Bridging the Inferential Gaps in Healthcare

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Abstract. Inferential gaps are the combined effect of reading-to-cognition gaps as well as the knowledge-to-action gaps. Misdiagnoses, medical errors, prescription errors, surgical errors, under-treatments, over-treatments, unnecessary lab tests, etc. – are all caused by inferential gaps. Late diagnosis of cancer is also due to the inferential gaps at the primary care. Even the medical climate crisis caused by misuse, underuse, or overuse of antibiotics are the result of serious inferential gaps. Electronic health records (EHR) had some success in mitigating the wrong site, wrong side, wrong procedure, wrong person (WSWP) errors, and the general medical errors; however, these errors continue to be quite significant. In the last few decades the disease demography has changed from quick onset infectious diseases to slow onset non-communicable diseases (NCD). This changed the healthcare sector in terms of both training and practice. In 2020 the COVID-19 pandemic disrupted the entire healthcare system further with change in focus from NCD back to quick onset infectious disease. During COVID-19 pandemic misinformation in social media increased. In addition, COVID-19 made virtual healthcare a preferred mode of patient-physician encounter. Virtual healthcare requires higher level of audit, accuracy, and technology reliance. All these events in medical practice widened the inferential gaps further. In this position paper, we propose an architecture of digital health combined with artificial intelligence that can mitigate these challenges and increase patient safety in the post-COVID healthcare delivery. We propose this architecture in conjunction with *diseasomics*, *patholomics*, *resistomics*, *oncolomics*, *allergomics*, and *drugomics* machine interpretable knowledge graphs that will minimize the inferential gaps. Unless we pay our attention to this critical issue immediately, medical ecosystem crisis that includes medical errors, caregiver shortage, misinformation, and the inferential gaps will become the second, if not the first leading cause of death by 2050.

Keywords: Inferential gaps · Reading-to-cognition gap · Knowledge-to-action gap · Digital health · Knowledge graph · AI · IoT · Patient temporal digital twin · Patient spatial digital twin · Patient molecular digital twin · Physician digital twin · Digital triplet · Healthcare science · Medical ecosystem crisis

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1 Introduction

The inferential gap is the gap between the accurate true knowledge and the consumed or used knowledge. Inferential gaps may be the reading-to-cognition gaps at the cognition level or the knowledge-to-action gaps at the decision making level. Reading-to-cognition gap is the distance between interpreted knowledge by a caregiver at the cognition level compared to the accurate error-free knowledge. Knowledge-to-action gap is the gap between the knowledge applied by a caregiver at a point-of-care and the accurate knowledge required to make an error-free decision.

In the context of healthcare, knowledge-to-action gap can be defined as the distance between knowledge required for error-free medical decision and erroneous knowledge used by a physician or a nurse during patient encounter. In contrast, reading-to-cognition gap refers to the gap between the true error-free knowledge and the way it is presented or understood by a caregiver. This can be attributed to underdeveloped or incomplete evidence, incomplete design of system and processes of care, as well as the inability to accommodate every patient's diverse demand and needs. Inferential gaps are measured by the quantification of medical errors, the adverse events, never events, patient injury, and medical ecosystem change.

Misdiagnoses, medical errors, prescription error, surgical errors, under-treatment, over-treatment, unnecessary pathological test or unnecessary radiology orders, etc. – are all caused by the inferential gaps during a patient-physician encounter. Even the late diagnosis of cancer is caused by inferential gaps at the primary care. Antibiotic resistance crisis is caused by inferential gaps as well.

A physician is required to make a perfect decision with imperfect information. During a clinical decision, a professional is required to "fill in" where they lack knowledge or evidence. This is also the case in empirical decision making under uncertainty and missing or unknown knowledge. The breadth of the inferential gap varies according to the experience of the physician, the availability of the medical knowledge and its relevance to clinical decision making. It also depends on the active memory and the recall capability of the caregiver. There is another dimension of inferential gap due to the time lag between clinical research outcome and its use at the point-of-care which is estimated to be 17 years [1].

