

Frontiers of Artificial Intelligence,
Ethics and Multidisciplinary Applications

Kavita Sharma
Padmavati Manchikanti

Artificial Intelligence in Drug Development

Patenting and Regulatory Aspects

Frontiers of Artificial Intelligence, Ethics and Multidisciplinary Applications

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Artificial Intelligence is now present in numerous spheres of our everyday lives. It is poised to lead new and efficient business models for effective and user-centric services in the private and public sectors. Advances in AI in deep learning, (deep) reinforcement learning, and neuroevolutionary techniques can pave the way forward for artificial general intelligence (AGI). However, the development and use of AI also present challenges. Inherent biases prevalent within data corpora used to train AI and machine learning systems attribute to most of these challenges. In addition, multiple instances have highlighted the need for privacy, fairness, and transparency in AI-powered decision-making. This book series will provide an avenue for researchers, leaders, decision-makers, and policymakers to share research and insights on the forefronts of AI, including its use in an Ethical, Explainable, Privacy-Preserving, Trustworthy, and Sustainable manner.


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The series publishes research monographs, authored works by practitioners and case studies to highlight innovative and best practices, and edited volumes putting together varied perspectives.

Kavita Sharma · Padmavati Manchikanti

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Kavita Sharma 
Rajiv Gandhi School of IP Law
Indian Institute of Technology Kharagpur
Kharagpur, West Bengal, India

Padmavati Manchikanti
Rajiv Gandhi School of IP Law
Indian Institute of Technology Kharagpur
Kharagpur, West Bengal, India

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Preface

Access to medicines and healthcare is essential. Technological advances have assisted doctors and the healthcare system to be able to better diagnose, predict, assess and treat patients in a disease/disorder condition. The enormity of healthcare and practice demands frontline approaches to promote safety and efficacy. New approaches and tools continue to be required to address the challenges of accessibility and affordability in healthcare. The justification provided for the development of tools and services based on new technologies is to improve quality of care and address healthcare costs. Information technology developments have significantly impacted the drug discovery process and development and healthcare documentation and management. Advances in machine learning have helped in understanding causal relationships and correlations. Predictive algorithms in the healthcare have the ability to advance precision medicine. Supervised and unsupervised learning is used in the drug discovery process. The ‘pseudopodic’ growth of artificial intelligence (AI) has been phenomenal. As one of the disruptive technologies of the times, AI’s growth trajectory indicates virtually implementation in all socioeconomic sectors vital for human development. The attribution of ‘citizenship’ to humanoid robots just speaks of the transformative value of AI. International and national discourse continues on the various facets of AI and its impact.

This book is a continuing effort of the research on the analysis of how the twin aspects of intellectual property rights and drug regulation affect industry and society. The aim of the book is to inform the developments and implementation of intellectual property laws, particularly patents and drug regulation. This book is divided into five chapters. In Chap. 1, the evolution of AI/ML applications in drug discovery and development and healthcare is discussed. The growth of individual tools to AI expert systems is discussed in definite time periods to analyse the nature and scope of AI applications. The type of collaborations for development of AI tools is discussed along with the widely used AI platforms in drug discovery and healthcare. Technology-rich businesses consider patents important to restrict competition. The granting of patents creates monopoly rights for companies to either own the patent or create licencing opportunities for the use of the patent. In Chap. 2, the interpretation of patent legislation with respect to AI inventions from the perspective

of eligible subject matter, patentability criteria are discussed. The cross-jurisdictional judicial precedents are analysed. The definitional considerations related to AI, development of guidelines at patent offices and patent prosecution are explained. The analysis of the patenting activity of Indian companies and identification of the challenges based on the survey of the selected companies provide important insights. The analysis of patent family information indicates how companies utilise patenting in several jurisdictions as an important strategy to leverage markets. IP and regulation are both equally important for industry with respect to manufacturing and marketing products. While patent rights are held and are exclusive rights, industry requires clearance under relevant drug regulation to bring AI-based medicines or medical devices. The area of AI-based medical devices has witnessed a tremendous growth, and there are already several such devices used in healthcare. While innovations are rapidly being developed, their deployment is subject to the country regulation. In Chap. 3, the focus is on the analysis of how existing drug regulation retains the flexibility to accommodate the various types of AI-based medical devices. The development of international norms and how they impact country-based regulation, cross-country developments in regulation of these devices in the context of the USA, EU and India and the legislative basis are discussed. Regulation of these devices is necessary as it could affect doctors, patients and consumers alike. The emergence of the approval system is examined from the regulatory developments when initially few devices (software as medical devices or SaMD) were approved to the current times when several of them have not only been approved but are already in use. The analysis of the drug regulatory process from the substantive and procedural aspects indicates to the development of norms and their applicability. All AI-based software may or may not be considered as medical devices. Cross-country comparison of regulations indicates varied levels of application and differences in certain norms. It becomes clear, hence, that there are technical, legal, social and normative aspects. This book does not deal with the liability as well as the data protection regime. There are several approaches for AI policy development from international and national perspectives. These policies provide a platform for engagement of the government, stakeholders and society to discuss implementation, capacity building, standards development, governance and guidance. In examining the emergence and current discussions in relation to AI policies, Chap. 4 provides an account of several international organisations that are framing ethical guidelines for use of AI and governance mechanism for the wide adaptability of AI in multiple sectors. The Indian central and state policies that support healthcare start-ups and companies through various initiatives under different ministries are discussed. The conclusion chapter, Chap. 5, summarises the discussion on how technology leads, intellectual property protection and regulatory changes inform on the path forward. It also discusses what kind of policy and law changes could assist in the development and deployment of AI-based products and improved the trust in their use.

