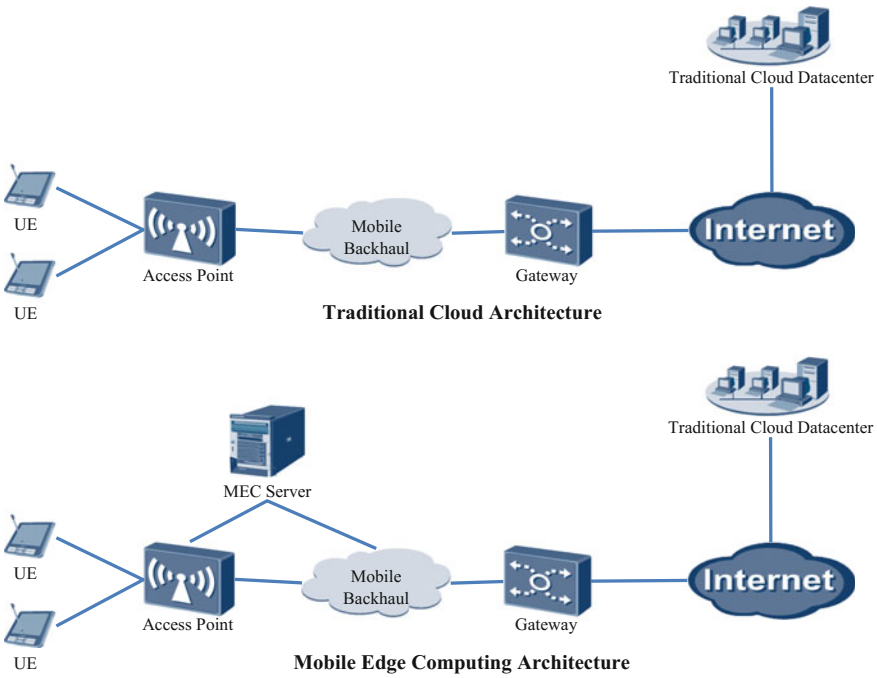

Fig. 9.1 MEC versus traditional cloud architecture

sector. In MEC, a cloud based platform is made available at the network edge capable of dynamic service provisioning. The platform is also closely coupled with the edge elements of the network thereby providing a trustworthy and geographically localized application environment that is aware of the true network conditions of different User Equipment (UE) in its proximity. This is in stark contrast to the traditional cloud environments wherein the platforms are connected to the core network. Figure 9.1 shows a comparison between MEC and traditional cloud architectures.

Paradigm of MEC though in principle is independent of the network access technology; one can expect MEC to be fully integrated into the network architectures within 5G deployments. Additionally, one can observe that MEC is one of the few systems where the system architecture has been proposed by providing a joint consideration to the networks and service platforms. Up until now communication networks were primarily designed for catering to the Human-Type-Communications (HTC) such as browsing, audio/video streaming, social networking, etc., as evident from the evolution of the cellular networks. The development of network technologies on the other hand was also traditionally delineated from the evolution of the service platforms employing them. In light of massive Machine-Type-Communications (MTC) and the evolving IoT ecosystem, this approach might no longer meet the system requirements especially within e-Health. They could however be perfectly

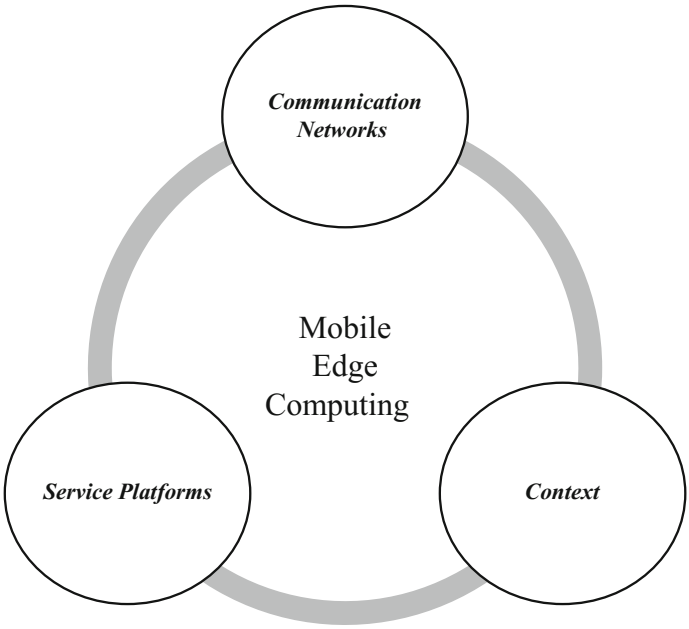

Fig. 9.2 MEC Encompassed by communication networks, service platforms and context

fulfilled by MEC since MEC design sits perfectly encompassed by networks, service platforms and context as shown in Fig. 9.2.

Service subsystems can be built using MEC both at infrastructure and application level in order to effectively address some of the major challenges faced by current day health sector. In this chapter, we will first take a brief look at existing literature on MEC in Sect. 9.2. We will then present the architectures under consideration for the realization of MEC along with its features and challenges in Sect. 9.3. In Sect. 9.4, we make an attempt to show how MEC could be employed to implement some of the infrastructure and application subsystems under discussion for health sector and finally conclude in Sect. 9.5.

9.2 Related Work

MEC until recently has very much been a theoretical concept with no full-fledged MEC servers deployed in commercial cellular networks. This situation however is fast changing and a first real-world MEC platform was introduced in 2014 jointly by Intel and Nokia Networks [2]. The platform is termed as Radio Applications Cloud Server (RACS) and is currently being marketed as liquid applications platform.

One of the pioneering ideas in MEC has been proposed by Bonomi et al. in the name of fog computing which aimed to extend the cloud computing paradigm to the edge of the network [3]. The primary motivation behind fog computing was to address the challenges from the evolving mission-critical IoT ecosystem and to enable a new breed of services complimentary to the existing cloud systems.

Augmenting mobile environment by introducing cloud architecture at the edge has very much been under the radar of the research community during the last decade. In this context, the idea of Virtual Machine (VM) based cloudlets proposed by Satyanarayanan et al. in [4] can be recognized as one of the early precursors to the present day MEC paradigm. The cloudlets are resource-rich VMs capable of compensating for the resource-poor hardware of the mobile devices. They are designed to be in physical proximity to the mobile terminals and were accessed via thin clients.

In contrast to the idea of cloudlets, Habak et al. in [5] proposed a femto-cloud system that pools in the computing resources of different colocated and underutilized mobile terminals into a dynamic self-configuring cloud computing system. Though the femto-clouds lie at the edge, one can clearly see that this is a different approach to the current idea of MEC in terms of creating an edge cloud. In a similar fashion, Abdelwahab et al. proposed REPLISOM [6], an architecture for MEC wherein they introduced cloud resources at the eNodeB in order to improve the responsiveness of the cloud services for IoT. Specifically, they provide an edge cloud based memory replication system that pulls the memory replicas of the IoT devices. This significantly reduces the delay involved for memory replication and at the same time, improves the eNodeB resource allocation.

Computational offloading from mobile devices happens to be one of the key application areas of MEC. Chen et al. present an efficient methodology in [7] for computational offloading under multi-user scenarios using game theoretic approaches whereas Gao in [8] presents an opportunistic approach for offloading computationally intensive tasks to nearby mobile nodes.

With MEC one can however also bring in improvements to the traditional telecom services such as video calling as demonstrated by Beck et al. with Mobile Edge Computing enabled Voice over LTE (ME-VoLTE) [9]. In ME-VoLTE, the process of video encoding and decoding is offloaded to the MEC server. In a similar fashion, web browsing, the classic usage of the Internet can also be accelerated by MEC as demonstrated by Takahashi et al. in their Edge Accelerated Web Browsing (EAB) prototype [10].

The idea of MEC though provides an efficient platform would require novel frameworks as well as programming models to assist the traditional mindsets of application developers with building their applications for effectively exploiting the elasticity and scalability of the edge cloud platform. Mobile Fog [11] by Hong et al. can be considered as the first high-level programming model in this direction that aims to enable geospatially distributed, large-scale and latency-sensitive future internet applications. In terms of concrete approaches, Orsini et al. provide a ready-to-use solution known as CloudAware [12] which facilitates a holistic approach between computational offloading and context adaption, the two key

elements of MEC. CloudAware offers a flexible architecture complemented with programming abstractions, transparent multi-level distribution and context adaption all without any modifications to the underlying operating systems provisioning the MEC.

9.3 MEC Realization

Initial ideas in the direction of edge computing existed from as early as 2004 within the domain of accelerating enterprise web applications [13]. However with the initiation of Industry Specifications Group (ISG) on MEC by European Telecommunications Standards Institute (ETSI), edge computing suddenly found itself immense traction within the mobile environment. As a consequence, the term MEC though generic is currently being understood to represent edge computing in cellular networks. In this Section, we will first briefly delve into the architectures and deployment scenarios being proposed for consideration by the ETSI ISG on MEC followed by a short overview of its features and challenges.

9.3.1 Architecture

ETSI ISG on MEC envisions MEC platform to be a cloud like environment existing at one of the 3GPP Radio Access Network (RAN) elements [14]. The envisioned environment is shown in Fig. 9.3. Similar to a traditional cloud system, MEC is a software–hardware platform with a virtualized hosting infrastructure. On this infrastructure, the MEC applications can be dynamically deployed to run either within individual VMs or software containers. However, in contrast to the traditional cloud, all MEC applications would have immediate access via the virtualization manager to the wide range of network as well as context services exposed by the RAN element.[1]

With respect to the physical deployment of MEC, ETSI ISG provisions for three widely plausible scenarios in line with the existing 3G and 4G technology architectures. Considering the generic nature of these deployment scenarios, they could very well also fit with any of the future cellular architectures of 5G.

In Scenario 1, an MEC platform is expected to be colocated with each and every LTE macro base station in the network as shown in Fig. 9.4. The communication range of a macro base station is typically in the order of tens of kilometres and the colocated MEC server is expected to serve the entire geographic region covered by

[1]The implementations of individual interfaces between different entities of the MEC platform are provider specific and are beyond the scope of the current discussion. For more details, readers are recommended to refer to http://www.etsi.org/technologies-clusters/technologies/mobile-edge-computing and https://portal.etsi.org/tb.aspx?tbid=826&SubTB=826.

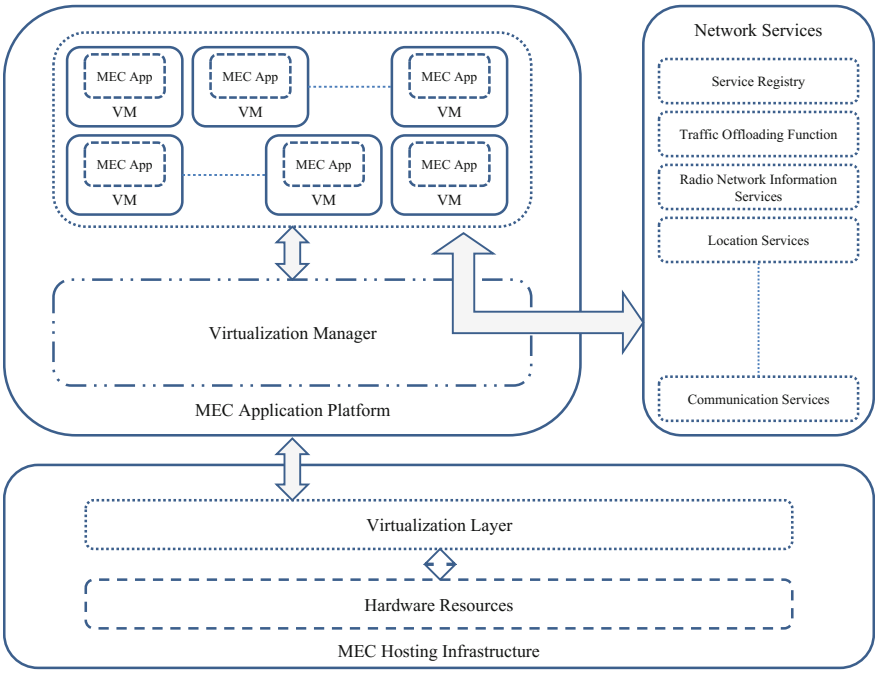

Fig. 9.3 MEC platform architecture

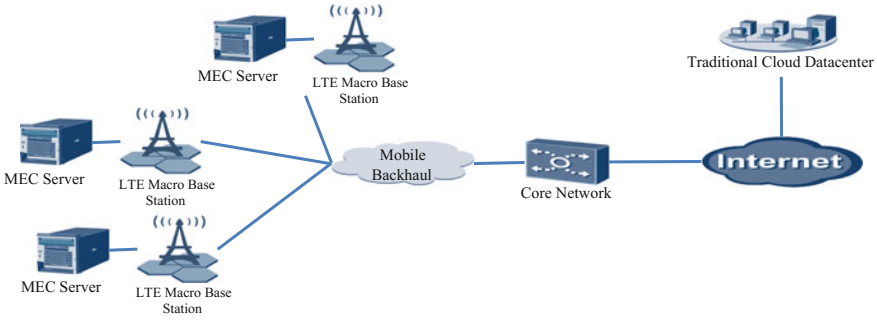

Fig. 9.4 Scenario 1: MEC at LTE macro base station

the corresponding macro base station. This scenario in particular encompasses the present day 4G network deployments.