A landmark report "To Err Is Human: Building a Safer Health System" released in November 1999 by the U.S. Institute of Medicine (IOM) resulted in increased awareness of U.S. medical errors [2]. The report was based upon two large analyses of multiple studies; one conducted in Colorado and Utah and the other in New York, by a variety of organizations. The report concluded that between 44,000 to 98,000 people die each year as a result of preventable medical errors. In Colorado and Utah hospitals, 6.6% of adverse events led to death, as compared to 13.6% in New York hospitals. In both of these studies, over half of these adverse events were preventable. For comparison, fewer than 50,000 people died of Alzheimer's disease and 17,000 died of illicit drug use in the same year. As a result of the report more emphasis was put on patient safety such that President Bill Clinton signed the Healthcare Research and Quality Act of 1999.

A 2016 study in the US placed the yearly death rate due to medical error in the U.S. alone at 251,454. This study found that medical error was the third leading cause of deaths in the US only after heart attack and cancer [3]. A 2019 meta-analysis identified 12,415

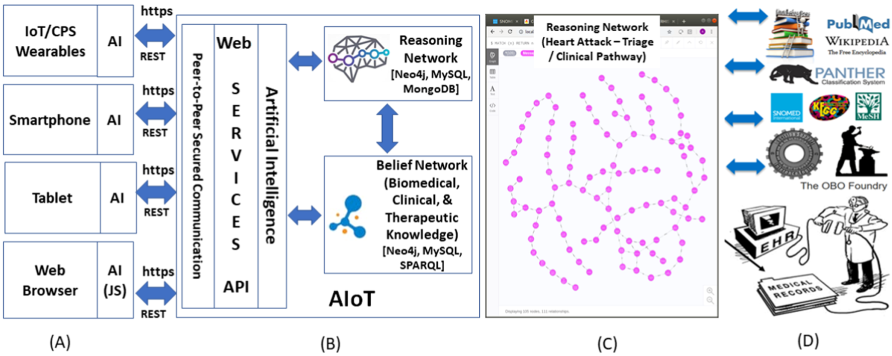

Fig. 1. No-error architecture that will eliminate the inferential gaps in Healthcare

scientific publications related to medical errors and outlined the impactful themes of errors related to drugs/medications, medicinal information technology, critical/intensive care units, children, and mental condition (e.g., burnout, depression) of caregiver. The study concluded that the high prevalence of medical errors revealed from the existing literature indicates the criticality of future work invested in preventive approaches [4]. Though all these reports were related to US healthcare delivery -- it does not imply that inferential gaps or medical errors are absent outside of the US.

In the last few decades, the disease demography changed across the world from infectious disease to non-communicable diseases (NCD). NCDs kill 41 million people each year, equivalent to 71% of all deaths globally, out of which 77% deaths are in low- and middle-income countries. Each year, more than 15 million people die from NCD between the ages of 30 and 69 years; 85% of these “premature” deaths occur in low- and middle-income countries. Cardiovascular diseases account for most NCD deaths which is 17.9 million people annually, followed by cancers (9.3 million), respiratory diseases (4.1 million), and diabetes (1.5 million). These four groups of diseases account for over 80% of all premature NCD deaths [5].

Infectious diseases are quick onset diseases whereas NCD are slow onset disease with high interdependence of conditions. Low and quick onset infectious diseases need different processes of medical management compared to NCD. The shift from infectious to NCD was mainly due to mass vaccination and the discovery of the miracle drug penicillin and other antibiotics that reduced morbidity and mortality due to viral and bacterial infections respectively. However, indiscriminate abuse of antibiotics caused antibiotic resistance in the bacteria and made most of the antibiotics useless. Antibiotic abuse is an example of serious inferential gap, which is causing antibiotic resistance and likely to overpass the mortality of cancer by 2050 making inferential gap the second leading cause of deaths globally. Antibiotic resistance is called medical climate crisis that is estimated to cost the world up to 100 trillion US Dollars by 2050 [6].

The COVID-19 pandemic has been a wakeup-call for the healthcare sector across the globe. It has disrupted the whole medical ecosystem and the entire healthcare system starting from patientcare to medical education. Healthcare systems, be it in a high-income country or a low-income country is in a critical state and needs urgent attention.