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Kharagpur, India

Padmavati Manchikanti

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About the Authors

Kavita Sharma is currently pursuing her doctoral studies in patenting and regulation related to AI in health care from Rajiv Gandhi School of Intellectual Property Law, Indian Institute of Technology, Kharagpur. She has also completed her LL.M. from the same institute in 2017. She completed her B.A. LL.B. from Dibrugarh University, Assam. She worked as Assistant Professor prior to joining IIT Kharagpur for her Ph.D. studies. She had worked on standard essential patents as a part of her LL.M. dissertation. Her research interests primarily include IP Law. She has presented her research papers in various national and international seminars and conferences. Her articles have been published in renowned journals. She has also gained experience through internships in inter-governmental organizations such as AALCO.

Padmavati Manchikanti is Professor in Rajiv Gandhi School of IP law, Faculty of Interdisciplinary Sciences and Engineering, Indian Institute of Technology Kharagpur. With more than fifteen years teaching and research experience, she specializes in patents. She teaches the subjects of patent law, patent procedure and drafting, biodiversity law, and TK protection among other subjects to undergraduate and master students of law. Her primary area of research includes intellectual property and commercialization of recombinant and herbal drugs and drug regulation, biodiversity law, studies on implementation of IP. Prior to joining IIT Kharagpur, she was Senior Scientist at Monsanto Research Center, Bengaluru, where she coordinated invention disclosure filing. She has many research as well as consultancy projects, from Ministry of Human Resource Development, DST etc. She has been awarded the Microsoft–Young Faculty Scholarship in Intellectual Property. She is Advisor to the IPR Cell, IIT Kharagpur.

Chapter 1

Artificial Intelligence in Drug Development and Healthcare—Nature and Scope



1.1 Introduction

Technology continues to impact human life; from small inventions like needles to as big as space shuttles. As rightly pointed out by the Greek philosopher Heraclitus of Ephesus, ‘change is the only constant in life.’ Technology has shaped and reshaped human life and lifestyles in many ways. The twenty-first century is categorised as the information age with growth of several technologies. The diffusion of several technologies has led to economic and social changes across the globe. Of particular relevance is the convergence of technologies that has led to important developments in science and engineering. The emergence of digital technologies has enabled several advances in terms of processing vast amount of data, improving performance and considerable gains in speed, size and cost. Newer developments in computational methods have led to their utilisation in all spheres of human activity. Truly, the knowledge economy has opened several opportunities. Greater diffusion of innovations and development of markets has been realised with technological trends such as the 5G, 3D printing, genomics, Internet of Things (IoT), robotics, blockchain and so forth. New names of technologies continue to be coined. Digital interventions have blurred local, regional and national borders and expanded the scope of collective work in several areas. Globalisation has connected individuals and societies in an unprecedented manner. Six important areas have been identified as important enablers that would impact the future for humans. They are technologies related to genetics, energy, materials, brain, information technology and those related to environment. Decoding the structure and function of the brain opens up an enormous advantage of developing solutions for various behavioural and genetic disorders (Coates 1998).

The intersection of information technology and genome sequencing has paved the way for developments in gene therapy, gene editing and solutions not only for common, lifestyle diseases but also rare diseases/disorders. Improved diagnostic tools have helped in early assessment of the health problems. On the other hand,

advances in brain computing and developments in brain-computer interface help in identification the signal pathways and how they control human metabolism. The development of brain signal recording techniques has unravelled the complexity of neural functions. In this backdrop, mimicking human intelligence became possible. Artificial intelligence (AI) technologies began to be developed to better utilise and steer human functions and hence serve to augment human capabilities. Artificial Intelligence and its developments are a set of disruptive technologies that have impacted several sectors worldwide, such as education, agriculture, banking and finance, healthcare and manufacturing.

Modern drug discovery and development have been impacted by new technologies. There are five stages of drug development; target selection, validation, screening of compounds and optimisation of lead compounds, preclinical stage and clinical trials. The analysis of the large-scale correlation between targets and processes, which hitherto was burdensome, is now easily possible due to the use of AI algorithms. Further, AI-based recognition technologies assist in finding data similarities. The analysis of fifteen pharma and biotech companies (with equal number of small, medium and large companies) in relation to the impact of AI on their business revealed effects that included research and developments among others. Large companies emphasise on the development and use of internal AI-based drug developments and have a greater capacity to use and develop AI tools. The analysis of interviews revealed opportunities for use of AI in identifying individual patient factors for development of personalised drugs, assessment of compatibility of several drugs for an individual patient, identification of solutions for rare diseases, improving patient care and also in the selection of the best candidates for clinical trials. Small- and medium-sized companies tend to use AI developments at the R&D stage unlike large companies that use them more for forecasting. Reducing steps in routine activities, introducing automation and use of AI in decision making is varied in the companies. AI could affect change of business processes. So, the lack of successful integration would affect its promotion. It was observed that medium sized companies had a greater need for AI specialists unlike large companies (Kulkov 2019). High-throughput screening based on computer applications, molecular modeling, utilising computational means to identify potential targets and develop rational drug design are now routine in drug development. Automation of laboratories, robotised screening facilities, increased outsourcing have reduced drug development timelines and costs. Computer modelling programs have been also useful in *in silico* discovery of lead molecules (Eder and Herrling 2015). Analysis of the strategies in the drug discovery process of the three major worldwide pharmaceutical companies indicates the use of advanced information technology systems. The convergence of genomics, genetics and proteomics has brought in a new technological paradigm in medicine compared to erstwhile approaches. The study revealed that use of platforms of strategic information technologies early in the drug discovery process is essential for an integrated process of innovation (Coccia 2015). It was found that the use of computational tools is a requirement in most cases for the optimisation of compounds either from a random screening or from known drugs. The use of Quantitative Structure Activity Relationship (QSAR) method has been found to be more

prevalent with larger data sets compared to smaller data sets in medicinal chemistry. As a traditional machine learning (ML) technology, it has been used in predicting properties of compounds. The analysis of convergence aspects of medicinal chemistry and computational methods indicates that there is a need to develop explainable and auditable AI systems to improve decision making in the area (Griffen et al. 2020).