Scenario 2 mainly focuses on catering to the existing heterogeneous environment of wireless networks. Specifically, it attempts to address the question of MEC deployment in a multi-technology cellular environment consisting of 3G and LTE wireless networks. The MEC server in this scenario is expected to be located at each of the multi-technology cell aggregation sites as shown in Fig. 9.5. The

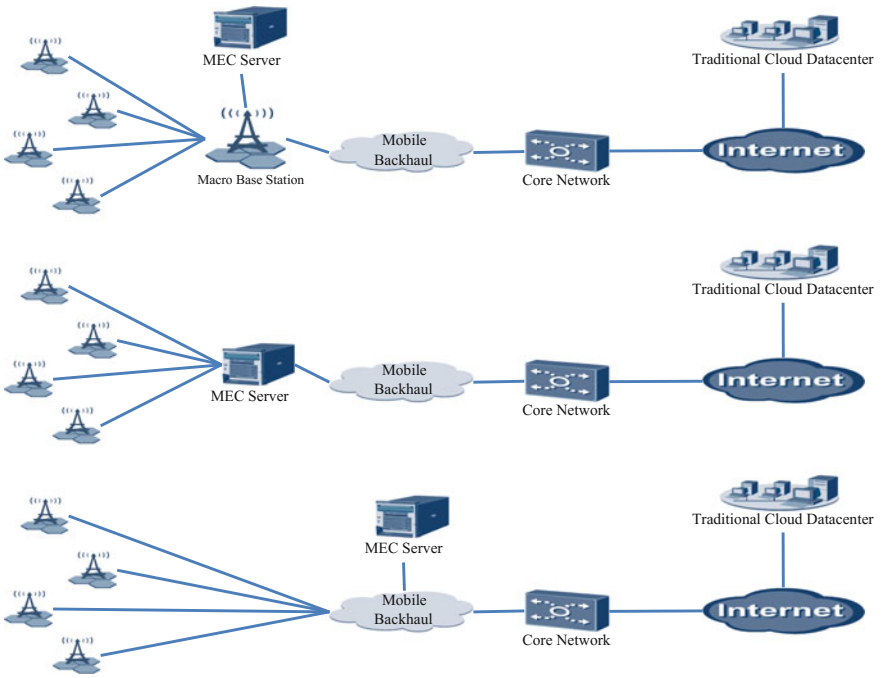

Fig. 9.5 Scenario 2: MEC at multi-technology cell aggregation sites

aggregation site could potentially be either (i) a master base station or, (ii) the MEC server itself together with routing functionality between access points and mobile backhaul or, (iii) a network element in the backhaul. Furthermore, the multi-technology cell aggregation site could either be located indoor within an enterprise such as hospitals, corporate campuses, etc., or indoor/outdoor in cases of special public coverage needs such as stadiums, shopping centres, etc.

Scenario 3 in contrast to the above two scenarios fully caters to deploying MEC within legacy 3G network architectures. In legacy 3G networks, the radio functions of different base stations such as radio resource management and mobility management are performed by the Radio Network Controller (RNC) network element unlike LTE where each base station manages its own radio functions. Appropriately, as depicted in Fig. 9.6, the MEC server is suggested to be located at RNC within such legacy cellular networks.

9.3.2 Features

Unique architecture of MEC in terms of it being a localized cloud with immediate access to contextual information can be characterized by the following key features:

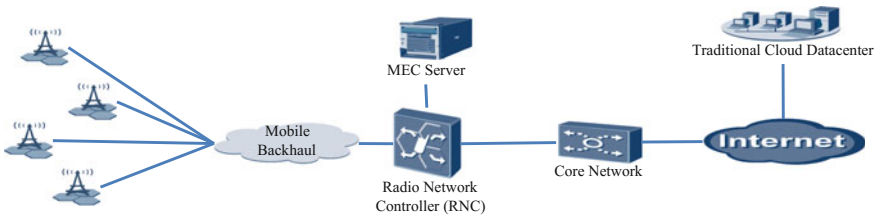

Fig. 9.6 Scenario 3: MEC at radio network controller

(a) **Platform Localization**: MEC servers can be physically established on-premises for specialized environments such as that of hospitals. The applications running on these MEC servers can be maintained isolated from the core network while at the same time retaining access to the local network resources. This inherently provides physical bounds for data as well as applications which is essential for safety critical scenarios in terms of accessibility, confidentiality, and security.

(b) **Physical Proximity**: Compared to existing application environments which are often located in data centres connected to the core network, MEC servers are in close proximity to the end devices. This enables more devices to be connected to the platform via Device-to-Device (D2D) and adhoc communications thereby making application outreach under device densification in a wireless environment plausible.

(c) **Low Latency**: Communications in MEC will be of extremely low latency since they do not traverse through the core network and are mostly limited to the access part of the edge network. On one hand, this could potentially reduce the congestion in the core network whereas on the other hand, this fits well with the low-latency mission-critical requirements of Machine-to-Machine (M2M) communications. Additionally, a short latency for communication could potentially also reduce the power consumption of a device which happens to be a critical factor in IoT environment.

(d) **Location Awareness**: Edge network elements typically maintain awareness of the approximate location, as well as mobility patterns of the individual connected devices in order to provide communication services to them in an efficient way. MEC applications are capable of accessing this information from the edge elements. This combined with fact that a MEC platform is geographically localized, it is would be possible to design geographically relevant services such as notifying the nearest emergency response teams with the exact location of the vehicle in case of an accident, etc.

(e) **Network Context Awareness**: MEC applications can have real-time access from the edge network elements to the network context such as radio context, network congestion status, etc., of different devices. This information could be exploited at the application level to optimize the communications in place as well as the content delivery strategies thereby bringing vast improvements to Quality of Service (QoS) and Quality of Experience (QoE).

9.3.3 Challenges

The idea of MEC as a viable technical architecture is still in its infancy. A plethora of challenges had to be overcome in order to evolve MEC as a robust technology platform and currently, a significant amount of attention is being paid by both academia and industry alike to make it happen. Here we outline some of the key challenges that must be overcome in order for MEC to succeed:

(a) **Interfaces and Protocols**: The domain of wireless communications is mostly governed by well-defined standardization bodies such as IEEE, 3GPP, ETSI, etc. In contrast, the cloud domain mainly evolves through contributions of open-source communities. Additionally, the markets in each of these domains are served by widely fragmented vendors. Since MEC brings together these two complex worlds, a key success factor for MEC would be to design well-defined interoperable interfaces and protocols that could easily be adapted into the existing technical products by different vendors.

(b) **Functional Split**: With applications being deployed at the network edge in MEC, it is clearly evident that certain application and network level functions that are typically performed in the core must now either be moved or replicated at the edge. Some of these functions include authentication of devices, QoS monitoring, etc. Efficient solutions must be designed to establish application and network level functional split between the edge and core networks while maintaining backward compatibility with existing systems.

(c) **Network Heterogeneity**: Different wireless networks such as 3G, LTE, WiMax, etc., differ widely in terms of offered latency guarantees, bandwidth and other network services. Some of the services may not even exist in certain wireless networks. As a consequence, the MEC platforms implemented on top of these networks would be heterogeneous in terms of their capabilities. This in turn makes generic implementation of MEC applications a challenging task.

(d) **Privacy and Security**: In contrast to traditional applications, the applications on MEC platform has real-time access to fine-grained network, context and location information of each of the individual devices. On the one hand, this opens up possibility for enabling a novel set of comprehensive services. On the other hand, this level of exposure to data creates multiple plausible vulnerabilities that did not exist previously. To comprehensively address this issue, targeted security architecture must be designed for MEC. And, privacy by design principles must be adhered to in the evolution of the platform.

9.4 MEC for e-Health

The health sector unlike other industry verticals is a strictly regulated and complex domain with multiple human and non-human actors at play. Especially in hospitals a wide range of devices with diverse technical capabilities are deployed in an

extremely dense environment. Furthermore, the services in such an environment are often mission-critical requiring low-latency communication and strict guarantee for QoS while simultaneously adhere to physical and technical restrictions on accessibility of sensitive data. MEC with its characteristic features described in Sect. 9.3.2 addresses these technical requirements and beyond. Specifically, the platform aspect of MEC is capable of tackling some of the unique challenges faced by e-Health domain. In this subsection, we will describe how MEC is able to provide for some of the challenging scenarios in e-Health.

9.4.1 Real-Time Context-Aware Collaboration Platforms

Absence of successful context-aware collaboration between service subsystems of different industry verticals has been a major drawback of the platforms of the present day. In [15], we theoretically argued that MEC could potentially fulfil this gap due to its features. Being at the network edge, MEC becomes an ideal candidate for hosting collaborative applications. In other words, MEC in principle can be envisioned to be a collaborative middleware into which service subsystems of different service providers could be integrated into. Furthermore, such a collaborative system would even make extreme mission-critical scenarios feasible in case the communication networks involved are of 5G characteristics.

Health services when exposed to a robust collaboration platform can easily exploit the knowledge from other service domains to provide better planned and faster treatments. As an example, consider the context-aware collaboration platform shown in Fig. 9.7. The platform consists of an automotive services subsystem and e-Health services subsystem. These subsystems can access information from the automotive service providers and e-Health service providers, respectively, and vice versa via secure links. This information can then be utilized in implementing real-time context-aware collaborative applications.

Using the example collaboration platform described above, it is feasible to build a collaborative service which can improve the response times of emergency dispatch services during accidents. The arrival of ambulance services during an accident might be delayed due to traffic congestion. However, with the above system, it is possible to build an application that coordinates with the traffic management system in real-time thereby clearing up the way for emergency services. In a similar fashion, consider the case of robotic surgeries where multiple surgeons have to often collaborate in real time during the surgery. The e-Health services subsystem in the above could be an excellent choice to host the mission-critical collaborative surgical applications. Additionally, the services subsystem might even be able to pull in health of the data patient in question from different health service providers such as laboratories and perform real-time analytics thereby assisting the surgical decision process.

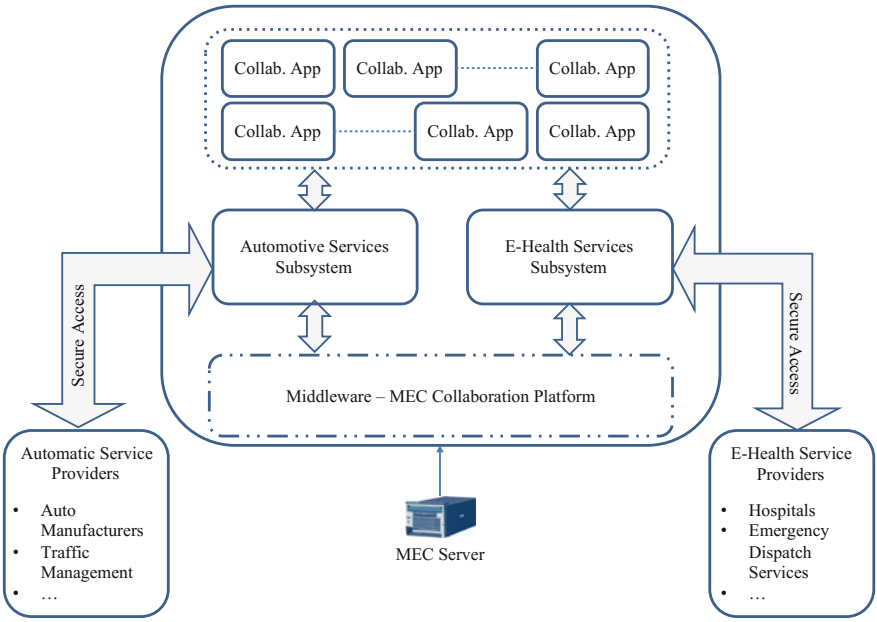

Fig. 9.7 MEC as real-time context-aware collaboration platform

9.4.2 Hybrid Network Architectures

Physical premises in health sector such as hospitals are often simultaneously covered by a multitude of wireless network technologies, these technologies include but are not limited to NFC, Bluetooth, WiFi, ZigBee, 3G, LTE, etc. With the introduction of new wireless systems such as 5G, this list would definitely increase many fold in the future. In this context, one can easily come up with a swarm of factors that lead to this scenario. First, health domain employs a wide variety of devices with diverse technical capabilities ranging from battery powered sensors to complex surgical robots. This in turn leads to different devices capable of supporting different radio technologies. Second, due to slow development and time-to-market timelines arising from regulatory compliance efforts, the upgrade cycle of devices in health domain is relatively slow when compared to other domains. This eventually results in having to support many legacy devices incorporated with previous generations of wireless technologies. Third, there could simply be physical restrictions on usage of certain wireless technologies to only certain areas of the hospital due to interference concerns. For example, WiFi could be allowed in the out-patient areas and it might be not be allowed in the operation theatres.

This complex terrain of wireless networks makes a unified inter-device communication arising from different radio technologies extremely challenging.

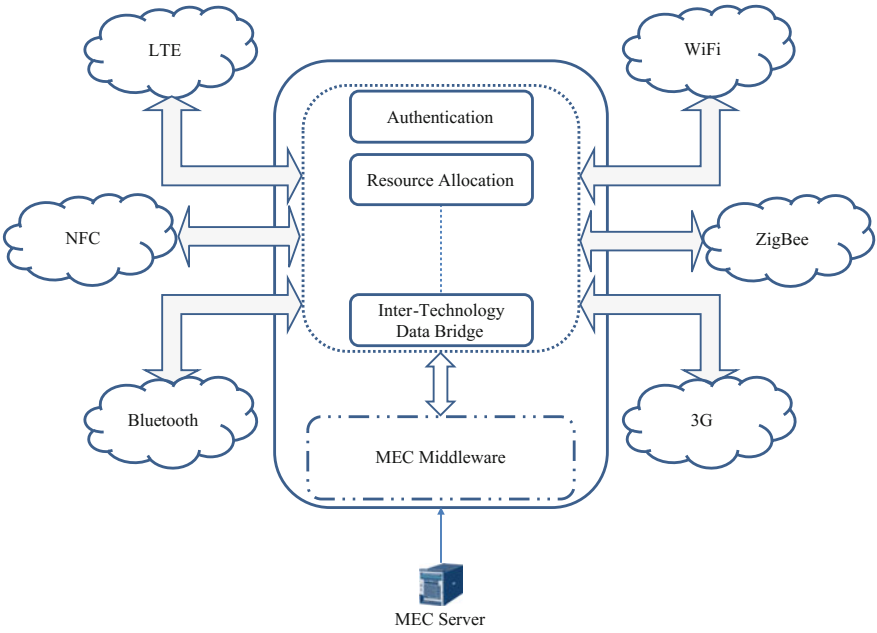

Fig. 9.8 Hybrid network architecture using MEC

Furthermore, it also turns the task of resource allocation and prioritization during contention to be a complex one. This gap could, however, be bridged by MEC. A heterogeneous network management system in principle could be designed over MEC wherein the MEC platform is simultaneously connected to different radio access technologies. In other words, using MEC one can realize a hybrid network architecture that bridges communications from different wireless technologies.

Figure 9.8 presents an example of hybrid network architecture designed over MEC. In this example, network functionalities that commonly exist in every radio access technology such as authentication and resource allocation are isolated and implemented as part of the MEC platform. Different access networks connect are then linked to this platform and share these functionalities. Furthermore, the platform also acts as an inter-technology data bridge which facilitates hassle free data exchange between the networks. This bridge could be implemented either at Layer 2 or Layer 3 of the OSI network model.