COVID-19 has changed the focus from NCD back to infectious disease, though the mortality and morbidity of COVID-19 was mostly attributed to the comorbidity of NCD. The indiscriminate use of antibiotic drugs during COVID-19 pandemic has made the medical climate crisis even worse [7].

Misinformation is false, misleading, incomplete, or inaccurate information, knowledge, or data. Misinformation is communicated regardless of an intention to deceive. Misinformation increases the inferential gaps be it reading-to-cognition or knowledge-to-action. The popularity of social media increased the spread and belief on misinformation during COVID-19.

COVID-19 also made virtual healthcare to become mainstream [8]. However, the chances of error in virtual healthcare are higher and need higher level of accuracy and audit. Virtual healthcare in many setups use telephone consultation and video consultation without any medical records. Virtual healthcare also makes the medical data vulnerable to ransomware and security attacks.

Cancer disease progression can be divided into three phases, namely, (1) pre-cancerous or premalignancy, (2) malignancy or early-stage cancer, and (3) metastasis. The pre-cancerous and the early-stage cancers show some signs and symptoms that are often misdiagnosed at the primary care due to inferential gaps. This reading-to-cognition and knowledge-to-action gap prevents the timely referral to the specialized care. Cancer mortality and morbidity can be reduced substantially if phase-1 and phase-2 diagnosis are made efficient with oncology knowledge available at the primary care.

Fig. 2. Differential diagnosis at the point-of-care by No-error technology

In this position paper we discuss the modalities of how the inferential gaps in healthcare can be eliminated in the post-COVID era and in virtual healthcare. Patient safety will be ensured with the use of No-error architecture as shown in Fig. 1. In this figure, (A) shows various user interfaces (smartphone, Web) for nurses, physicians, surgeons, and wearables, IoT, CPS (Cyber Physical Systems) devices for caregivers and patients, etc., (B) shows the basic architecture of secured peer-to-peer communication with IoT, AI and knowledge graphs, (C) shows the rule-based reasoning engine, and (D) shows the knowledge sources that include actionable and machine interpretable knowledge networks. To realize No-error here we propose healthcare science that will include digital health, digital twins, digital triplets, machine interpretable actionable knowledge, and the use of artificial intelligence (AI).

2 Digital Health

Digital health is a multi-disciplinary domain involving many stakeholders with a wide range of expertise in healthcare, engineering, biology, medicine, chemistry, social sciences, public health, health economics, and regulatory affairs. Digital health includes software, hardware, telemedicine, wearable devices, augmented reality, and virtual reality. Digital health relates to using data science, information science, telecommunication, and information technology to remove all hurdles of healthcare.

EHR (Electronic Health Records) is at the center of digital health transformation. EHR systems are made up of the electronic patient chart and typically include functionality for computerized provider order entry (CPOE), medical notes, laboratory, pharmacy, imaging, reporting, and medical device interfaces. Ideally, the system creates a seamless, legible, comprehensive, and enduring record of a patient's medical history and treatment or a digital twin of the patient. EHRs have been widely adopted for both inpatient and outpatient settings that reduced the medical errors and increased the patient safety. The EHR is currently underutilized – it is used only as a repository of medical encounter records. However, it is required to mature as a knowledge source.

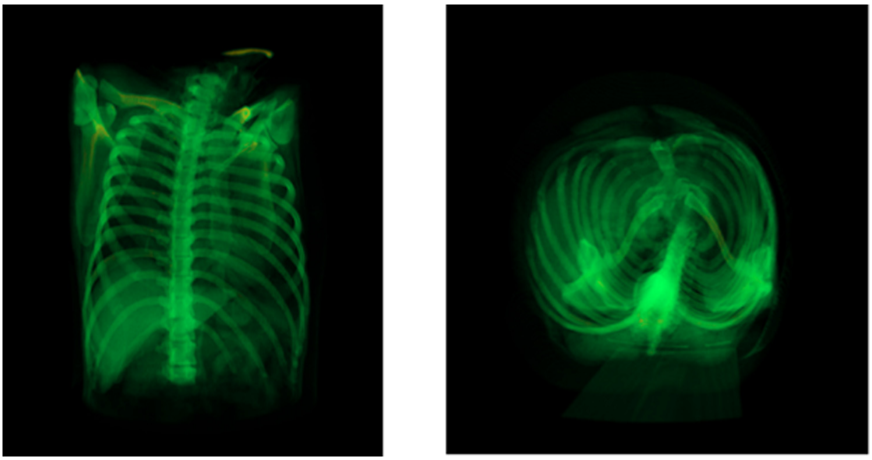

Fig. 3. The volume rendering of chest CT image using Computer Vision and WebGL as part of healthcare science.