This chapter analyses the evolution of AI/ML technologies and their applications in drug discovery and healthcare, development of tools and the growth of these technologies pre- and post-2000. In what ways AI programs advance therapy and diagnosis and use of different types of neural networks that have been developed so far are discussed. Deep learning tools predict chemical reactions between candidate compounds and target molecules in cheminformatics and decipher chemical structures. The development of different *de novo* drug design tools based on deep learning and machine learning techniques by AI-based companies are elaborated. The development of AI platforms (such as IBM Watson, etc.) are discussed to understand the pervasive nature of the current applications of AI. The expanding role of AI in predictive analysis, clinical trials, robotic-assisted surgeries, telemedicine, drug discovery and medical devices for diagnosis and radiological purposes and current use of AI in healthcare are discussed in this chapter.

1.2 Definitional Considerations

Before discussing the evolution of AI and related developments, it is important to understand the nature and scope of the term ‘artificial intelligence’. AI, in simple terms, can be explained as the use of intelligent machines to replicate and augment the intelligence of human beings.

The Association of Computing Machinery (ACM) announced a classification system called the ACM computing classification. In this classification, artificial intelligence is categorised under ‘Computing Methodologies’. Under Section I.2, artificial intelligence covers applications and expert systems, automatic programming, programming languages and software, natural language processing (NLP), distributed artificial intelligence among others (2012 ACM Computing Classification System). In 1950, Allan Turing proposed a test, the imitation game. The Turing test was propounded to show what factors determine whether a machine operates on artificial intelligence. This test is passed if the human judge cannot essentially distinguish between the human and the computer (Turing 1950). John McCarthy defined AI as “the science and engineering of making intelligent machines, especially intelligent computer programs” (McCarthy 2007). Another proposition has been that of ‘strong AI’ and ‘Weak AI’ suggested by Searle as an exception to the Turing Test. ‘Weak AI’ refers to a position in which computers could appear and behave intelligently but not understand as opposed to ‘Strong AI’ which can actually have a mind (Searle 1980).

The wide range of AI applications has made it easier and advantageous for use in fields such as finance, education, healthcare, agriculture, law, manufacturing, urban

planning, transportation, entertainment, and so forth. The role of AI is not limited to being used as a tool and has become a subject matter of recognition as a legal being. In 2017, the human-like AI robot Sophia was granted citizenship for the first time, which makes the United Arab Emirates (UAE) the first country to give legal personhood to AI. The far-reaching effects of AI have necessitated the need for the development of international policy in relation to AI. Based on complementary mandates on AI, the OECD along with eight international organisations has developed the Global Policy AI platform which has two objectives. The objectives are to provide a common platform for sharing of work related to AI from each organisation and relevant resources and utilise the cooperation to develop common goals. The OECD Principles on Artificial Intelligence were adopted in 2019 which take into consideration. They include growth, sustainable development, transparency, explainability, respect for human rights, security and safety and accountability.

There are several legislations enacted in relation to AI for promoting innovation and regulating its use. The National AI Initiative Act of 2020 of the USA came into force on January 1, 2021. This sets a framework for coordinating AI-related research and policy across the federal government and national AI research institutes. Under Section 5002 (3) the term “*artificial intelligence*” means a machine-based system that can, for a given set of human-defined objectives, make predictions, recommendations or decisions influencing real or virtual environments. Artificial intelligence systems use machine and human-based inputs to—(A) perceive real and virtual environments; (B) abstract such perceptions into models through analysis in an automated manner; and (C) use model inference to formulate options for information or action. Further under subsection 11, machine learning is defined as “*machine learning*” means an application of artificial intelligence that is characterized by providing systems the ability to automatically learn and improve on the basis of data or experience, without being explicitly programmed. The Act also provides the administrative mechanism for the various initiatives in relation to research and education, science and technology, commerce, energy and other areas. The Act establishes a National Artificial Intelligence Initiative Office which provides technical and administrative support to the Committee on AI, promote access to innovations, best practices and coordinate interagency activities and public outreach activities. Under the AI Advisory Committee, a subcommittee on AI and law enforcement is tasked with the work on aspects such as ethical consideration, security of data, adoptability and legal standards. At least seventeen states in the USA have enacted AI-related legislations. In early 2022, the Algorithmic Accountability Act has been introduced in the USA. This legislation would empower the Federal Trade Commission (FTC) to announce regulations that would necessitate organisations using AI to perform impact assessments among other compliances.

The draft AI Act 2021 of the EU sets forth the objectives of the regulatory framework for harmonising rules, prohibiting certain practices, identifications of risks and obligations, transparency, monitoring and surveillance in relation to AI. As per Article 3 (1) ‘*artificial intelligence system*’ (AI system) means software that is developed with one or more of the techniques and approaches listed in Annex I and can,

for a given set of human-defined objectives, generate outputs such as content, predictions, recommendations, or decisions influencing the environments they interact with. The need to ensure high levels of data protection, digital rights and ethics have been highlighted in the legislation. The focus of the EU legislation is more on risk regulation. An elaborate discussion on the regulatory aspects is dealt with in chapter three of this book.