9.4.3 Data Controller Framework

Sensitivity of data in terms of data security and privacy is undoubtedly high with respect to health data. It therefore happens to be one of the highly regulated entities.

In order to maintain strict compliance, health service providers often maintain in-house datacenters for storing and processing health data. Furthermore, in practice, there may even exist individual data silos corresponding to different subsystems. For example, in a hospital, the out-patient data might be strictly isolated from the data of its diagnostic center.

Because of such fragmented data storage scenarios, it becomes a major challenge when it comes to sharing health data by health service providers with internal and external entities. This situation becomes further complicated when it comes to regulatory compliance. For example, in Germany, the law requires that each and every use of health data must be explicitly authorized by the involved parties. Additionally, it may even require complete anonymisation of data in certain cases. Organizing such fine-grained data controls would be manually tedious and a well-designed data controller framework with MEC could very well address these issues. Since MEC could be deployed on-premises at the edge, it will suit well for this purpose.

To provide a better understanding, we present an example of data controller framework through MEC in Fig. 9.9. The MEC platform in this example is expected to be deployed on-premises and has access to various internal data silos. Both external as well as internal entities can request data from the silos via the data

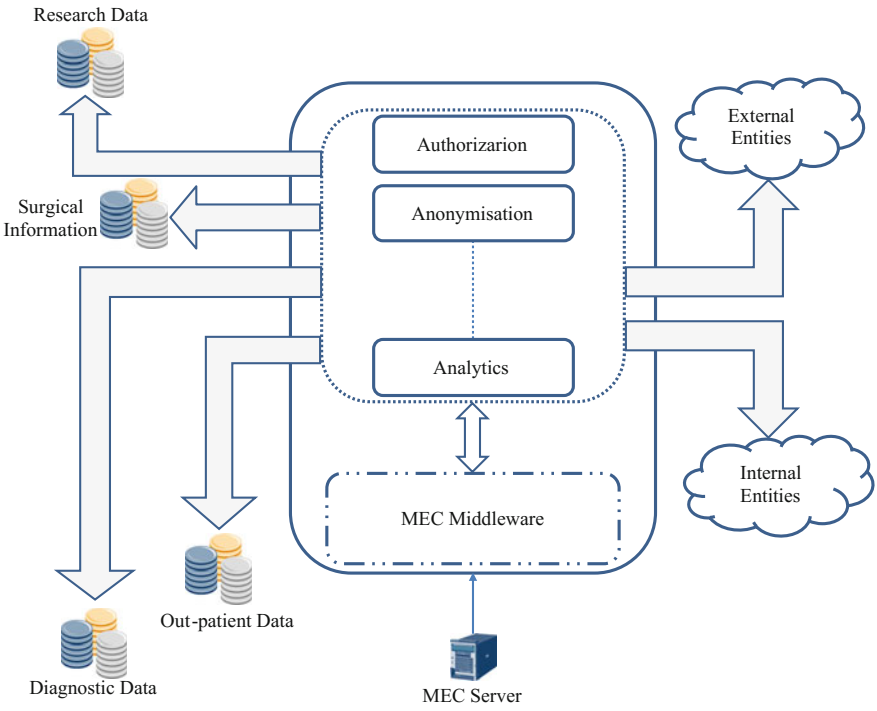

Fig. 9.9 Data controller framework through MEC

controller framework and the framework would then act as an intelligent firewall. The primary responsibility of the controller framework would be to authorize data access. It would even perform an explicit authorization and data anonymisation in cases its needed. As an extended functionality, the framework is also capable of performing pre-defined analytics on the data in order to handle the cases where raw data access is not allowed.

9.4.4 Software-to-Data

Fundamental requirements of confidentiality, accessibility, security, governance and QoS for private health data often tend not to be met by data processing in public clouds. As a consequence, a reverse cloud approach for healthcare sector has recently been under discussion which envisions bringing software from the cloud to data in contrast to the traditional approach of bringing data into the cloud for processing. The FI-STAR project under the European 7th framework (FP7) has successfully devised a practical architecture for this novel approach [16]. In this architecture, dynamically upon need, software termed as Generic Enablers (GE) are downloaded on to a private edge cloud that has access to local data repositories. The processing is then performed in the edge cloud to provide eventual results.

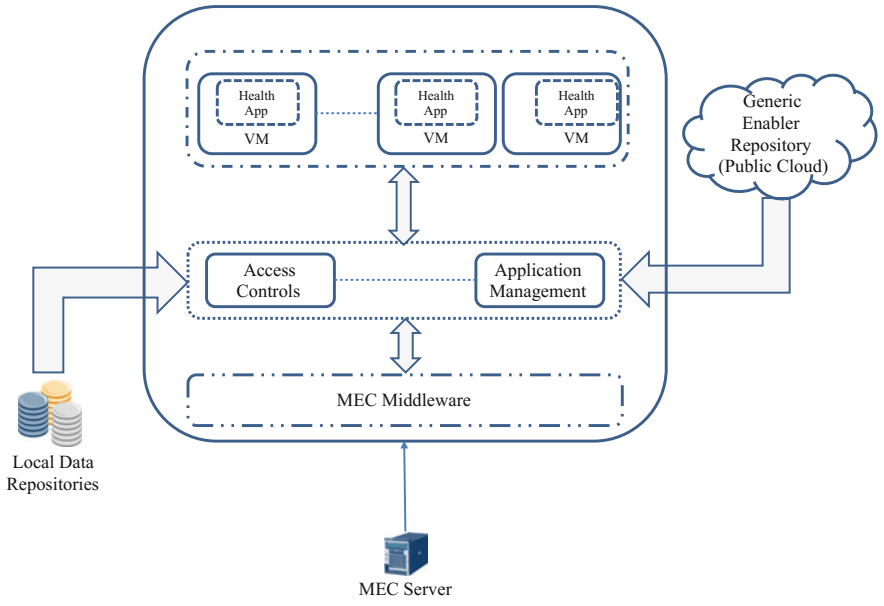

Fig. 9.10 Software-to-data with MEC

A major challenge with realizing the software-to-data approach has so far been the availability of a comprehensive edge cloud infrastructure. However, with MEC this might no longer remain a question. MEC is an easily deployable edge cloud solution by its design. It could very well fulfil the role of edge cloud envisioned in the software-to-data architecture provided that the MEC platform has access to the repository of generic enablers on one side and local data storage on the other.

A concrete example of software-to-data approach with MEC is shown in Fig. 9.10. In this example, as expected from software-to-data edge cloud, the MEC platform has access to the local data repository as well as to the GE repository in the public cloud. It also consists of typical cloud platform features such as access controls. Upon need, the application management platform on the MEC pulls in a GE from the public cloud and data from the local repository, deploys a dynamically created health application, performs necessary processing using the created application and delivers the results.

9.5 Conclusion

Rapid evolution of IoT with the environment of everything connected everywhere is revolutionizing the healthcare sector and thereby requiring adaption of novel platforms and application architectures. MEC happens to be a strong contender in this context which can effectively meet many of the unique needs of health domain such as QoS guarantee, compliance, data security, etc. In this chapter, we provided an extensive overview of the evolution of MEC together with a qualitative outlook on its characteristic features and challenges. We also attempted to show with extensive examples how comprehensive platforms could be built using MEC for addressing some of complex scenarios in health domain. The examples provided by us include building a real-time context-aware collaboration platform, a hybrid network architecture, a data controller framework and a software-to-data architecture realization, all employing MEC. However, as of now, the ideas of MEC are mostly limited to research prototypes even though initial MEC based products having minimal functionality such as accelerating content delivery were released into the market during the last couple of years. The technical development and standardization of MEC has still a long way to go and the platform is quickly evolving with strong coordinated efforts between academia and industry. In the near future, one can definitely expect to witness deployments of MEC containing a multitude of functionalities especially within e-Health.

Acknowledgments We would like to extend our sincere thanks to our colleagues Dr. Holger Rosier and Mr. Joseph Eichinger whose constant support and guidance made this chapter possible. We would also like to express our gratitude to Mr. Markus Dillinger for providing us this opportunity.

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Chapter 10
A Health 4.0 Based Approach Towards the Management of Multiple Sclerosis

Nikolaos Grigoriadis, Christos Bakirtzis, Christos Politis, Kostas Danas, Christoph Thuemmler and Ai Keow Lim

10.1 Introduction

The use of hyperconnected devices through cyber-physical systems in the management of diseases has already been demonstrated for asthma and diabetes. However, to demonstrate that Health 4.0 is a truly universal concept in the health domain we will discuss the application of Industry 4.0 design principles in health care (Health 4.0) for a very complex condition, namely Multiple Sclerosis. Multiple sclerosis (MS), is a representative inflammatory demyelinating disease of the central nervous system (CNS). Both genetic predisposition and environmental factors are essential for the development of MS. It is estimated that more than 2.3

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million people are affected globally [1]. Importantly enough, MS is one of the world's most common neurological disorders and the cause of non-traumatic disability among young adults in many countries [2]. MS exhibits a variety of symptoms, though some of them are typical particularly at the initial stages of the disease. They may result from involvement of sensory, motor, visual, and brainstem pathways. The majority of patients with MS initially suffer from relapsing remitting episodes of new or recurrent neurological symptoms [3]. In general, standardized definitions for 4 MS clinical course phenotypes are provided: relapsing remitting (RR), secondary progressive (SP), primary progressive (PP), and progressive relapsing (PR) [4] with some recent modifications [4]. The first clinical event suggestive of demyelination though not yet of MS is termed clinically isolated syndrome (CIS) and can be optic neuritis, incomplete myelitis, or brainstem syndrome [5]. About two-thirds of these patients develop clinically definite MS (CDMS) [6]. The McDonald criteria are used for MS diagnosis. They incorporate clinical and/or MRI data for the identification of dissemination in time (DIT) and space [7]. However, there are a number of other diseases to be differentially diagnosed [3].

10.2 Pathophysiology

A rather variable underlying pathology, similarly to the clinical profile of the disease in MS is currently considered a primarily autoimmune disorder of the CNS characterized by focal lymphocytic infiltration and demyelination [8] and one of the main causes of non-traumatic neurological disability in young adults. However, diffuse axonal and neuronal degeneration is evident although early in the disease process [8–11], the Wallerian degeneration (WD) being a major component of axonal pathology [12]. In particular, neuroaxonal damage accumulates with disease progression and it is thought to be the major cause of neurological disability in the long term [13]. During the past years several mechanisms potentially underlying neuronal damage in MS have been hypothesized [10]. There is increasing evidence for a potential energy metabolism failure leading to neuroaxonal death [14] since mitochondrial defects have been demonstrated during the course of the disease [15, 16], despite increased mitochondrial content [17]. These defects could, at least in part, explain the hypoxia-like tissue injury seen in MS lesions. Indeed, reactive oxygen species (ROS) and nitric oxide (NO) produced by activated microglia, may impair mitochondrial function [18] and thus may link microglial activation in MS lesions with a hypoxia-like tissue injury [15].

10.3 Impact of the Disease

Given the variety of symptoms and clinical course together with the unpredictable and progressive character of the disease, MS has a profound and life-long impact on patient's quality of life (QoL) affecting not only physical, (visual and cognitive function), but also psychological and social aspects already from the moment of diagnosis [19, 20]. Moreover, it is estimated that as soon as (on average) three years after diagnosis, unemployment is a major issue for as many as half of the MS patients and may therefore depend on a disability pension or on their family and friends for the rest of their life [21]. Consequently, it is evident that MS exhibits a high burden for patients, their caregivers—family members and society as a whole.

10.4 The Aim of Treatment

There is currently no cure for MS. However, much progress has been made during the last few years in the management of disease activity and progression through specialized care. The early diagnosis and the establishment of patient-centered therapeutic strategies together with the use of appropriate medication, such as disease-modifying drugs (DMDs) and symptomatic therapies have largely contributed to a better outcome of MS patients.

The therapeutic armamentarium of DMDs includes five interferon formulations, two versions of glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethyl fumarate and alemtuzumab. After a disease-modifying therapy is chosen, vigilance for clinical or radiographic breakthrough disease is very important, as this may suggest a suboptimal response to the chosen therapy. Furthermore, symptom management and wellness should always remain part of overall therapeutic strategy [22]. Last but not least, pharmacovigilance and close monitoring for potential side effects and potentially harmful iatrogenic complications are of great importance in the overall management of MS.

Our aim is to control the disease activity, i.e., the reduction of annual relapse rate and the ongoing disability progression. To this aim, the early initiation of treatment at the early stages of the disease is of importance for the better outcome of the patients. It is of importance to keep in mind that there is usually latent period from the time point when pathology initiates until the clinical expression either as a relapse or as progression. Consequently, using clinical and/or laboratory criteria we need to anticipate the potential of future disease activity and make appropriate adaptations in treatment. All DMDs have the potential to provide a long-term control of disease activity. It remains to determine which DMD may be the most appropriate one on an individual basis.

10.5 Problems in Care and Management of the Disease and the Potential Role of the 5G Technology

The early identification and evaluation of symptoms is very important in the disease management. In clinical practice, it has been noticed that patients may under-estimate a particular change in their neurological function until it becomes particularly evident. Moreover, patients may not be able to determine precisely during their follow-up the initiation of any kind impairment the have had. This impaired provision of accurate information may be attributed to concomitant cognitive impairment and/or memory disturbance [23]. Therefore, a loss of information on their recent medical history in between the follow-up time points may lead to an overall impaired clinical evaluation of the disease burden.

A good example of an early identification of functional impairment on MS is walking ability of the patients characterized by decreased walking endurance and confidence and falls [24]. Walking impairment is one of the most noticeable and serious manifestations of MS, usually occurring early during MS. Walking disturbances have been reported to have the greatest impact on socioeconomic outcomes occurring during the early stages of disability. In Europe, only half of the MS patients with an Expanded Disability Status Scale 3 (EDSS 3; fully ambulatory patients) are employed and this is further decreasing to 20 % of patients with an EDSS 6 (patients needing a walking aid) [25]. Interestingly enough, the affected individual prior to relevant clinical manifestation often perceives walking impairment. It would therefore be important that the patient would be able to provide such a notice in real time and not after a period of time until the scheduled appointment with the doctor. Patient perceptions should lead to pre-emptive management strategies to maintain independence and delay as long as possible the need for walking assistive devices or caregiving.