A study conducted from 209 primary care practices between 2006–2010 showed that, within all domains, EHR settings showed significantly higher rates of having workflows, policies and practices that promote patient safety compered to paper record settings. While these results were expected in the area of medication management, EHR use was also associated with reduction of inferential gaps in areas that had no prior expectation of association [9]. Moreover, EHR increased the efficiency in insurance claims settlements. In a review of EHR safety and usability, researchers found that the switch from paper records to EHRs led to decreases in medication errors, improved guideline adherence, and enhanced safety attitudes and job satisfaction among physicians. There are indications to suggest that WSWP errors are reduced through the use of EHR as well. However, the transition to this new way of recording and communicating medical information has also introduced new possibilities of errors and other unanticipated consequences that can present safety risks [10]. The scale down version of EHR is personal health record (PHR) which is suitable for medical records storage and retrievals in small clinics or individual family doctors who cannot offer investments in large EHR.

Figure 2 shows a knowledge-driven digital health example. This use case uses knowledge graph and AI as presented in Fig. 1. The upper part of this Fig. 2 shows elimination of reading-to-cognition gaps, whereas the lower half shows elimination of knowledge-to-action gaps. In the upper half, the clinician enters the signs and symptoms as described by the patient in the 'Chief Complaints' section of the screen. In this example, symptoms are "fever", "night sweat", "coughing blood". The human understandable symptoms are converted into machine interpretable UMLS, ICD10, and SNOMED codes using NLP and MeteMap2020 [11]. The machine interpretable codes are C0015967-Fever - (50177009/_), C0424755-Fever - (248427009/_), C0028081-Night Sweat - (42984000/R61), C0019079-Coughing Blood - (66857006/P26.9,R04.2). These three symptoms co-occur in three diseases namely, DOID:552 (pneumonia: SNOMEDCT:266391003 UMLS:C0032285 NCIT:C3333), DOID:117 (heart cancer: SNOMEDCT:126730001;SNOMEDCT:93825008 ICD10CM:C38.0, UMLS:C0018809;UMLS:C0153500, NCIT:C3081;NCIT:C3548), and DOID:399 (tuberculosis: SNOMEDCT:15202009, UMLS:C0041295). It may be noted that both input and output have been converted from human understandable English language to machine interpretable codes. This ensures no-error documentation as well.

3 Digital Twin

A digital twin is the accurate digital representation of an object in computers. The first practical definition of digital twin originated from NASA in an attempt to improve physical model simulation of spacecraft in 2010. One of the basic use cases of digital twin is simulation of various states of the object. In the context of healthcare there are two different types of digital twins, namely, (1) the patient digital twin, and (2) the physician digital twin.

The patient digital twin consists of the complete physical, physiological, molecular, and disease lifecycle data of a patient (or person) constructed from EHR, pathological test data, radiology images, medication history, genetic test, behavior, and lifestyle related data. The patient digital twin can be further divided into patient spatial digital twins, patient temporal digital twin, and patient molecular digital twin. The physician digital twin is the physicians' brain or mind that houses the actionable medical knowledge.

The physician digital twin will be constructed from the literature, textbooks, biomedical ontologies, clinical studies, research outcomes, protocols, and the EHR (Fig. 1).