Several scholars in science and engineering have identified operational definitions for AI based on applications as definitions adopted for one stream cannot be merged with other streams due to subject matter constraints. The use of AI can help deliver better services and also hasten bureaucratic processes. AI-based pilot projects are being utilised in several countries. For instance, ADELE¹ is used to detect and classify changes in land use, and ML_SoSi² is used for understanding patterns related to receipt benefits in the social security system respectively in Switzerland. FreeFlow is a project developed for automatic toll system for road transportation in Italy. In Sweden, Tengai³ is a project to automate recruitment process and CopKit is an NLP-ML based for intelligent warning system tackling the use of new communication technologies in organised crime. Deep AR is a ML-based application used in EU to enhance police operations. An organisational framework for AI classification has been proposed for public sector applications. The framework consists of three components; data, tasks and impact. While AI can help governments and public administration in enabling a broad range of public functions, there are risks and challenges in the implementation (Ballester 2021). Interactive AI is another aspect of AI that is relevant in human-centric applications. In the interactive human centred AI, the properties such as real-time interaction with individual, user observations to study impact of changes and manipulations, ability to decipher data, benefits and risks are considered. In such a system, abstraction and granularity are core aspects (Schmidt 2020). AI mimics human-like attributes like creativity, problem-solving, comprehension, learning, reasoning, etc. AI has been there over the decades, but the augmentation in the current decade has been noticeable. For the purpose of this book, the operational definition of ‘artificial intelligence in drug discovery and development’ includes AI-assisted tools/systems that aid drug design and development and those that are developed/implemented in healthcare area.

¹ ADELE: Overview of a deep learning application for land use and land cover change detection and classification in Switzerland https://dgins2021.stat.gov.pl/images/presentations/Claudio_Faccinetti_20211027_DGINS_ADELE_Overview.pdf.

² ML_SoSi: Individual trajectories in the social security system. Accessed from <https://www.experimetal.bfs.admin.ch/bfsstatic/dam/assets/9847954/master>.

³ Tengai: <https://tengai.io/resources/tengai-robot/>.

1.3 Evolution of AI in Drug Discovery and Development

Drug development broadly has five stages—target selection, validation, screening of compounds and optimisation of leads, preclinical stages and clinical trials. The field of medicine has expanded from when people used natural ingredients to current times when modern-day technologies are used to treat patients. AI has shifted the roles of traditional medicine in a new way which was not possible previously. AI in medicine has improved the drug development process and whole healthcare. AI in medicine was introduced during the early 1960s. Medical AI is defined as “Medical artificial intelligence is primarily concerned with constructing AI programs that diagnose and make therapy recommendations. Unlike medical applications based on other programming methods, such as purely statistical and probabilistic methods, medical AI programs are based on symbolic models of disease entities and their relationship to patient factors and clinical manifestations” (Clancey and Shortliffe 1984). In the review of the developments in the field of medicine based on AI, three distinct approaches have been suggested. The first approach takes into consideration developments of AI techniques based on real-world problems. General purpose developments in AI formed the background to develop AI tools. In the second approach, AI technologies are evaluated for their outcomes based on how well they solve real-world problems compared to the traditional approaches. The third approach is with respect to medical practice. This forms a major area for applications in AI to enhance clinical outcomes and the ability to identify and analyse data based on the electronic health records (Coiera 1996). The gradual shift from the traditional to modern approach in medicine has reduced the timeline of drug discovery and process for the most part and in other stages of the drug development pipeline.

Machine learning (ML) is a practice of using algorithms to parse data, learn from it. This assists in the prediction or determination of any new data set. The application of ML is achieved by two main techniques; supervised and unsupervised learning. There are open-source frameworks as well as proprietary ML-based tools. Different ML techniques achieve different performance outcomes. Deep learning (DL) is a subset of ML and a newer form of artificial neural networks (ANNs). The scope and complexity of handling data is higher with DL. There are several developments in ANN such as recurrent neural network, feed/forward network, Boltzmann network and convoluted neural networks that have brought notable achievements in drug discovery and healthcare, in general, in the last few decades.

1.3.1 Drug Discovery and Development

The use of AI in traditional drug discovery has impacted the development phase entirely. The lengthy and expensive drug discovery process has been reduced with the intervention of modern technology. Artificial intelligence and machine learning are a key to drug discovery, and medicinal chemistry and mainly help in identifying

drug targets and lead compounds, optimise their designs against multiple property profiles of interest and identify a synthetic route to realise the composition of matter (Sellwood et al. 2018). Traditional approaches are target driven, applicable for well-defined structures and work well for diseases with well-established information. The limitation of the traditional approach is that considerable knowledge has to be generated to identify the first step of drug discovery itself, i.e. target identification. The process of target identification to clinical trials entails several years of research and development in the pharmaceutical industry. Failure rates are high and very few drugs are successful. Drug discovery and development is a very time-taking, resource intensive and costly process. It is highly complex as much is not understood in a cross-pathway context. Pharmaceutical companies are collaborating with AI tool-developing companies and are aiming to reduce the time by half and achieve cost-effectiveness. This process is driven by a complex set of algorithms that can not only extract meaning but can ‘learn’ through and make meaningful information. Thus, not only time is reduced for target drug discovery but also related information on the interactions is also obtained (Vamathevan et al. 2019). Using AI tools makes the drug development process predictable and accurate; 90 out of 100 results are accurate, making AI tools highly accurate. In the traditional approach, out of every ten drugs, only one drug makes it to the market, thus making it an extremely risky business for pharmaceutical companies whereas with the AI-based drug discovery the benefits are higher. Hence, AI technologies work for prediction and accuracy, which comes when an extensive data set aid it. From drug discovery to clinical trials, the data supplied to the AI system plays a crucial role (Fig. 1.1). The more the data to be processed, the more the chances of data being reliable and accurate.