However, time is an important factor and any delay of the appropriate identification and management of the symptoms may ultimately lead to a rather permanent functional impairment. Evidently, when used in tandem, patient-reported measures in real time and objective evaluation by the physicians either concomitantly or during scheduled appointments, can help monitor changes and facilitate patient-clinician discussions of problems, management strategies, and long-term goals related to walking impairment [26]. Moreover, due to the various factors interfering with symptom appearance or severity throughout a time period (concomitant infections, environmental conditions, such as temperature, humidity, etc.) it may very well be that the evaluation of patients during a scheduled follow-up may not correspond to the burden of this particular symptom on a daily basis. It has recently been reported that using in-home sensors to analyze gait parameters in real time is feasible and could lead to better analysis of gait in persons with MS [26]. Moreover, internet-guided interventions can encourage MS patients to implement more physical activity in their lives [27]. Therefore, the use of cyber-physical systems which connect the physical world and the virtual world in next to real time could flag up sudden changes in their day-to-day activities, which might well be

associated with a flare-up of their disease. This would not only to respond much earlier to a deterioration of a patient's condition but could also open the door to algorithm based analysis of individual data sets or even "big data" analysis. Ultimately there is a realistic chance to even predict flare-ups and subsequent deterioration thus minimizing the damage and delay a general deterioration which otherwise might be irreversible. Using biosensors, cyber-physical systems and next generation mobile network technology IoT paradigm and the advent of the 5G technologies will inherently allow for easing the symptoms of this chronic disease.

Importantly enough, MS patients may exhibit other symptoms, such as fatigue, anxiety, depression, bladder and bowel dysfunctions and sexual problems. These symptoms may either be transient or permanent and their intensity varies throughout time. Some of these symptoms may also be a sign of a forthcoming relapse or neurological worsening. Again, the notification of these symptoms in real time as well as their record on a daily basis may provide detailed information to the clinical team. Moreover, in the future it might even be possible to support patients with motoric and/or cognitive deficits in real time through neuronal stimulation or user interfaces.

Although many tests and scales are available to evaluate the severity or impact of specific symptoms, they may hardly be used in daily clinical practice. Presumably, time constraints for physicians to perform comprehensive assessments and/or their unfamiliarity with specific metrics of clinically meaningful differences, make interpretation of the relevant evaluations rather difficult. Moreover, not all clinicians may value patient-reported measures as they are potentially biased by mood swings [28]. However, when the patient perspective is provided in real time, then any impact of concomitant factors may be easily examined thus resulting in a more reliable evaluation. Moreover, most of the relevant information would already be available if recorded in real-time, thus saving time during patient's scheduled follow-up.

10.5.1 Smart Pharmaceuticals to Improve Adherence

A prerequisite for treating MS, similarly to most chronic diseases, is the regular intake or administration of drugs, i.e., the high adherence to therapy [29, 30]. Decreased adherence in MS treatment may increase the relative risk of relapses. MS patients may exhibit variable loss of adherence to treatment due to a number of factors, such as forgetfulness, fear of the injection, missing efficacy as assessed by the patient, side effects, problems with complex treatment schemes, as well as fatigue [31]. On the other hand, it is very important for the doctor's evaluation of treatment effectiveness to have reliable information about the adherence to treatment. Technology may largely contribute to solve this problem. A good example is the use of an electronic auto-injection device for subcutaneous injection of interferon (IFN) β-1a 44 μg three times weekly. In a recently published clinical trial it has been reported that the use of this device was associated with high treatment

adherence, as objectively assessed using electronic injection logs [32]. Doctors may also have in real-time information via Internet about any missing administration doses. Smart electronic auto-injection devices might be fitted with radio access technologies, such as narrow-band IoT (NB-IoT) devices, which would be able to transmit status information to a central server. NB-IoT devices have recently been standardized by 3GPP the governing body for the standardization of 3G, 4G and 5G technologies and could soon be deployed as a radio access technology (RAT) for smart pharmaceuticals [33]. Similar developments in order to improve adherence are currently on the way for the management of diabetes and asthma [34, 35].

In order to improve the patient's QoL and Quality of Experience (QoE) and reduce the burden on society, MS patients should be comprehensively assessed while being empowered to remain active both in their family and social lives as well as in their work environment. This can be achieved by providing optimal care (rehabilitation, multi-disciplinary assessment and services) and DMDs adapted to the needs of every single patient [28]. In order to better meet the patients' needs, good communication and collaboration between the different stakeholders is essential. This includes MS patients, their caregivers, policy makers, health care professionals, researchers, regulators and payers [36]. Unfortunately, a wide variation in access to care and treatment exists nowadays across European countries [28, 37]. New technologies such as the 5G ecosystems may be of help to facilitate optimal care and (self-) management [28]. Cyber-physical systems which will be using 5G technology and various RATs, for example NB-IoT, mobile telephony and wifi have certainly the potential to establish a completely new way of patient and formal and informal carer support. Smart pharmaceuticals utilizing NB-IoT Technology hold the potential to massively improve adherence.

10.5.2 Individualized Medicine

Individualized Medicine or Personalized/Precision Medicine has become a buzzword referring to the latest paradigm for the (self)-management of chronic, non-communicable diseases [38]. In the new era of MS treatment and on the basis of our current knowledge about MS management, it became pretty clear that the overall therapeutic strategy should always be scheduled on a strictly individualized basis. To this, MS patients should be encouraged to take control over their own disease. They should be educated to record any change in their condition together with any potentially relevant factor they may notice or on the basis of their doctor's advice. The advent of the 5G technologies and the rapid progressive deployment of the IoT can provide the technological framework and support patients in doing so. Future applications of the already existing technologies, such as IoT, NB-IoT and 4G need to provide tools to support seamless various parameter recording in real time. This would display a huge step ahead with regard to an increase in the accuracy of patient assessments. In a next step more complex cyber-physical systems should be

implemented in experimental setups to allow for feedback loops to support patients with neurological deficits, especially during relapses.

Relevant clinical studies may further highlight 5G technology in MS management. This is an absolute necessity for a variable, fluctuating and largely unpredictable disease such as MS. The current white paper of the European 5G PPP initiative on 5G requirements already foresees several categories of requirements for the health domain which sits perfectly with the notions of emerging smart pharmaceutical strategies [39]:

- Ultra-low latency
- High reliability
- High mobility
- Positioning accuracy.

However, there can be no doubt that the deployment of smart pharmaceuticals will trigger a massive increase in the amount of connections required in any given area. This has been a general driver of 5G as a generic enabler of the Internet of Things all along the way. Increasing the wireless capacity by factor 1000 and connecting 7 trillion things are key targets of the European 5G initiative [40].

10.6 Virtualization and mHealth Strategies to Facilitate Behavioural Changes in MS Patients

Multiple Sclerosis is a complex disease affecting the physical and mental state of patients. Pharmaceutical approaches have been discussed above. However, there is also clear evidence for the effectiveness of psychosocial interventions [41]. Following a comprehensive systematic literature review cognitive behavioural therapy (CBT) was found to be effective and feasible. According to Vischedijk (2007) "…there was a statistically significant improvement in relevant health related quality of life domains (HRQoL)" [41]. There is also some evidence for the effectiveness of peer support, especially peer telephone intervention in patients with affective problems [41]. On the other hand there is evidence for the ability of individuals to change behavior in order to improve their mental and physical health through satisfaction of "autonomy, competence and relatedness" following the Self-Determination Theory (see Fig. 10.1) [42, 43]. This might well be achieved by applying telemetric strategies, mHealth applications and smart algorithms. mHealth approaches may enhance the autonomy of patients by avoiding a controlling health care climate but give patients the choice to use applications at their leasure. The applications might contain individually tailored predictive algorithms which could prove useful with regard to moodswings and anxiety levels and might also be used to control stress levels and encourage activity. mHealth applications or tailored algorithms might also hold the potential to enhance disease specific awareness and confidence levels, although this might be difficult to the progressive and oscillating cognitive limitations of MS patients. However,

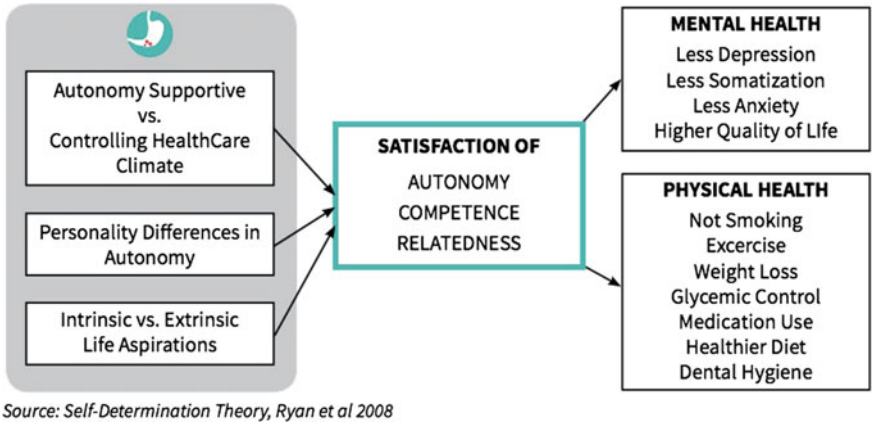

Fig. 10.1 Self-Determination Theory (Ryan et al. [43])

individualized algorithms may help with specific information in response to real-world challenges in real time. Health 4.0 systems will provide the technology and support MS patients to build individual ecosystems where participants can be weighed differently. A social network component within the application will help to increase relatedness by allowing patients to exchange personal information with third parties. Information may be exchanged selectively. Also information transfer would be auditable. This would build and preserve social capital. Figure 10.2 provides an overview of a typical Health 4.0 hybrid ecosystems including cyber-physical systems. Cyber-physical systems in the context of MS would be sensors, such as the phones accelerator sensor to map activity or sensors to monitor sleep to deliver data from the real world to the virtual world and obtain processed and aggregated information back via a feedback loop [44].

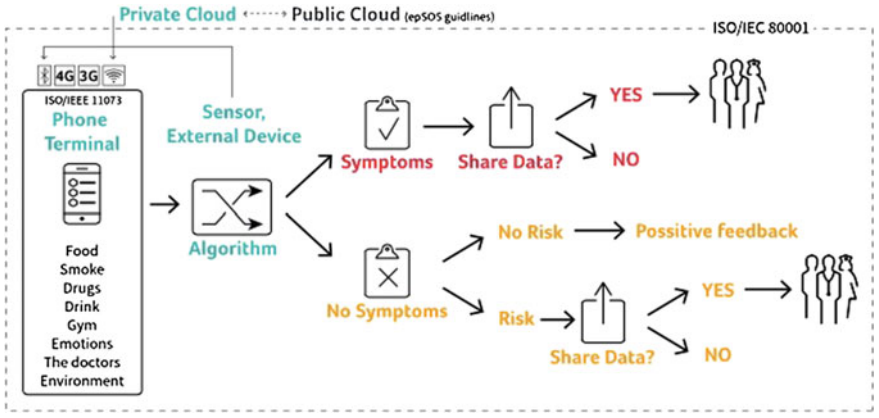

Fig. 10.2 Information flow in Health 4.0 hybrid ecosystems

As explained in Chap. 7, virtualization of health care can be achieved through capacity building. Telemetry solutions, mHealth applications and smart algorithms can empower MS patients by increasing their knowledge about and skills in effectively self-managing their health and illness. As patients take a more active role in the management of their health and condition, from using technologies to change their lifestyles, manage their daily lives and adhere to medication, this will dramatically increase their QoL. Increasing the confidence of MS patients could ultimately lead to better acceptance and adoption of telemetry solutions and mHealth applications.

Another important aspect of mHealth and Health 4.0 strategies is the monitoring of daily activities to capture relapses early and realize behavioural changes. Massive technological progress in the biosensor domain has been made over recent years. Some authors consider mHealth a viable solution "to enable evidence-based practices to wirelessly reach into the homes and communities of people who cannot readily or affordably access health care" [44]. Over recent years massive progress has been made and although the quality of health applications is still difficult to rate and to verify a variety of health applications especially for MS patients are available on the market. By the time of writing in 2016 these applications include MS Journal, and app to manage medication, MS self for tracking symptoms and medication, MSAA Self-care manager from the Multiple Sclerosis Association of America, My Multiple Sclerosis Diary, SymTrac and others [45]. While the authors cannot make any recommendations with regard to the quality or suitability of the applications mentioned the number of the apps on the market is a good indication for the rapid progressive developments in the field. However, mHealth applications must not be confused with Health 4.0 strategies. While applications might well be part of Health 4.0 setups Health 4.0 design principles are clearly defined and Health 4.0 frameworks go well beyond the realms of mHealth applications.

10.7 Health 4.0 Design Principles

Health 4.0 design principles are deferred from Industry 4.0 design principles which were originally defined by Hermann et al. mainly for the automotive industry [46]. The design principles and their translation into the health domain are comprehensively discussed in Chap. 2, Health 4.0: Application of Industry 4.0 design principles in future asthma management. In summary, the following design principles have been identified for the health domain:

- Interoperability
- Virtualization
- Decentralization
- Real-Time Capability
- Service Orientation
- Modularity
- Safety, security, resilience.

10.8 Application of Design Principles in the Context of Multiple Sclerosis Management

While the implementation of Health 4.0 frameworks is clearly complex and first testbed scenarios are still under construction this section will discuss the implementation of the design criteria in future MS management scenarios.

10.8.1 Interoperability

As discussed above technologies to support MS patients, formal and informal carers and medical professionals are already existing. Health 4.0 settings should support interoperability with legacy systems and relevant existing technologies. Any implementation process should start with a careful requirements assessment considering existing technologies, standards, ethical and legal requirements and social requirements [47].

10.8.2 Virtualization

One of the typical feature of Health 4.0 systems is the ability to integrate the physical world with the virtual world in order to enable real-time data exchange and the processing of this data through autonomous systems. Virtualization is a process where a copy of the real world is created and digitally stored in a storage device which typically is an integral part of the system. The process of virtualization allows for the use of autonomous and non autonomous algorithms and the creation of a personalized memory.

10.8.3 Decentralization

Health 4.0 is disruptive to the notion of centralized data bases. Health 4.0 allows data capture, processing and management anywhere, anyhow and at any time. Local data will be processed and stored locally. Distributed processing occurs if more processing power or input from other centres is required. The essence of Health 4.0 is that more tasks can be managed locally with support by autonomous systems.