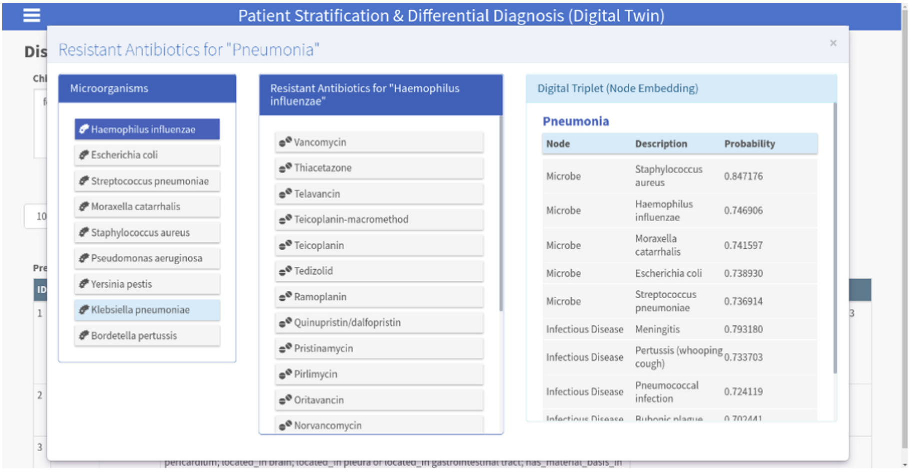

Fig. 4. The 2AI&7D use case to counter the Medical Climate Crisis.

3.1 Patient Digital Twin

The patient digital twin is the digital equivalent of the patient or a patient population. Patient digital twin is further broken down into (1) Patient spatial digital twin, (2) Patient temporal digital twin, and (3) Patient molecular digital twin. These will have all the spatial, temporal, and molecular (genomic) records and history of the patient's life combined with the environmental factors related to the individual's health.

Patient spatial digital twins are constructed from patient's medical records, diagnostic records, medical images, and medication records at any point-in-time. A point-in-time will include a single episode of a disease incidence. A single episode of disease incidence can combine multiple patient-physician interactions over a short time duration. Also, the lifestyle data like exercise, smoking, alcohol, regular health indicators captured by wearables are added as the environmental data. The challenge with this data is that these data may contain unstructured data like medical notes in text, handwritten notes, voice as well as images of ECG, X-rays, or CT/MRI etc. These data are human understandable and cannot be used for simulation. However, EHR combined with AI/ML/DL will convert the human understandable data into machine interpretable data as shown in Fig. 2, that can be used for simulation. Figure 3 shows the digital twin of a chest CT scan of a patient. This is the volume rendering of the 169 CT frames using WebGL. Some impressions are visible in this digital twin which were not visible in the naked eye and the radiologist missed when a normal DICOM Viewer was used.

Patient temporal digital twin is constructed by combining multiple episodes of disease incidence of a patient over a period-of-time. This will include the trajectory of different diseases for a person over a long period of time. This digital twin helps understand the disease and health patterns as a person grows older.

Patient molecular digital twin is the genomic data of a patient or a person. This digital twin may be of the whole genome or the exome data. It may be clinical exome or even targeted genetic test data as well. This will include the genetic mutations of a patient and their disease associations. DNA dosages is an example of patient molecular digital twin [12]. The DNA dosages use stochiometric matrix over genomic (exome) data to simulate the cancer states. This principle can be used for early detection of cancer and reduce the reading-to-cognition gaps and knowledge-to-action gaps at the primary care.

3.2 Physician Digital Twin

A physician digital twin is the digital equivalent of the physician's brain, memory, and the mind which includes the medical knowledge and the reasoning logic (Fig. 1 (C) and Fig. 1 (D)). There are two types of physician digital twins, namely (1) Physician belief digital twin, and (2) Physician reasoning digital twin. The physician belief digital twin is an acyclic directed graph whereas, the physician reasoning digital twin is a cyclic directed weighted graph,

The physician belief digital twin will include all the universal medical knowledge that is essential at any point-of-care – be it primary, secondary, tertiary, or specialized care. Universal medical knowledge includes biomedical ontologies combined with supplementary knowledge from PubMed, textbooks, Wikipedia, clinical research, biomedical networks, and other medical literature.

An ontology is a formal description of knowledge as a set of concepts within a domain and the relationships between them. Open Biological and Biomedical Ontologies at the OBO Foundry contains about 200 ontologies (http://www.obofoundry.org/). These ontologies are manually curated by experts with the best possible knowledge available as of date. The greatest advantage of ontologies is that they are peer-reviewed and eliminate the reading-to-cognition gaps altogether.