AI systems walk hand in hand or under the supervision of the researchers during decision-making in the drug discovery process. In 2013, a multi-problem Quantitative Structure–Activity Relationship (QSAR) machine-learning challenge in drug discovery posted by the company Merck drew public attention. A deep learning network won this competition on drug property and activity prediction with a relative accuracy improvement of approximately 14% over Merck’s in-house systems (Gawehn et al. 2015). Deep learning predicts chemical reactions between candidate compounds and target molecules and cheminformatics. New chemical structures have been generated through neural networks. Several companies use deep learning for drug discovery. The flexibility of neural networks enables deep learning technology to distinguish itself from other machine learning methods.

Researchers worldwide have used different machine learning or deep learning techniques for drug discovery. The two deep learning architectures used for drug design and discovery are the Restricted Boltzmann Machine (RBM) and Convolutional Neural Networks (CNN). In the drug discovery process, both traditional rule-based and model-based approaches have been introduced. For instance, DENDRAL is believed to be the first expert system that helped in automating the decision-making process for organic chemistry and assist in the analysis of mass spectra. It has been a starting point for further tools developed (such as MYCIN etc.). Another tool, LHASA, a Japanese computer program had been developed for the analysis of chemical and biological data based on logic and heuristics. Several AI tools are

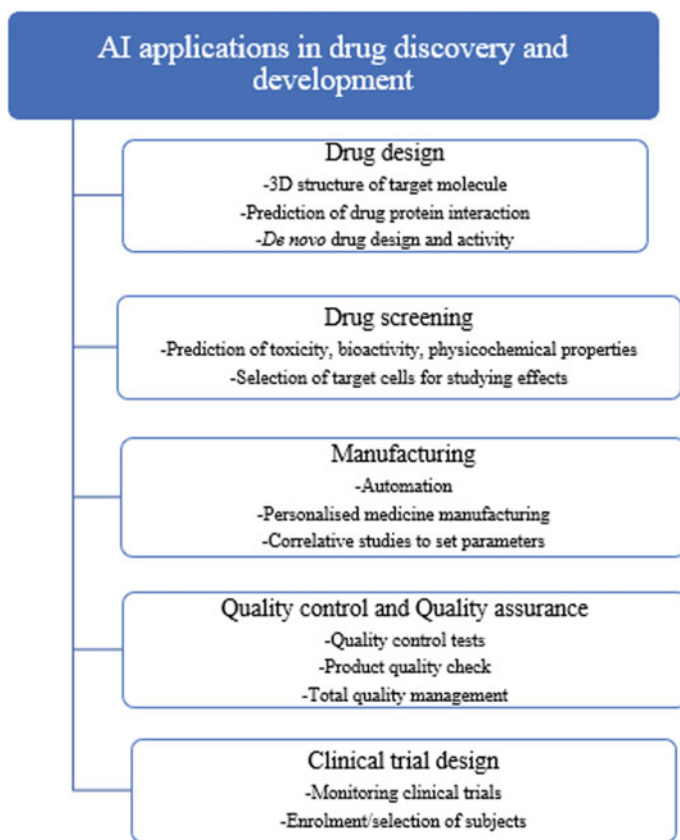


Fig. 1.1 Application areas of AI in drug discovery and development

available for different aspects of molecule prediction. Currently, there are also several freely accessible AI tools that provide an ease of use for researchers and scientists alike. One such example is the IBM RXN, a web-based tool hosted in the cloud by IBM that utilises deep learning to predict reactions and develop novel reaction design. *De novo* molecular design and prototypical robotic systems that are AI based are also a significant development. They are used for automated target and finding hits in the laboratories (Schneider 2018). Adam, a robot scientist, was developed in 2009 by a group of researchers at the University of Aberystwyth and Cambridge. It became the first to discover new scientific knowledge independently. The same group of researchers, based at the University of Manchester, had developed Eve whose role was to speed up the drug discovery process and make it low-priced. The robot can help to identify new drug candidates for malaria and neglected tropical diseases like Chagas, and African sleeping sickness.

AI as a technology has evolved from simple to much more algorithmic complexities from the early 1900s to the 2000s. The evolution of AI is being discussed in two phases, i.e. pre-2000s, and post-2000s in the foregoing text.

1.3.1.1 Pre-2000s

Although the area of medicine was well established, the use of AI technology in the earlier days was considered unconventional. Before the 1980s, machine learning techniques were prominently used. After the 1980s, deep learning techniques expanded, allowing computers to learn from their own experience. Various expert systems were created to mimic the decision-making process of human beings, primarily using traditional AI subsets like machine learning (ML) and deep learning (DL). Academicians and medical experts designed the early AI systems in collaboration. The functions of those systems were limited to specific tasks like inferences or decision-making. The widely used systems in the 1980s and afterwards were based on variations of “if-then” rules, primarily used for clinical decision support. It was observed that efficacy remains when the function of the extensive series of rules remains within a certain limit. The result might be conflicting if limits are exceeded.