10.8.4 Real-Time Capability

Health 4.0 requires real time capability in order to respond instantaneously to emerging situations and the task at hand. The support for MS patients needs to be at hand when needed. Although in current scenarios, for example in the context of

behavioural therapy, time delays will not be mission critical this might be different in the future when autonomous systems might be used to correct cognitive deficits. Latest initiatives to deliver on the fifth Generation mobile networks are aiming at ultra-low latencies in the range of 5 ms to accommodate the requirements of future proof systems.

10.8.5 Service Orientation

The notion of services goes beyond the concept of an application. A service needs to provide functionality anywhere and is typically covering a range of users. Health 4.0 frameworks are aiming to turn real-world processes into services. In MS, this could be to virtualize a face-to-face psycho-therapist and turn it into a service. This would allow the patient access anywhere, any how and at any time. Or a patient might want to assess their performance levels without waiting for an appointment with their doctor. Also it might be helpful to setup individualized services on an in-patient basis and then transfer the service package into the home environment—which might require automated adaptation to the specifications of the home network requirements.

10.8.6 Modularity

Modularity is an important principle with regard to individualization. In order to be efficient and meet the needs of an individual patient services have to be tailor made. In progressive conditions modularity would allow services to be extended without having to start to build everything from scratch.

10.8.7 Safety, Security, Resilience

Safety, security and resilience are anchored within the legal requirements of most countries with regard to patient safety and privacy protection. It is subsequently embedded in the clinical governance rules. The consideration of safety, security and resilience is mandatory for health care and ambient assisted living scenarios.

10.9 Instead of an Epilogue

The integration of verticals, such as Health, is one of the key differentiators between 4G (4th generation mobile) and 5G systems to reach global open markets for innovative digital business models. Use cases stemming from verticals have to be

considered as drivers of 5G requirements from the outset with high priority and covered in the early phases of the technology standardization process. The 5G networks will be built around people, things and machines and will inherently meet the requirements of three technical use cases groups [48]:

- Massive broadband (xMBB) that delivers gigabytes of bandwidth on demand
- Massive machine-type communication (mMTC) that connects billions of sensors and machines
- Critical machine-type communication (uMTC) that allows immediate feedback with high reliability.

The evolution of this 5G ecosystem provides the opportunity for the health care industry to drastically increase its efficiency, decentralize its services, deliver treatment and manage chronic diseases outside hospitals or healthcare centres. This is evident in the cases of chronic diseases where the cost pressures are increasing. As an example of future technology support to chronic diseases management consider the case where a health angle (consisting of IoT wearable devices that capture your heart rate or other organs functions) will produce alarms where specific irregularities are identified and transmit these signals to alert the attention of specialists. Under this scenario the patients will not be required to have regular check-ups and visits to hospitals or other healthcare centres and as a result the cost of such expenditure will be decreased. The 5G ecosystem will provide the opportunity for new, innovative value chains, business models, and new services based on cloud/fog and mist applications. It will become vital for current protagonists to rethink their role and provide health as a service (HaaS).

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Chapter 11
Towards Trust and Governance in Integrated Health and Social Care Platforms

William Buchanan, Christoph Thuemmler, Grzegorz Spyra, Adrian Smales and Biraj Prajapati

11.1 Introduction

The way we are sharing health and care data will be changing considerably over the years to come. One of the reasons is an increasing move towards patient-centric approaches where services are built around the citizens, rather than citizens integrate with the existing health and social care system. Often our health and social care services have evolved as separate entities where data around the citizen cannot be shared in a structured, safe and secure manner, and thus we often have non-integrated care systems. This lack of integration in the United Kingdom (UK) and in many other countries involves a lack of sharing between primary and secondary health care, but also spans to social care and relevant third sector organisations.

The healthcare domain and the inter-domain space between healthcare and relevant third party domains such as social care are high-risk area for data sharing. Healthcare data are notably the most desired data by hackers which are valued 10 times the value of credit card information on the black market [1]. There is an increasing requirement for strong cybersecurity practices, such as for cryptography

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and strong access control. The roles and services, though, have often been developed for health care systems which only have local significance, and lack any integration with external systems. There is thus a requirement for strong governance and security for the sharing and aggregation of data across systems, networks and domains in order to operate data sharing in full compliance with existing national legislation thus protects the rights of patients, organisations and citizens.

The rise of Cloud Computing has helped to make computer resources scalable and available when and where needed. Virtualisation has provided a new method to decouple data from services and servers. These strategies taken together may simplify data sharing across agencies in the future.

The use of global health data is not limited to the care of citizens but is also of huge relevance in a public health context and for governments to analyse the dynamics of the health and social care systems. There is also a vested interest by academics and researchers, for example in the pharmaceutical industry, or with regards to the development of smart algorithms to access real patient data for R&D purposes. However, these desires by different stakeholders need to be carefully balanced with the patients' privacy rights. Recent court rulings in Europe have clearly demonstrated that data sharing practices which were believed to be compliant with legislation and thus fair might after all be not safe and in line with existing legislation [2]. New Governance strategies have to be established to restore trust in order to allow for data sharing with confidence for all stakeholders.

Social and technical issues are to blame for the slow adoption of digital health in the UK and Europe (Fig. 11.1).

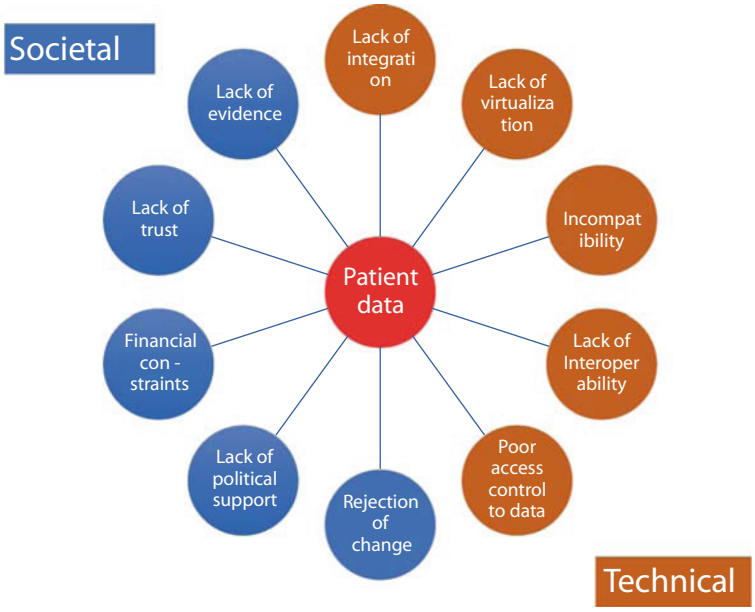

Fig. 11.1 Technical and societal barriers to the adoption of integrated e-Health platforms

Typically the target of integration across platforms, domains and systems is the improvement of the functionality of the existing platform components and the creation of new services. Data users frequently label the following attributes as desirable:

(a) More integrated and cost effect. This will allow inter-agency and collaborative work.
(b) More scalable and flexible.
(c) Better patient care. Support for patient history.
(d) Support sharing of resources.
(e) Reduced costs.
(f) Better quality. This includes generic quality metrics.
(g) Support research. This supports the analysis of data.
(h) Support national security. This helps with the monitoring of the spread of infectious diseases and/or other disease outbreaks, and look at infection patterns.
(i) Support strategic planning. This allows for analytics across the platform.
(j) Support financial operations. This supports the brokering of costs across the platform.
(k) Facilitate clinical trials.
(l) Facilitate forming registries. This allows for the targeting of special groups for care and well-being support.

This document will discuss a number of features such as:

(a) The infrastructure will have a strong definition of data owner of every data element, and for the rights of ownership and governance to these elements.
(b) Care, well-being and health care may all be supported within an integrated platform.
(c) All accesses for requires will be logged and analysed.
(d) Data accesses scopes will be limited by policy and scalable but specific access credentials.
(e) Wherever necessary anonymisation and sanitisation will be integrated into services, in order to preserve privacy.
(f) There should be a break-glass feature within the system that allows access to data, based on various risk factors.
(g) On-chip hardware security might be considered for devices such as sensors and smart phones.

11.2 e-Health Platform Features

Many surveys have been carried out around the world in relation to the requirements for use of technologies in the medical field and there can be no doubt that security and privacy are among the most important requirements. Thus, security

and privacy plays a vital role in successful implementation of e-Health and other medical technologies. A survey found out that females and healthy adults are more security and privacy aware compared to the males and ailing elderly [3]. However, from the point of view from healthcare providers and other stakeholders violation of privacy regulation means exposure to litigation and subsequently heavy penalties and compensation on top of the damage to standing and credibility.

Eysenbach [4] has put together 10 e's that characterises e-Health. These 10 e's can also be classed as a requirement for the e-Health system. According to Eysenbach, an e-Health should be efficient, evidence-based and equitable. It should enhance the quality of care and also follow the patient-physician ethics. It should prioritise the education of health care workers via online sources and also enable the exchange of information in a uniform method. Finally, an e-Health should also encourage relationships between patients and health professionals, resulting in the extension of scope of health care beyond the conventional boundaries.

Although patient-centricity is clearly a future proof attribute of healthcare and consequently e-Health systems there are lots of technological challenges that need overcoming if it is to be successfully implemented over the coming years [5]. On the other hand social components such as especially trust and confidence might play an equal if not bigger role. Technological research and development needs to be aligned with specific legislation to clarify requirements, responsibilities and strengthen the rights of citizens with regards to their own data. All of these processes need to be tackled especially with regards to a unified digital single market [6].

Certainly challenging will be the fact that future e-Health systems need to comply with significantly higher standards but on the other hand be more open and available anywhere, at anytime, anyhow [7].

11.2.1 Simple e-Health Model

A simple terminology for e-Health was developed by Löhr [8]:

- Health Professional (HP). A person who delivers health care services, e.g. physician, dentist, pharmacists, etc.
- Health Care Provider (HCP). An organisation that provides services of health professionals, e.g. doctor's practice or hospital.
- Personal Health Record (PHR). A database of medical data objects and health-related data managed by a patient.
- Electronic Health Record (EHR). A database of medical data objects and health-related data managed by health professionals.

For a simple PHR model, as illustrated in Fig. 11.2, the citizen controls access to the PHR, and grants rights for a HCP to access it.

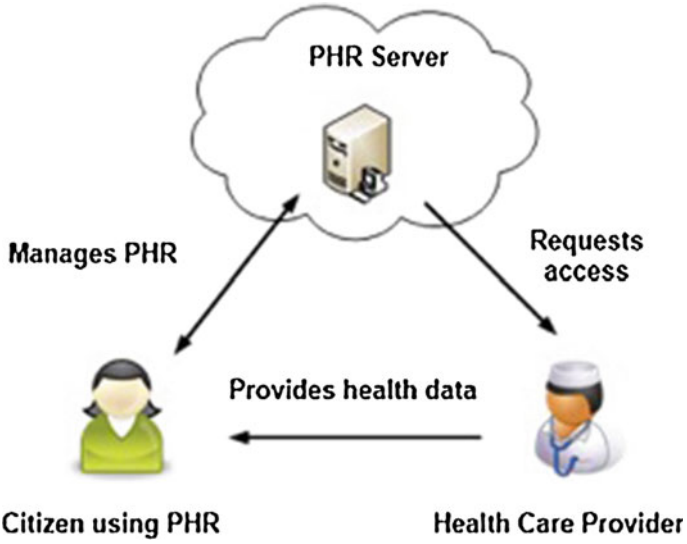

Fig. 11.2 Simple e-Health PHR model

11.3 Interoperating and Integrating Data Across Traditional Boundaries

For an enhanced model of health care, an interagency approach normally supports data to flow around the citizen, and for various care roles to interact, and look more holistically at individuals. Traditional health care systems within the public sector, though, have been built to support only internal accesses, and often fail to properly integrated less trusted access, such as within a home environment or with 3rd sector integration. The major challenge for new health and well-being care models is thus how to integrate systems across a number of domains, without significantly increasing the complexity but ensuring the same or enhanced level of security. This is especially challenging when considering the impact of any system alteration on warranties given by vendors with regards to the legacy system. From a legal perspective there are also issues where rights and identities flow across the different public sector agencies, and then out into even less trusted environments. Many government initiatives have tried to create common identities, but these often fail because they are too complex or citizens do not trust them. The method of BYOI (Bring Your Own Identity), Device/Location Authentication, Biometric Authentication and Multifactor authentication are now commonplace in supporting a more credible approach to identity provision.

Within patient-centric health and well-being systems the focus has to be on the patients and their formal and informal carers, their requirements and their multimodal interactions. This normally involves care services which integrate across different agencies, along with integrating the citizen and their trust circle. In order to

protect privacy and reduce the exposure to data breaches, the core health care data must routinely be kept within highly secure environments and under the control of the patient. However, where there is proper justification, there is a need for those external to a domain to have access to information, following due process.

This has to go hand in hand with a clear understanding of the risks resulting from the progressive use of cyber-physical systems which are based on real time connection of the real, physical and the virtual worlds. Here the risks are less associated with the break in into data bases but the interference with network infrastructures to intercept real time data communication. The different risk categories have been covered in more detail by Kashif Saleem and Ziyuan Tan in Chap. 12 in this book.

There are, of course, many different levels of risk within health and social care platforms. Within a data centre, we have different available requirements for the various tiered levels:

(a) Tier 1. Uses a single non-redundant distribution network path for equipment, and with an availability of greater than 99.671 %.
(b) Tier 2. Improves Tier 1 with redundant site infrastructure components/network connections, and with an availability of greater than 99.741 %.
(c) Tier 3. Improves Tier 2, but has multiple independent distribution paths with dual-power supplies, and an availability of greater than 99.982 %.
(d) Tier 4. Improves Tier 3, but with cooling equipment, dual-powered, with chillers/heater, ventilation and air-conditioning (HVAC). A longer term power outage will normally allow the infrastructure to continue to run, and an availability of greater than 99.995 %.

Normally, the security levels for the different tiers will increase, with Tier 4 data centres having strong security requirements.