Biological and biomedical ontologies are unipartite directed graphs like DOID (Disease Ontology) or GO (Gene Ontology). However, there are few bipartite networks as well like the DisGeNET (Disease gene Network) etc. There are some multipartite networks as well like NCIt, or SNOMED CT. These biomedical ontologies or networks will become knowledge when multiple ontologies and networks are integrated semantically and thematically into a multipartite properties graph. When this multipartite graph is stored in a properties graph database and accessible through application programming interface (API) over Internet, this experts' knowledge becomes knowledge graph. Figure 4 shows the physician digital twin that includes right disease-causing agent, and right drug for antibiotic stewardship.

The physician reasoning digital twin is the reasoning logic used by the physician to arrive at a medical or surgical decision at the point-of-care. It depends on factors that is not always deterministic and cannot be defined simply by if-then-else logic.

4 Digital Triplet

Digital triplet is the third sibling of the digital twins with added intelligence. Digital triplets are constructed from the knowledge graphs using vector embedding. Vector embedding helps construct a lower dimension knowledge space where the structure of the original knowledge is retained. This means that the distance between objects in the embedded space retains the similarity of the original space. Vector embedding of knowledge graph can be done through graph neural network (GNN) or node2vec. Digital triplets help predict missing links and identify labels. The digital triplet will address part of the challenges related to missing and unknown knowledge [13]. Figure 4 shows the digital triplet of pneumonia.

5 Artificial Intelligence and Related Technologies

The patient digital twin will grow as and when more data is generated. EHR data is converted into machine interpretable data through AI. Lifestyle data and health data captured by wearables and sensors will be filtered through AI models. In healthcare all components of AI will be used for the elimination of knowledge-to-action gaps and ensure patient safety. Following are the AI components used to reduce inferential gaps:

1. **Speech Recognition:** During the patient encounter, speech recognition will help capture the conversation and store the interaction in machine readable text during virtual patient-physician encounter.
2. **Speech Synthesis:** Speech synthesis is used for text to speech conversion. In virtual healthcare and home-care this will play a significant role.
3. **Optical Character Recognition (OCR):** Some prescriptions or test reports will be available as scanned image; OCR will be used to extract the content and convert in machine readable format.
4. **Natural Language Processing:** Natural language processing will be used to extract medical terms from human understandable text. Medical notes are human understandable; however, for virtual healthcare the human understandable medical notes will be converted into machine interpretable UMLS, ICD, NCI, and SNOMED codes through the use of NLP (Fig. 2).
5. **Deep Learning:** Deep learning is used for cognitive function of images and other unstructured medical contents. Medical image classification and computer assisted diagnosis (CAD) will increase the radiologists' efficiency.
6. **Image Segmentation:** Image segmentation is very useful for histopathology and medical images. Virtual reality and augmented reality will benefit from these techniques.
7. **Computer Vision/WebGL:** This is used for medical images. This is used for preprocessing of medical images like X-ray, ECG, CT etc. This will also be used for 3D image rendering as shown in Fig. 3.
8. **Generative Adversarial Network:** Generative adversarial networks (GANs) consist of a generative network and a discriminative network. These are very useful for construction of high quality synthetic medical images. Generative networks will be very useful in medical training.

9. **Bluetooth and IoT:** Bluetooth Low Energy (BLE) protocol is used for medical device or IoT devices integration to smartphone/edge computer communication [14].
10. **Smartphone Sensors:** Realtime data from inbuilt sensors such as accelerometer, gyroscope, GPS can be used to detect occurrence of fall due to stroke and send location to emergency contacts. Smartphone sensors are used for anemia [15] and breast cancer screening [16].
11. **Face & Facial Gesture Recognition:** Useful in mental healthcare sector for emotion analysis. Facial landmarks and cues such as lip biting or eye flipping can help to interpret patients metal condition for instance stress or anxiety.
12. **WebRTC and WoT:** Web of Things (WoT) and WebRTC will be used for secured realtime data exchange between two endpoints [14].