The beginning of digitisation in the 1960s of the Medical Literature Analysis and Retrieval System and the web-based search engine PubMed by the National Library of Medicine became one of the breakthrough events in medical research. The foundation of AI in medicine was promoted by developing clinical informatics databases and medical record systems (Kulikowski 2019). The SUMEX-AIM is an artificial intelligence medical project developed in 1973 by Stanford University researchers to address real world biomedical problems. A network of researchers began to use it for problem solving in several areas of medicine, psychology and biochemistry. This project continued to several years and many spin offs came out based on its applications. An AI-based model called CASNET was developed at the Rutgers University and demonstrated at a conference in 1976. This model was utilised in a consultation program for glaucoma. Based on the information on the disease from individual patients, the tool could be used to provide advice to doctors on patient management. In early 1970, MYCIN was designed based on the processed patient's information and a prestored knowledge base of approximately 600 rules to provide a list of possible bacterial pathogens and recommend antibiotic treatment accordingly. The same framework was used to develop the AI expert system, EMYCIN. The INTERNIST-1 was developed using the EMYCIN framework with an enlarged medical knowledge base. The other AI expert systems had, with time, evolved with more complex data and the use of ML and DL techniques. ML is one of healthcare's broadest and most commonly used AI forms, and in its traditional form, it was used for precision medicine. In 1986, the DXplain was developed in which a user can input information about a patient case and identify the diseases from an existing list that it most correlates. The knowledge base has several thousand disease lists and clinical findings. While DXplain is an expert system for general internal medicine area, it

also covers some specialised diseases. These developments spurred the growth of AI in the area of drug discovery and healthcare.

1.3.1.2 Post-2000s

By the early 2000s, use of AI increased and several goals in target identification and other aspects were achieved. This provided impetus to a wider use of AI applications. With time there has also been a shift in the use of AI subsets; the rule-based approach has shifted to the approach based on data interpretation using AI-based medical algorithms or medical software. Modern AI technologies like Natural Language Processing (NLP), text analytics, decision management, speech recognition, emotion recognition, image recognition and so on are presently used.

Previously, AI was used in a general way in the pharmaceutical industry. With the passage of time and the development, advanced AI, ML techniques have been used by researchers and scientists because of their ability to learn without explicitly being programmed. Researchers and scientists have focussed on advanced ML and DL techniques. DL techniques are widely used because they try to learn high-level functions from data incrementally without domain expertise interference. They help review data in pharmaceutical industries and can train and process a large amount of data due to hidden layer architecture. ML technologies, DL algorithms and various neural networks (NN) like artificial neural networks (ANN) or computational neural networks (CNN) and high content screening are a few examples of AI that have brought radical changes in the initial drug discovery process. Using AI in clinical trials has reduced the time of trials from about six months to three months (Nayak et al. 2016). After analysing the genomic data from different patients, AI allows only those whose genetic profile suggests it will help them to undergo clinical trial testing. The shift from academic institutions to private entities implementing AI application in medicine has been a significant change (Table 1.1).

A medical expert system is a well-built computer program that helps provide solutions, decisions and recommendations for diagnosis, treatment or prognosis (Kinney 1987). AI expert systems in healthcare have evolved with time. Previously, educational institutes began the initial development of AI-based expert systems in healthcare and later the public and private entities gradually got involved. The improvement in hardware and software advancements of computer programs and the availability of digitised medicine helped evolve AI in medicine. Different types of neural networks that have been developed so far and constitute the gamut of AI technologies; Deep Neural Networks (DNN), Convolutional Neural Networks (CNNs), Recurrent Neural Networks (RNNs) and fully connected Feed-Forward Networks (FFN). Different AI systems were introduced that used non-traditional techniques like NLP and various other searches to analyse unstructured data and generate probable results. The system eventually became more readily available, easier maintainable and cost-effective (Ferrucci et al. 2013). CNN is an algorithm applied to image processing to replicate the interconnected neurons of human brain behaviour (Hoogenboom et al. 2020). AI in medicine was limited to the laboratory practices of academic and research

Table 1.1 Representative AI tools used for drug discovery and development

Name of the AI tool/system	Target solution(s)	Name of the institution/company
DENDRAL (dendritic algorithm)	Decision-making and problem-solving processes of organic chemists	Stanford University
DeepNeuralNet_QSAR	Detection of molecular activity of compounds	Merck Biometrics Research, Merck Sharp and Dohme Corp, USA
Adam	Basic biology	Aberystwyth University and Cambridge University
Eve	Drug screening	Aberystwyth University and Cambridge University
Alphafold	Predicting 3D shape of protein	DeepMind
DeepChem	Identification of suitable candidates in drug discovery	Open source collaboration
DeepTox	Prediction of toxicity of drugs	Institute of Bioinformatics, Johannes Kepler University, Linz
ODDT (open drug discovery toolkit)	Drug discovery	Open source collaboration
POEM (Pareto-optimal embedded modeling)	ADMET predictions based on similarity	Cyclica
Match maker	Small molecule drug discovery	Cyclica
ORGANIC (objective-reinforced generative adversarial network for inverse-design chemistry)	Molecular generation tool for creation of molecules with desired properties	Open source
DeltaVina	Scoring drug ligand binding affinity	Open source
Exscientia AI platform	Drug design	Exscientia
AMPL (atom modeling pipeline)	<i>In silico</i> drug discovery	Open source collaboration
Benevolent AI	Drug discovery and development	Benevolent AI

organisations in the earlier times. But with time AI use in medicine started growing significantly, more products for commercialisation were available and wider use by the general public through healthcare service providers. The USFDA approved a drug library consisting of a diverse set of 1760 molecules utilised to screen for growth inhibition against *Escherichia coli* strain BW25113. By training a neural network model, about ninety-nine molecules unique to the drug repurposing hub were predicted. This was further screened to identify fifty-one molecules and predicted toxicity was analysed using a deep neural network model trained on the ClinTox database. One