11.4 Human and Digital Trust

One of the major challenges within integrated health and social care these days is the building up of both—digital trust and human trust (Fig. 11.3). The challenges in digital trust are the proving of identities of machines and individuals, their roles, and how that maps to the rights of access to the data. To provide a secure environment, all access to

Fig. 11.3 Integration of digital and human trust

data should be disallowed, unless it is explicitly allowed by a defined policy. This policy rule might relate to legal purposes, such as a static rule that allows the GP of a citizen to have access to their health record, or it might be dynamic where it is created by the citizen to allow access to part or all of their patient health record (PHR). The major issue within digital trust is the difficulty in properly mapping identities and rights onto the security parameters within IT systems.

A more serious issue relates to human trust, where few people actually trust the health and social care infrastructure to protect their privacy and rights. Along with this, the adoption of digital services within health and social care will only happen with applications which are useful for health and social care professionals.

However, this does not sit comfortably with a massively increasing trend towards self-monitoring and self-management. Far more than 100,000 e-Health applications are currently on the market globally, most of them not standardised and far beyond the security levels required by health care providing organisations. One of the prominent challenges of the coming decade will be to integrate these applications and a variety of patient-owned smart devices into a framework without creating any additional challenges with regards to responsibility and liability. Alongside new security technologies this will also require new risk management strategies in order to establish the notion of "trust" end-to-end across different networks and domains.

11.4.1 Cross-Domain "Trust" Through Translation Gateways

Within an integrated health and social care infrastructure data should be kept within the domain which governs the citizen's record—the data governor—and which is

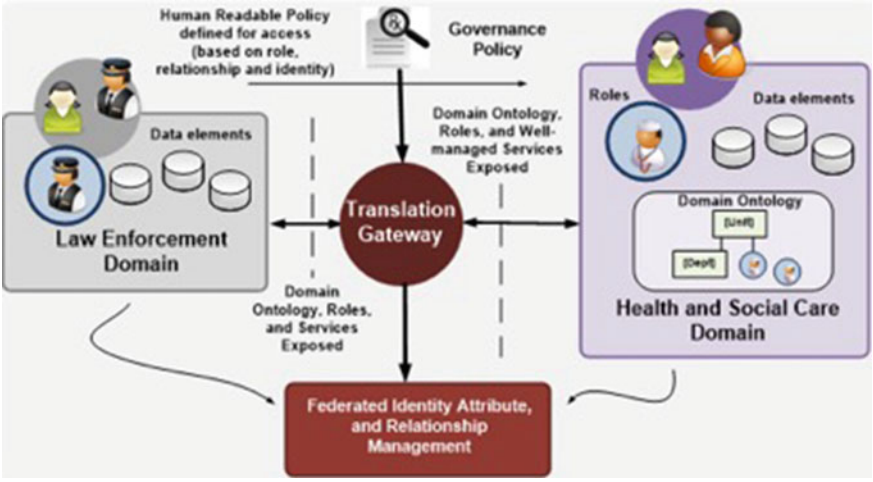

Fig. 11.4 Interdomain rights and mapping

trusted by all stakeholders to control access. All accesses from inside and outside the domain must then be controlled. This requires the mapping of the roles and rights from one domain into another domain. The most secure way to do this is through a translation gateway, which knows the structure of each of the connected domains, and can then check the access requirements for a role or individual from one domain to access a data within another domain. The two domains thus require a common language for the definition of the entities they are referring to, and the levels of identity provision that is required (Fig. 11.4).

The "Translation Gateway" supports a highly safe and secure digital interdependency which could be understood as an equivalent of "trust" in human interaction. The rights of access are defined by predefined rules. Along with this, it uses trusted identity verifiers, so that users can identify themselves in a secure way. Key features of the governance infrastructure are:

(a) Automated governance policy generation from the model.
(b) Ability to produce a human readable version of the information sharing policy, which maps directly to the agencies.
(c) Ability to change the policy in real time, in order to deal with changing environments.

11.5 Trust and Governance

One of the challenges of generic to multi-agency data sharing, such as integrated health and social care information, has been to agree how and what information should be shared across boundaries, without increasing risk and exposure. Traditionally this is solved by using a Master Data Management system which can manage the "trusted" exchange of massive amounts of data between agencies. This type of approach allows for a direct access method in order to "share" information, without actually permanently moving any data—thus keeping information where they are best maintained and managed but at the same time providing rich composite views of information. The system operates by translating the multi-agency model into a human readable policy, which defines the roles and rights of access to information from each of the agency partners. At any time the model can be updated, which, after a review, can be implemented within the translation gateway. The governance policy will then control the access to information between the agencies, in real time. Trust and governance promotes a sharing architecture across agencies, and then defines the information sharing governance policy between the domains. It thus translates identities and rights across the domains within the care of citizens, but where the data in each domain is carefully managed. The benefits are clear for organisations across both public and private sectors:

(a) Ability to share information securely within or across domains.
(b) Strong governance framework to prevent unauthorised access.
(c) Adherence to compliance and policy standards through strong governance framework.
(d) Prevention of cybercrime and more effectiveness and efficiency in cybercrime investigations.
(e) Collaboration between organisations enabling improved joint development and research.
(f) Reduced cost and risk through efficient, robust, secure architecture.

11.5.1 Trusted Identities

Once a governance model is in place we can have a complete provision of the services and roles exposed by each of the managed domains, and then control the access between them. At any given time the rights can be revoked. The governance layer thus just needs to sit as a service between each of the domains. This needs to be the only way to access a given domain in the sense of a single point of contact (SPOC). Just like a network firewall, it will block accesses which do not have the correct access requirements.

A user wanting to access an exposed health care service, such as viewing their child's immunisation record, would thus access the gateway of the domain exposing the service, and then present their credentials and required information of the scope of the request (such as the ID of the child, their relationship to the child, and the dates required). The system then would check its policy for access, and define the identity provision that is required. This will include defining the range of identity providers that the domain trusts, and other specific identity information required (such as a proof of being in a certain location or biometric information). The claim is then checked by a trusted entity to check that it has been signed correctly. If the requirements are met and all features of the request match the policy the access is allowed, and the service runs the query. Throughout the process a complete audit trail is kept for both successful and unsuccessful accesses.

Alternative or additional strategies would be the use of Blockchain technology. Here the access history is irrevocably linked to the data as a metadata tag. This strategy has been proven in the finance domain and might be used in the future to tighten security in the health domain further. This would especially enhance security with regards to the increasing amount of patient devices and e-Health applications.

11.6 Aggregated Records

Increasingly a major barrier for integrated care is to allow care agency partners, such as from healthcare, social care, and education to share information, and thus to allow trusted entities to access summary records or metric indicators. The usage of summary

records and metric indicators thus protect the original data, but allows formal and informal carers to make informed decisions around associated risks.

11.7 Information Sharing

A key aspect for the future of health and social care is the integration of a wide range of health care services within an integrated infrastructure. An important area for information sharing is within the holistic care, where information from different public sector agencies, for example from the health and social care domain can be used to improve the effectiveness and efficiency of care of citizens.

The UK Government and Caldicott [9] have both identified that key objectives of a modern health and social care information is for an improvement information sharing across the public sector, and increased integration of the citizen, and their formal and informal carers, into their health and social care. In this way citizens are more likely to take more ownership of their own healthcare, with an expected improvement in treating illnesses. Unfortunately most health and social care IT infrastructures in the UK have been designed with little thought of integration. Future systems must be built around the citizen, in which we move into holistic care, and where the health and social care professionals integrate with the citizen. This distributes their care, supports the virtualization of care into patients' homes, thus offering a digital infrastructure to empower people to manage their own (chronic) conditions and reduce hospital admissions.

11.7.1 Related Data Architectures

As part of the development of an integrated approach to health and social it is important to analyse current defined architectures, and understand their operation. The data within an e-Health platform will typically only be used internally to the infrastructure, but there will be external interfaces where citizens can access open dataset.

11.7.1.1 London Digital Programme

As part of Healthy London initiative [10], the Health and Social Care ecosystem in London is piloting new ways to provide a data sharing environment to allow the 7000 diverse organisations involved in patient care to access patient records. Symphonic Software is delivering the key governance layer to this important programme to ensure that any data access meets with data controller agreements, which codify the inter-organisational rules for patient data access, and also allowing citizens to express their own data sharing preferences [11]. There are a number of agencies that inter-connect, and the span of the integration of health and social care services [10]:

(a) 9 million people.
(b) 25 miles wide, 25 miles deep.
(c) 1500 GP practices.
(d) 1500 Dental practices.
(e) 1800 Pharmacies.
(f) 400 Opticians.
(g) 30 NHS Trusts.
(h) Hundreds of formal and informal care organisatons.
(i) 32 CCGs and 32 Councils.

11.7.1.2 NIB Framework

The NIB Framework [12] sets out an ambition for the delivery of digital care accounts. The Citizen Accounts project aims to deliver the technical solution design, via follow-on projects, and will support the transformation in the way information is used across health to deliver radical transformation in a number of key areas. Within this broad framework, the Citizen Accounts project explores the requirements and feasibility of establishing personalised identity, consent and preference services that can be set (by the citizen) once and subsequently be accessed/shared by provider systems. The key elements of the integration include covering a number of interlinked use cases supporting the data controller's role and the capture of patient preferences and consent in a platform which provides capabilities against a number of key themes:

(a) Creating data sharing agreements between data controllers, and defining the embodied data rules electronically.
(b) Providing a 360-degree audit view on the creation and use of these data rules.
(c) Providing assurance on identities of patients, clinicians, and 3rd party applications/services making data requests.
(d) Providing an API integration to make it easier for 3rd party applications to conform to the data sharing rules within the electronic platform.
(e) Providing flexible capability to restrict data, including personally identifiable patient data, according to those rules.
(f) Capturing and enforcing patient preference and consent.
(g) Notification services which can be used to inform data controllers of patient preferences.

11.7.1.3 London DataStore

The London DataStore provides access to city-related data [13], and which has the mission statement of [14]:

> We want London to have the most dynamic and productive City Data Market in the world. In our City Data Market, the capabilities, talents and capacity of all our city data partners

> will impact on our huge social, economic and service-based challenges. To make this happen, friction in the sharing and value-driven exploitation of city data will be reduced to a minimum. City data will be recognised as part of the capital's infrastructure. We will use it to save money, incubate innovation and drive economic growth. And London will achieve global renown for data impact.

It integrates data across the city and provides planners with trends which break down in boroughs and wards, and includes a wide range of health and social care services, including data around abortion rates for under 18s, loneliness ratings, and drug and alcohol usage. At present it has over 500 datasets which can be cross-referenced with the required linkage. An important factor is that there is great detail in demographic differences across the city, and each ward and borough can be analysed in great detail for its demographics and changes in its future requirements.

Within [14], the authors define that a major drawback in allowing data to flow is the architecture used, and there is a strong need for regulation and governance, along with culturally and organisational barriers, but that there were so many opportunities for the creation of new skills and jobs. They propose the following design guidelines:

(a) Use a federation of data stores/warehouses. This approach distributes the data, but aims to use an integrated security infrastructure to secure the data.
(b) Focus on cloud-based methods.
(c) Integrate new datasets, such as related to sensor data for IoT access.
(d) Reference data rather than duplicate it.
(e) Support active exchange of knowledge across the public sector in the UK, and elsewhere.
(f) Use and contribute to the open source community.

The initial phase is Phase 1—City DataStore, where there are static and non-standardised data files, along with published API calls for data. The second phase involves the integration of simple API calls, and identity solutions around security, data types, federated data stores, and for federated identity checking. The stages which follow include:

- City DataStore—Phase 3. This will include licensing models and full API integration and identify dataset with the greatest potential for commercial models.
- Data for London—Phase 4. This will include the integration into the WITAN and the Sharing Cities project, along with new tools for open data analysis and visualisation.
- Data for London—Phase 5. This will integrate data from a wide range of platforms.

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Chapter 12
Security for Cyber-Physical Systems in Healthcare

Kashif Saleem, Zhiyuan Tan and William Buchanan

12.1 Introduction

Sensor and network technologies and ubiquitous healthcare have evolved and matured over recent years, and are now in the process of being implemented into healthcare scenarios worldwide. The European Commission estimates that the market volume of mHealth technologies will exceed the 17 Billion Euro mark globally by 2017 [1] (Fig. 12.1).

Pervasive healthcare systems with real-time monitoring will enable Personal Care strategies (Personalized Medicine) or "Precision Medicine" as it is called in the US [2]. This will involve the use of smart algorithms and cyber-physical systems in order to support real-time processes to respond to individual requirements anywhere, anyhow, and at any time. This will be inevitably be linked to a new breed of telecommunication services, some of them in preparation under current 5G network initiatives in the US, Europe, China, and elsewhere [3].

There is a general assumption based on some evidence that the use of wireless-based eHealthcare systems outside hospital may increase effectiveness and efficiency [4]. One of the prime examples is that reminders generated by messenger systems may enhance the adherence of patients with chronic conditions such as Diabetes, Asthma, and HIV thereby reducing the number of severe events such as

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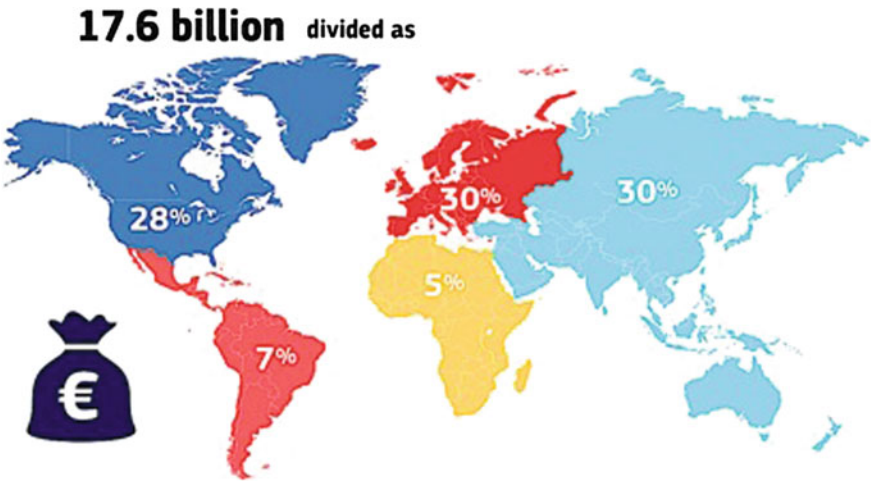

Fig. 12.1 Forecast: estimated global market value in 2017 [1]

hypoglycemic episodes, asthma attacks, or deterioration of blood counts [5]. This will result in fewer hospital admissions and increase of the overall quality of care. On the other hand, activities such as daily tasks, falls and movement detection, location tracking, medication intake, and medical status monitoring are very important features in Ambient Assisted Living (AAL) and tele monitoring [6].