AI driven digital health care is essential for a smart healthcare, smart hospital, and precision health that will optimize the clinical process and the time taken by the physician to provide the best possible patient care. Digital health care combined with AI will reduce disease burden and increase the health equity by offering the right care at the right time at the right price for everyone from anywhere at any point-of-care.

6 Knowledge Graphs

Human knowledge allows people to think productively in various domains. The ways experts and novices acquire knowledge are different. This is due to the reading-to-cognition function of human mind. Existing knowledge allows experts to think and generate new knowledge. Experts have acquired extensive knowledge that affects their cognitive skills – what they notice (read) and how they organize, represent, and interpret information in their environment. This, in turn, affects their abilities to remember, reason, and solve problems and infer [17].

In AI we save knowledge in knowledge graphs. Knowledge graph is a knowledge base that uses a graph-structured topology like synapses and neurons to represent knowledge in computers as concepts and their interrelationships. Knowledge graphs can be stored in any database; however, properties graph databases are most suitable for this function.

Knowledge graphs equipped with the latest and accurate medical knowledge accessible by machines can eliminate both reading-to-cognition gaps and knowledge-to-actions gaps. Following are examples of various machine interpretable actionable knowledge.

1. **Diseasomics** – Diseasomics contains knowledge of diseases and their associations with symptoms, genetic associations, and genetic variations (mutations). Diseasomics knowledge graph is constructed through the semantic integration of disease ontology, symptoms of diseases, ICD10, SNOMED, DisGeNET, PharmGKB. Diseasomics also includes the spatial and temporal comorbidity knowledge of diseases. The spatial and temporal knowledge of a disease is extracted from millions of EHR data and thematically integrated with the ontology knowledge [18, 19]. Figure 2 shows how the diseasomics knowledge helps perform the differential diagnosis.

Fig. 5. Integration of the patient temporal digital twin and the physician digital twin in Oncolomics knowledge graph stored in Neo4j properties graph database.

2. **Patholomics** – Patholomics includes the pathology knowledge and its association with diseases [18, 19]. This is constructed from the EHR pathological test data. The biomarkers outside the normal range of a test result namely the Hyper and Hypo markers are used for the construction of this knowledge graph. From a hyper or hypo marker we can determine the disease association.
3. **Resistomics** – Resistomics includes all knowledge related to antibiotic resistance and antibiotic stewardship. It is constructed from EHR data, and knowledge obtained from EUCAST and WHO, and WHOCC [7]. To stop the inferential gaps in antibiotic usage, antibiotic stewardship is proposed. A use case of eliminating the inferential gaps in antibiotic abuse is the 2AI&7D model [7]. 2AI is Artificial Intelligence and Augmented Intelligence. 7D is right Diagnosis, right Disease-causing agent, right Drug, right Dose, right Duration, right Documentation, and De-escalation. Figure 4 sows some interface to the knowledge extracted from 2AI&7d digital twins. The third column in Fig. 4 in the pop-up screen shows the digital triplet for pneumonia.
4. **Oncolomics** – For the early detection of cancer, specialized oncology knowledge must be available at the primary care. Oncolomics includes machine interpretable actionable cancer related knowledge that can be used by any caregiver agnostic to their level of expertise [13]. Figure 5 shows the oncolomics on the Neo4j browser. This knowledge graph uses the computer interpretable ICD-O codes.
5. **Drugomics** – Drugomics includes knowledge about drugs. It includes the drug ontology, drug-bank data, and the drug-drug interactions [20].
6. **Allergomics** -- Allergomics is the knowledge of allergies and their relationships with the allergy causing agents.

7 Conclusion

The Post-COVID healthcare is heading for a crisis. We call this crisis as the Medical Ecosystem Crisis caused by medical errors, caregiver shortage, misinformation, and the inferential gaps. The medical ecosystem crisis is the combined effect of inferential gaps caused by reading-to-cognition and knowledge-to-action gaps causing patient harm. The domain of healthcare is wide and complex with many unknown factors that a physician needs to deal with during the patient-physician encounter. In this position paper, we presented a No-error architecture that provides actionable medical knowledge at the point-of-care 24 × 7. We have also proposed how this knowledge can be used through artificial intelligence to offer the right care at the right time at the right price for everyone from anywhere at any point-of-care.

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