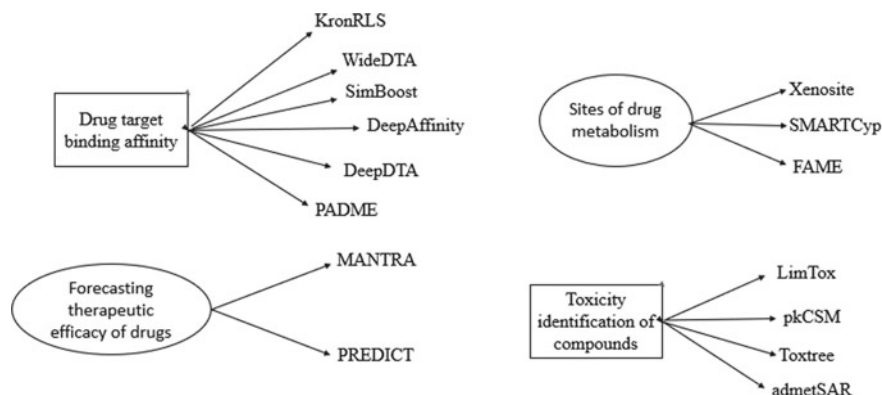


Fig. 1.2 Representative examples of ML and DL use in drug discovery and development

molecule, a c-Jun N-terminal kinase inhibitor SU3327 was identified which had been under investigation as a treatment for diabetes. A remarkable aspect of this molecule, that was named Halicin is that it showed growth inhibitory activity against *E. coli* (Stokes et al. 2020). A representative illustration of the use of ML and DL in drug discovery and development is shown in Fig. 1.2.

1.4 Development of AI-Based Medical Device

AI is not only used for bioactivity predictions but also to provide solutions to various drug discovery problems. AI technology has implementation across multiple healthcare domains like patient management, surgery, telemedicine, etc.

According to the World Health Organisation (WHO), “a medical device is an instrument, apparatus, implement, machine, appliance, implant, reagent for *in vitro* use, software, material or another similar or related article, intended by the manufacturer to be used alone or in combination for a medical purpose” (WHO 2022) (emphasis added). The definition by WHO is a comprehensive one which accommodates technological advancements. The use of the term AI-based medical devices is in relation to a device that is usually an algorithm attached to the hardware used for drug development or in any healthcare service. The AI-based software can be stand-alone or attached to any device for smooth and better functioning, depending on the conditions. The International Medical Device Regulators Forum (IMDRF) defines ‘Software as a medical device’ or SaMD as ‘software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.’⁴

⁴ Software as a Medical Device (SaMD): Key Definitions. Accessed from <https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf>.

The United States *Federal Food, Drug and Cosmetic Act, 1938 (FD & C Act)* in Section 201 (h), defines a device as an instrument, apparatus, implement, or machine, contrivance, implant, *in vitro*, reagent, or another similar or related article, including a part, or accessory which:

1. Recognised in the official National Formulary, the United States Pharmacopoeia, or any supplement to them,
2. Intended for use in the diagnosis of disease or other condition, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
3. Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purpose through chemical action within or on the body of man or other animals and, which is not dependent upon being metabolised for the achievement of its primary intended purpose.

Section 520 of the *FD & C Act* was amended by section 3060 (a) of the *21st Century Cures Act* removing certain software functions from the definition of a device under Section 201 (h) of the *FD & C Act*. The definitional aspect of the USA is discussed here as it has a separate classification and regulatory approval mechanism, unlike any other country for software as a medical device class. The regulatory aspects in relation to AI-based medical devices are discussed in chapter three of this book.

The growth AI technologies in the healthcare sector has been the driving factor for the growth of AI-based medical devices in the global market. The market for AI-based medical devices is subject to various grounds, such as the dynamics of healthcare in the region, which includes the healthcare cost, healthcare data management, etc. and the regulatory and commercialisation framework. The countries comprising suitable market regulatory mechanisms and healthcare have seen several innovations in the healthcare sector. AI-based medical devices are most commonly seen in diagnostics, particularly in radiology. There is greater spread of these technologies worldwide due to uncomplicated regulatory approval for medical devices than drug approval. According to the Global Data survey 2022, 50% of healthcare industry professionals will invest in AI. While AI was listed as the top priority in a survey of hundred and sixteen respondents that included pharma companies and industry professionals, big data and digital media were the second and third priority areas, respectively. The range of AI-based medical devices includes *in-vitro*, *ex vivo*, the wearable devices such as smartwatches or patches. The European Union (EU) market, USA, China, Japan and Singapore have settled approaches regarding the innovation and commercialisation of AI-based medical devices. The demonstration of successful use case of AI's outcomes in advancing drug discovery and development has propelled greater interest in the area and growth further in the healthcare segment. There are three levels of FDA approvals for AI/ML-based medical technologies; section 510(k) clearance, premarket approval and *de novo* pathway clearance. Out of the five hundred twenty-three clearances listed at the FDA site, it is observed that four hundred alone belong to the area of radiology (Fig. 1.3).

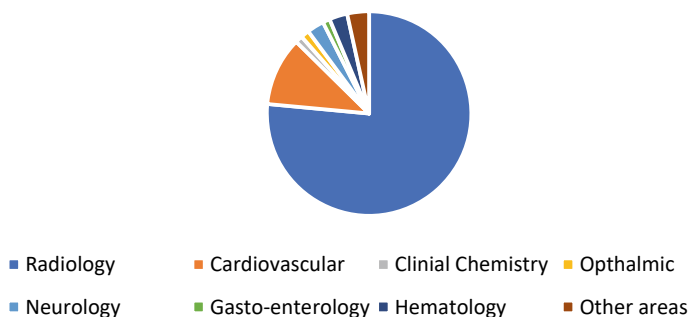


Fig. 1.3 AI based medical devices approved so far by the USFDA

1.5 Role of AI in Healthcare

Modern technologies like AI have made an impactful difference in healthcare. One of the significant changes medicine has seen over time is using modern technologies to ensure speedy, reliable and convenient patient service. The technology is extensive, from research and development to monitoring patients in the hospital or at home.