Next generation eHealthcare systems will be based on cyber-physical systems and will be composed of multiple components that work on the basis of Industry 4.0 design principles in Health 4.0 setups integrating the physical world (e.g., patients, doctors, community nurses, and informal careers) and virtual components (e.g., algorithms, databases, and virtualized biosensors, etc.) [7].

Many different types of data will be gathered with the help of biosensors inside and outside the body, for example blood pressure, heartrate, blood glucose level, ECG, EEG; Cyber-physical systems will also process data from artificial organs such as Brain—or Cardiac Pacemakers, Insulin Pumps, and endoprothersis as knee and hip implants.

Especially those sensors deployed inside the body may be integrated into Wireless Body Area Network (WBAN) that integrate environment conditions and biometrics of the patient in order to present real-time analysis of biomedical processes. These networks typically communicate with network gateways following the IEEE 802.15.6 standard, which aims to provide an international standard for low power, short range and extremely reliable wireless communication with the surrounding of the human body [8].

12.2 WBAN Overview

WBAN and environment sensors use different protocols for communication. When the body sensors communicate with each other or with a node head, they are classified as Body Area Network (BAN). Communication between gateway devices/access points to the local management systems is normally wired. For indoor connectivity between sensors and PDA we have to use low range, reliable, and robust communication technologies like WiFi, Zigbee, 802.15.6, or 802.15. We can see from the literature [9] that Zigbee is the most widely used wireless protocol for BAN, while 802.15.6 is a specially crafted protocol, which focuses especially on WBAN medium access control mechanisms.

12.3 The Components in WBAN-Based eHealthcare System

A WBAN-based eHealthcare system generally consists of the following main components.

12.3.1 Wireless Sensor Node

A sensor or node is a tiny device measuring Physiological Values (PV) of a patient. As sensors are mostly attached to the body of the patient networks of body sensors are collectively called a Body Area Network or Body Sensor Network (BAN/BSN). These networks are normally wireless in nature due to the ease of use and mobility of the patient. They communicate to a relay or access point to transfer measured or sensed data. These sensors play a very important role in eHealthcare systems where secure, reliable, and ubiquitous patient monitoring are the key factors and data is generated at the sensor nodes. Therefore, reliable, secure and attack resistant acquisition, and transmission of data are of utmost importance for the efficiency and feasibility of eHealthcare systems. Rashidi and Mihailidis in [6] tabulated different types of sensor nodes that are used in eHealthcare. Sensors used can be of a versatile nature using different wireless technologies like Zigbee [10], Bluetooth [11], and UWB. The processing capability of a sensor is very low, as its main function is to sense and transmit data to the sink node or a smartphone. In the scenario where the data is required to transfer at long range the Long-Range Low-Power End Node Solution (LoRa) technology can be used [12]. LoRa is enabled with long range and with long life to perform environmental monitoring.

12.3.2 Gateway or Sink Node

An access point, a gateway, or a personal digital assistant function acquires data securely from sensors and transmits it securely to the required location [13]. This can be a personal device allocated for every patient in a hospital or a personal smartphone configured to handle data from sensors in a patient's home. It has more processing and storage capabilities as compared to measuring sensors. It is suggested to implement anonymity on such a device so that the patient's identity is ripped off when data is sent to the gateway and only a random patient ID is used onwards.

The access point is directly connected to a hospital information system in the case of local storage or to the Internet in the case of global data storage [14]. This part does not require data processing or computation capabilities as it just delivers data to the storage server. Usually WiFi compatible devices are used in this part. The patient should have the control to filter and allow which data to send to the network. The access point should support both communication technologies (e.g., sensor data aggregation) and transmission of data to relay node/gateway usually using Wi-Fi and a cellular technology present at the time. Other cases where the devices are communicated wirelessly to acquire critical data over long distances [15], the technology developed is narrow band radio for the IoT (NB-IOT), eMTC, and EC-GSM-IoT [16, 17] and is included in LTE [18, 19].

12.3.3 Authentication Server

A Public Key Infrastructure (PKI)-based authentication server is responsible for root level authentication of each and every actor in the whole infrastructure and also managing authentication across multiple domains and systems or multiple Electronic Health Record (HER) systems [14]. Every node, device, medical representative, emergency personnel, medical store personnel, and caretakers over the network are authenticated with the help of this server. The authentication server can be local to a hospital system or global system or can be based on a hierarchy. Recent architectures involve Cloud computing and Cloud servers for this purpose [20]. In Cloud-based architecture the encrypted data is directed toward the Cloud service provider authenticated and stored over multiple servers.

12.3.4 Storage Server

A storage server consists of all the databases and encrypted Protected Health Information (PHI) of patients. This can be a local storage server or a global connected one where a hospital stores the patients' data to access it globally [14].

This part requires a high performance and storage capabilities as well as high availability. In addition, access control mechanisms are also present on the server to make sure access is given to the authorized personnel only and also to run specific queries.

12.3.5 Policy/Delegation Server

A server for policy implementation check, creating and managing logs for accountability, and securely sharing information as controlled by a patient and delegated by a primary physician [14]. Policies are implemented and tested continuously so that no security breach occurs which can save an organization from a law suite of patient data privacy. This server can also handle delegation services like when a general physician refers a patient to another specialist and shares patient data and, after treatment, access to data is revoked [14]. This server requires global access to data for policy checking and verification. It is also required to have heavy computation capabilities.

12.4 Common Threats to Wireless Body Area Networks (WBANs)

Due to the heterogeneous and versatile nature of eHealthcare systems, it is essential to secure the health records from the monitoring side till the storage and/or retrieval. The violation of any aspect like patient confidentiality, privacy, integrity, patient approval, or data availability can have serious consequences to patient's life [20]. This is because the failure in generating and obtaining the authentic medical data by the WBAN can also prevent a patient from being treated effectively, or can lead to life-threatening situations.

An adversary can eavesdrop on the communication and/or temper with a patient's medical data if it is not encrypted, thus violating patient privacy. In the case of an emergency, if eHealthcare monitoring system is under Denial of Service (DoS)/Distributed Denial of Service (DDoS) attack can put the patient's life in danger due to the unavailability of patient's vital signs. An attacker can generate malicious activities in the network and can able to disrupt the normal operation of the patient's vital signs monitoring.

Furthermore, a number of attacks such as spoofing attacks, sybil attacks, wormhole attacks, session hijacking attacks, and resource consumption attacks against different communication layers, which are mentioned in [21, 22] can interrupt the overall system functionalities. Forward and backward secrecy are also important to ensure against attackers who read encrypted packets with an expired key. It has been shown that an eHealthcare system is prone to simple MAC and

network layer attacks like session hijacking, DoS/DDoS attacks, data corruption attacks, and multiple passive attacks [22]. Monitoring and eavesdropping have shown to be very easy to perform on protocols like Bluetooth and violate the privacy of patients [23].

12.4.1 Security Posture of Some Solutions

A complete eHealthcare history is discussed in [24]. A lot of work has been done, resulting in multiple types of solutions available, yet only few solutions propose complete system end-to end solutions addressing all the issues related to all the layers of the architecture. The following are some of the popular eHealthcare solutions along with their security standpoints and weaknesses.

A distributed eHealthcare system based on the Service Oriented Architecture (SOA) was proposed in [25]. It uses web services to provide support to nurses, pharmacists, physicians, and other healthcare professionals, as well as for patients and medical instruments used to monitor patients. Its main components include PDA, web Server, doctor PDA/computer, patient PDA, and Bluetooth for sensor communication. Its main security features include user authentication and session information logging. However, it lacks support for data storage on the local PDA for offline uses, and there is no support for emergency case scenarios as in HIPAA, no integrity checks, no availability issues handled, and no pseudonymization of the patient data.

CodeBlue is another important eHealthcare prototype defined over an architecture and a complete eHealthcare framework [26]. Its architecture allows for the integration of heterogeneous medical sensors. The framework provides protocols for device discovery, publish and subscribe routing layer, and query-based software to help caregivers in a hospital to request data from a group of patients. Its main components include PDA and mote sensors. Elliptic Curve Cryptography (ECC) was implemented on motes using integer arithmetic while Tinysec was proposed for symmetric encryption. It also lacks HIPAA compliance, no confidentiality on remaining architecture except sensors, no integrity check, and no privacy of data details.

Egbogah et al. [27] presented another project named MEDISN. It utilizes a wireless sensor network composed of a network gateway, Physiological Monitors (PMs), and Relay Points (RPs), to monitor the health, and transmit physiological data, of patients. Its main components were physiological monitors, relay points, a network gateway, and backend data-based server. No security feature was implemented other than client authentication which was done using an unknown authentication scheme.

Hamdi et al. presented another modular eHealthcare system called CAALYX in [4]. The system was composed of three subsystems: (1) A mobile monitoring system to collect and monitor PV of patients; (2) A home monitoring system to monitor patients at home and help them to keep in touch with their caregivers; and

(3) A monitoring system for caregivers to provide monitoring of elders by specialized personnel. Its main components were PDA and environmental sensors. It included privacy protection using local data processing but there was no encryption, authentication, or pseudonymization discussed in the paper.

Alarm-Net is another solution that consists of a body sensor network and an environmental sensor network [28]. Its main components include PDA, environmental sensors, body sensors, a network gateway, and a database. It used AES for encryption, a built-in cryptosystem for sensors and authentication using their own secure remote password protocol while HIPAA compliance, integrity check pseudonymization was absent from the solution. We can observe that most of the solutions use a PDA for end user connectivity and Bluetooth for the primary communication protocol for sensor interfacing which has multiple security limitations. Moreover, every solution has security shortcomings which include basic features like confidentiality, integrity, and pseudonymization.

12.4.2 WBAN Security Requirements in Healthcare Environment

Efficient communication in eHealthcare is defined as reliable, secure, fast, fault-tolerant, scalable, interference-immune, and low power. Attacks can be classified as active or passive [21]. Moreover, attacks can also be classified based on the layers they target, i.e., physical layer, MAC layer [22], network layer and application layer. We can mention the essential security and privacy requirements and issues in healthcare systems, by generally classifying them into four main categories based on the papers in the literature [6, 23, 26, 29–32].

(A) **Administrative level security**

This category of security includes nontechnical requirements. Privileges regarding policies and access control should be clearly defined and implemented. These policies should be context aware and adaptive to ensure data availability and access flexibility especially in the case of any emergency conditions. This category contains the following subcategories:

- Data access control: refers to the patient's data privacy. Multiple access control mechanisms can be implemented to enforce multiple levels of authorization to different categories of the patient's data [32].
- Accountability: includes the policies that bound users who are using the patient's data to be held accountable for their actions on data; nonrepudiation is one factor that can be achieved by enforcing those policies [32].
- Revocability: refers to revocability of any user from the patient's data when he/she seems malicious or performs a violation against the policies or set rules [32].

- Activity tracking threats: includes the privacy of the patient's data from any adversary that can measure or eavesdrop on the data and thus can monitor the patient's daily activities [31].
- Patient permission: is in accordance to international health laws and policies like HIPAA by which the patient has all the rights to his health record and he can allow or deny anyone to have access to his health records [14].
- Patient anonymity: includes sharing patient information to third parties without exposing the patient identity for research, surveys, or global health measures. This includes cases like when the government will likely take a precautionary measure of a disease if it sees its rapid increase in a specific area or a research student can analyze the health records of a disease without knowing the patient's real identity [14]
- Timeliness: is another important factor in eHealthcare systems as it may have an impact on the patient's health status. Even some minutes of delay can cost a patient's life [27].

(B) **Network level security**

Network layer security plays a crucial role in ensuring the security of an eHealthcare system. This layer provides secure transmission of patient data between body sensors and the gateway/relay point or the Internet. The protocols at this layer should also be attack resistant and reliable. Moreover, the adopted protocol should be energy-efficient, interference-immune, and reliable. In what follows we present the key security features that need to be ensured at this level.

- Secure routing: Secure routing is one important feature required in successfully transmitting data packets from wireless sensors to the head node or the gateway. Routing protocols should be attack resistant and reliable to transmit data packets [32, encryption].
- Intrusion Detection System: There should be an intrusion detection/mitigation mechanism built into the network layer protocols that identify malicious nodes/sensors and exclude them from the wireless network whether it is a single hop or a multiple hop wireless network [31].

Below are some of the famous routing attacks summarized from [21, 22, 28] that a network layer protocol should be resistant to:

- Selective forwarding attacks: An intermediate malicious node only forwards selective routing packets to the next node. This usually happens in multi hop routing protocols.
- Blackhole attack/Sinkhole attack: A malicious node sinks/ drops all packets that it receives.
- Sybil attack: A malicious node uses a valid node's identity to enter the network or disrupt it.

- Spoofing attack: A malicious node spoofs its identity in order to affect the normal operation of the network.
- Wormhole attack: It works by recording traffic from one part of the network and transmitting it to another part to poison the routing table, which may result in unreachable valid nodes.
- Rushing attack: A malicious node rushes to send its malicious packet to a destination node before a valid packet is received from a valid node.
- Cache Poisoning attack: A node's cache is poisoned by a fake node by sending wrong route updates to nodes in the network.
- Resource consumption/energy exhaustion attack: Valid packets are distributed in a network, which are not required to deplete the energy of nodes and thus reducing lifetime of the whole network.
- Session hijacking attack: An authentication session is hijacked just like a man in the middle attack in regular networks.
- Packet delay attack: A malicious node forwards packets but adding delay. This attack can be a critical one in case of an emergency.
- Jellyfish attack: A malicious node sends packets but in a disordered manner so that the destination node does not reorder them, if it can even reorder the packets it will at least cause latency in a network.

(C) **Physical/MAC level security**

Data generated by sensors are first converted to a specific format at the physical layer and they are transmitted through a wireless medium using a medium access control mechanism. The MAC layer defines the nodes' channel use, whether it is time division-based or CSMA-based. Following security features need to be considered at this layer:

- Fake node detection and mitigation: Protocols used at this layer should be resistant to fake nodes and identification of a fake node should be a part of these protocols. There should be an authentication mechanism as in [33, 34]. Moreover, mitigation at this level can stop many routing layer attacks.
- Secure and efficient MAC layer: Security is the best when it is implemented at the lower layers so a secure and efficient MAC layer protocol can save us from many upper layer attacks [6].
- Immune to DoS/Jamming attacks and other wireless technologies coexistence [30]: DoS and jamming attacks are the most common at this layer. A high gain noise transceiver can disrupt the communication of all the nodes and thus result in a total system failure.
- Monitoring and eavesdropping on patient vital signs: Monitoring is embedded in eHealthcare systems so solutions proposed at this layer should be aware of eavesdropping and mitigate those sources to avoid the privacy violations of patient data [14].

- Threats to information when in transit: security should be enforced in both modes, whether data is residing on the node and whether it is traveling in the network [32].

12.5 Securing Cyber-Physical Healthcare Networks

The current development of eHealthcare systems has gradually evolved from simple WBANs to Cyber-Physical Systems (CPS) owing to the recent advances in medical sensors, wireless sensor networks, and Cloud computing. CPS leverages sensing, processing and networking technologies to host computationaly expensive personalized healthcare applications, which make intelligent decision based on massive patient data. A typical cyber-physical healthcare system includes not only the components listed in Sect. 12.3 but also a high-capacity Cloud-based data center and analytical system.

As data storage and decision making are moved away from WBANs to Cloud, network security becomes vitally important. Securing only WBANs is far less than enough to prevent a cyber-physical healthcare from being compromised. The network segments formed with data sinks/gateways and Cloud are often the targets of attacks. Compared to hacking individual heterogonous sensing devices in WBANs, compromising the network segments between data sinks/gateways and Cloud is more lucrative, which results in higher information gain as patient data are aggregated and transmitted across the networks to Cloud.

Data and system security deserve top priority in this mission and time critical CPS. Confidentiality, integrity, freshness, and availability of patient data need to be guaranteed [35] as the reasons that (1) the privacy of patients should not be violated from legal and ethical perspectives, and (2) the correctness and timelessness of patient data are vital to promptly accurate decision making, especially in life-threatening cases.

Apart from the security and privacy of patient data, the confidentiality of patient identities and their clinic wearables is equally critical in the context of cyber-physical healthcare [36]. To prevent illegal/malicious devices gaining access to cyber-physical healthcare systems, entity authentication needs to be in place. Mutual authentication between wearables and networks has to be enforced.

Moreover, the availability of the network and decision making services should be under protection too. It will be life-threatening if they remain not accessible for just a few minutes in the case of an emergency. The impact will be more severe if the entire network comprised of multi-hypervisors is struck down by a massive attack. Hence, protecting systems from DoS/DDoS attacks is equally important [36]. Several common network attacks [37], which target the network layer of general-purpose computer networks rather than that of WBANs, are summarized as follows.

- Eavesdropping: An adversary, having access to data paths in a network, sniff or interpret the unsecured, or "cleartext" traffic.
- Data modification: An adversary modifies the data in his intercepted packets.
- IP address spoofing: An adversary constructs IP packets with forgery valid source IP addresses to hide the sender's real identity.
- Man-in-the-Middle attack: An adversary, having access to the data path of the communication between two network users, actively monitors, intercepts, and manipulates the communication without being known by the victims.
- Application-lLayer attack: The adversary exploits the vulnerabilities of applications to gain control of the applications and even the host machines or the connected networks.
- Denial-of-Service attack: The attacks attempt to force victims out of service by imposing intensive computation tasks or huge amount of useless packets.

12.6 Healthcare Cloud Security

Cloud Service Providers (CSP) are offering services that in large organizations and enterprises were previously delivered only on-premises. This introduced completely new challenges that potential CSP customers have to take care of. Major security organizations offer tough security standards that CSP have to comply with and standards that customers from governmental, financial, and public sectors have to implement [38]. Security standards compliance, however, is a regulatory form of information security practice not a safeguard that can actually protect the data.

To compete with new challenges many data protection services that were previously only delivered within strict security boundaries are offered as a cloud service. Some providers took additional security countermeasures, i.e., Microsoft enables on-premises Hardware Security Module (HSM) support [39] for its flag cloud-based Information Rights Management (IRM) product MS Rights Management Services (RMS) Online.

CSP or online data sharing services can protect data at rest using database encryption. Recently, Microsoft researchers published results around a new efficient homomorphic encryption that might be applicable for medical data [40] that should be processed in a secure manner without divulging underlying information. However, just a few months earlier Microsoft researchers demonstrated that database CryptDB encryption, previously acknowledged as a secure data protection technique can be broken with a single trick [41]. It has been shown that every cryptographic scheme currently believed to be secure could be broken with an emerging quantum technology [42], which has been hanging as sword of Damocles over the Cloud computing for a decade. Another threat can be directly related to Big data, which shows that machine learning and business intelligence as a service is a way to efficiently process large amounts of anonymized or encrypted personal data. Illegitimate data analysis applied on a large scale could have potentially a serious social impact [43].

With regards to frameworks for Cloud data sharing, data hosted by one cloud service provider cannot be securely transferred outside of a single CSP security boundary. Such a migration would require either data to be re-encrypted before migration or cloud providers would have to exchange cryptographic master keys. Cloud data hosting very often is based on storing data by homogeneous application in a public Internet space, what bends initial cloud service principals. Theoretically, cloud provider should offer a transparent service that could be dynamically transferred or seized by other cloud service provider without loss of actual service quality and data availability [44].

Furthermore, in [45], it is stated that "a single cloud is far more vulnerable to failure of service unavailability and malicious insiders and due to this reason it is less popular in healthcare, as medical healthcare systems are concerned about its security. From this notion of security concern an advanced model has emerged; multicloud also known to be Cloud-of-Clouds". Future research directions in securing IoT-Cloud-based SCADA systems are the managmenet, security, real-time data handling, cross-layer collaborations, application development migration of CPSs and the impact on existing approaches, sustainable management, engineering and development tools, sharing and management of data lifecycle, and data science that are illustrated [46].

12.7 Shaping the Future of Healthcare with 5G

The Fifth Generation (5G) networks are now at the heart of the development of future mobile telecommunication, and fully commercial ones are expected to be rolled out until 2020 [47]. 5G will be characterized by high broadband speeds, reliability, scalability, and intelligent networks [48]. Numerous wireless access technologies, including WiFi, LPWA, 4G, and millimeter wave, will be enclosed in 5G [49]. Rather than an upgrade of mobile network technologies in the sense of a Long Term Evolution (LTE), 5G represents a quantum leap from mobile networking to new networking/computing paradigm. It combines cloud infrastructure, Virtualized Network Functions (VNF), "intelligent edge services, and a distributed computing model that derives insights from the data generated by billions of devices" [50].

With its high-speed connectivity and mega data transmission capabilities, the 5G networks serve a new means to deliver healthcare including imaging, data analytics, diagnostics, and treatment at affordable prices. Patients can gain access to doctors worldwide through 5G networks for multimedia medical consultation which not only lowers medical cost but also increases accessibility to medical resources. Besides, instead of expensive in-patient hospital care, patients will be monitored remotely by smart algorithms through clinical wearables [51]. Medical data, such as body temperature, blood pressure, heart rate, respiratory rate, physical activity log

and medication adherence, will be transmitted to healthcare systems for analysis. These multisource medical data contribute more precise analytics and raise early warnings that help medical practitioners detect potential problems and provide proactive medical treatments to patients. However, there is absolute clarity amongst European governments and the European Commission that health care data are typically owned by the patients. Personal data may not even be stored outside the European Union against the wish of an individual according to European legislation as clearly demonstrated through the ruling of the Court of Justice of the European Union on "Safe Harboring" [52].

In spite of showing great potential to host Health 4.0 [53], 5G introduces challenges to the development of eHealthcare applications. In particular, one of its core technologies (i.e., network virtualization) poses new security requirements that cannot be effectively addressed with conventional security solutions. This requires network security personnel to have a thoughtful rethink of their strategy. To start up a discussion on the topic, several critical security issues with virtualization are introduced in the following section.

12.7.1 Security Challenges with Virtualization

5G is featured as smart networks that facilitate intelligent traffic routing and prioritize data traffic with automatic decision making. Network Function Virtualization (NFV) and Software Defined Networking (SDN) act as building blocks toward intelligent 5G networks. They enhance the capability of flexible computing resource allocation for real-time data aggregation and analytics. This, therefore, helps users gain a better insight into data and optimize healthcare applications accordingly.

NFV leverages virtualization technologies to decouple network functions from proprietary hardware [54]. To accelerate service provisioning and allow for new flexibilities in operating and managing mobile networks, network functions are implemented in software packages and deployed on high-capacity general-purpose computing platforms within the IT environments of service providers rather than dedicated proprietary hardware [55].

Based on the same technology with a different focus, SDN separates the control and forwarding plane of a network. SDN renders dynamic reconfiguration of network settings, including network function characteristics and behaviors, as well as real-time changes of a network topology [56]. Furthermore, SDN supplies a global view of an elastic decentralized network for efficient coordination of network services [57]. SDN allows businesses to tune their network bandwidth on the fly.

In CPS healthcare applications, both patients and healthcare providers can benefit from SDN. Patients, on the one hand, will be able to control access to their data even though these data will be stored in databases distributed across networks operated by different organizations [57]. Individual healthcare providing

organizations, on the other hand, will be allowed to perform allocation of "isolated" virtualized networks on a high level in order to prevent interference from third parties [57].

(D) **Security Issues**

However, new technologies always raise new challenges on security. NFV and SDN are not exceptions. The vulnerabilities of their underlying virtualization technologies result in undesirable security loopholes in CPS eHealthcare applications. There are five key security issues with NFV and SDN, which could lead to compromise of 5G CPS eHealthcare applications. They should be given proper consideration in design and carefully addressed during implementation.

- Hypervisor vulnerabilities: A system can hardly be secured with a vulnerable infrastructure. 39 critical vulnerabilities of hypervisors were recorded by the National Vulnerability Database (NVD) between January 2012 and June 2015 [58]. These vulnerabilities allow an adversary to directly compromise a hypervisor and to gain access to a less secure Virtual Machine (VM). Such that the attacker possibly takes advantage to manipulate SDN controllers that are not properly secured [59].
- SDN vulnerabilities: A conceptual SDN architecture consists of application, controllers, and networking devices. The vulnerabilities in these three SDN components could be exploited by adversaries to compromise the entire system. The adversaries might seize control of a SDN system, impersonate a host, cause network traffic congestion through diverting network flows to a heavy loaded network device, or intercept and manipulate traffic [59].
- Improper network isolation: Not all Cloud computing architectures properly isolate their data network from control network. An adversary could compromise the control plane of a shared SDN architecture through its fellow data network. Underlying data network traffic routes would be manipulated following a successful attempt, and then malicious traffic could escape from monitoring of NFV security devices [56].
- Security service insertion: Conventional security schemes are not originally designed to be deployed with NFV, where logical functions and physical hardware are separated to accelerate service provisioning. So, there is often no simple insertion point for a conventional security scheme to be deployed logically and physically inline in a hypervisor with NFV [56].
- Stateful inspection: NFV promises elastic networks. Asymmetric traffic flows created by on-demand alteration of virtual network functions may add complexity to stateful security control, in which every packet needs to be seen in order to provide access control [56].

(E) **Security Requirements**

The elastic nature of 5G networks poses new security requirements to CPS eHealthcare applications. Network function virtualization, a unique characteristic of 5G networks, enables flexible and cost-saving deployment of services and prompt

adjustment to networking. Virtualization, however, increases the complexity of implementation of security. Thus, the security of all parties should be given thoughtful consideration in this setting. Several requirements as follows are recommended to be addressed too.

- Dynamic security policies: Static security policies are not applicable in virtualized network environments, where virtualized services will be moved around to meet technical or business requirements on the fly. It is, therefore, critical to provide a solution to set up dynamic security policies self-adaptive to the relocation of virtual workloads [60].
- Impact on performance: The impact of a security scheme on the performance of an eHealthcare application is of importance. A feasible security scheme should protect an application from being compromised while ensuring that its performance remains meeting requirements [60].
- Comprehensive Protection: Standalone security schemes are incompatible to virtualized networks. It is impossible for them working alone to gain a clear vision on what are happening in the networks due to the dynamic nature of virtualized environments [53]. It would be wise to consider collaborative schemes with self-adaptive features.
- Fully virtualized network security solutions: Instead of deploying physical, hardware-based network security products on 5G networks, fully virtualized security solutions are viable and easier to cope with the changes of the virtualized networks.
- Elastic network boundaries: The network boundaries in NFV architecture are not as clear as those in physical one. These unclear boundaries complicate security matters [56]. VLANs are traditionally considered insecure so that there is no clear boundary in NFV architecture protecting services from being accessed by unauthorized third parties.
- Network segmentation: To be fault-tolerant, a large network is suggested to be divided into smaller segments. When one or more network segments start getting congested or becoming unavailable, the network administrator can use the SDN controller to route traffic to other healthy segments to maintain the vitality of the network.

12.7.2 Security Enhancement with Virtualization

Although NFV and SDN raise security challenges, they in the meanwhile offer numerous benefits in deployment of security services as well as potential enhancement to network security.

(A) **Benefits to deployment of security services**

- Reduced costs: Deploying virtualized security services on general-purpose computing platforms with NFV significantly reduces management costs.

SDN provides on-demand configuration for the data forwarding plane [56]. This saves service providers paying costly bills for changing physical network topology.

- On-demand deployment: NFV promises on-demand deployment of security services and scaling of their functional capabilities [61].

(B) **Enhancement to network security**

- Global and real-time view: The centralized management architecture of SDN renders a real-time global view of a distributed network, including topology, routes, and traffic statistics [53]. This capability is particularly useful for detecting and responding to cooperative attacks, such as DoS/DDoS attacks.
- Dynamic threat response: NFV together with SDN provide dynamic real-time response to threats [62]. SDN can be utilized to rearrange service chains or traffic route to optimize the performance of virtualized security services.

12.8 Conclusion

Health 4.0 will play a key role in future healthcare systems. These digitally connected healthcare systems will provide better quality personalized medical services. However, their security issues should be thoughtful addressed to ensure system reliability and user privacy. This is particularly important when 5G networks come into play its role as the network backbone to connect the different components of cyber-physical healthcare systems.

Therefore, proper security solutions are required to secure the entire systems, including the core components and their connected networks. The aforementioned security requirements are recommended to be taken into account when drawing security strategies and making choices of security schemes. Moreover, attention should be given to take advantages of NFV and SDN in deployment of these schemes.

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