The applications of AI in e-health systems have been examined from the perspective of expert systems as well as agent functionality. Expert systems have been used for the purpose of diagnosis by doctors and self-treatment. In fact, use of web-based applications for self-treatment is as much as 70% in the USA alone. Expert systems and agent systems differ in the knowledge base utilised. Agent systems could be people, robots or computational agents which have intelligence, autonomy, cooperation and learning ability. The application of multi agent systems in relation to AI in e-health systems has been suggested to increase in future (Furmankiewicz et al. 2014). The role of AI across numerous healthcare segments is illustrated in Fig. 1.4.

1.5.1 Precision/Personalised Medicine

Precision medicine or personalised medicine seeks to deliver individual care as required and suited to patient needs. The scope of AI in personalised medicine is to provide a completely individualised strategy in treatment. The convergence of precision medicine and AI is suggested to impact personalised care in five different ways. They are planning of therapies based on genomic information, environmental considerations, clinical factors, genomic considerations in prediction of risk or in diagnosis and non-genomic considerations (Johnson et al. 2021).

AI can play a pivotal role in all relevant phases of clinical development. Its ability to advance personalised medicine has been examined. AI-based tools have been leveraged for identifying patterns from DNA sequence data, pathology imaging, mining DNA sequence information for diagnosis of genetic diseases. The review of

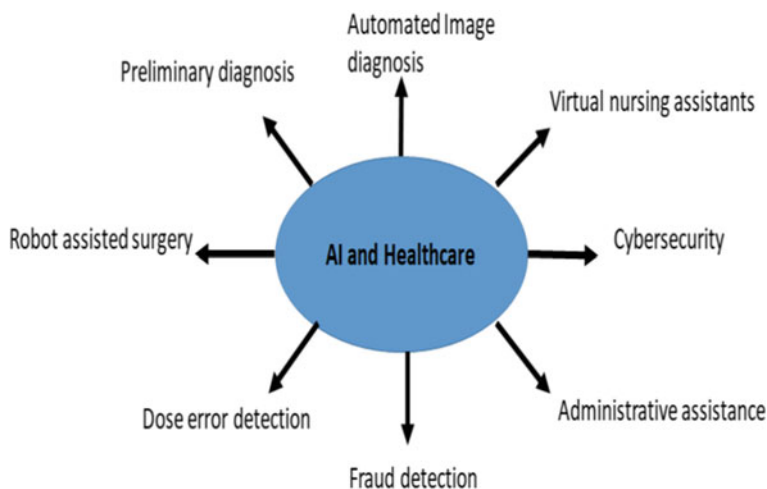


Fig. 1.4 Application areas of AI in healthcare

traditional methodologies to track individual therapy requirements revealed that AI-based simulation studies can forecast potential treatment strategies (Schork 2019). Deep learning has been utilised to predict risk in cancer (Esteva et al. 2017) and detection of disease progression in case of breast cancer (Ehteshami et al. 2017). Customised treatment plans according to patient's genetics, lifestyle environment and other factors are made with the help of AI for precision/personalised medicine. The availability of gene expression databases, gene sequence information and genotype–phenotype correlation assist the development of AI applications for resolving problems related to neurodevelopmental disorders. ML-based prediction could be utilised to detect causal genes. The identification of genotype–phenotype correlation can be done by ML clustering or classification models. Similarly, inferring risk scores for effects due to multiple genes and determining biomarkers in multistage clinical trials would be possible due to the use of AI technologies. The AI-trained systems are helping physicians consider customised treatment plan for any particular disease (Uddin et al. 2019).

In developing precision and personalised medicine, figuring out precise phenotypic patterns from population-scale clinical data is a necessary computational task. The traditional approach implements supervised learning but lacks scaling and there is poor analyses of patterns. The unsupervised feature of AI collectively overcomes these shortcomings from a compact and expressive representation of the source data, with no need for expert input or labelled exams.

Various start-ups have developed their business models to provide precision medicine. InsightRX, a California-based health tech start-up, uses ML to understand the patient's response to customised treatment. The US-based Encellin developed a thin-film cell encapsulation device which can be implanted in the skin for continuous monitoring without recharge or refill (Encellin 2022). GNS Healthcare provides the

most effective personalised treatment using ML techniques. “23andMe” is a start-up that collaborated with “PatientsLikeMe” for a study on Parkinson’s disease to look at how factors like ethnicity and environment affect disease risks and treatments. “DiabetesConnect”, a community created by Alliance Health in the USA, offers information therapy through people sharing their problems in social media, videos, and podcasts about wellness and other related issues. “iGuard” is a medication monitoring service for patients, which helps in knowing about medicines, its side-effects and other unknown effects. It notifies members about safety alerts concerning their medications and screens for drug-drug and drug-disease interactions” (Allison 2009).

1.5.2 Robot-Assisted Surgeries

AI has applications in surgeries where the robot assists surgeons in operation theatres. AI collects deep machine learning data looking at the surgeon operating, which can be used in future. Robot-assisted surgery is defined as ‘the use of a mechanical device to assist surgery in place of a human being or in a human-like way’ (Lane 2018). Based on the tasks performed, AI and robot systems are of three types; fully active systems with completely preprogrammed tasks, semi-active systems which allow a surgeon to complement the preprogrammed component and master–slave systems that are dependent on the surgeon’s activity.

The impact of AI and robotics on P5 medicine was analysed through use cases. Virtual and Physical systems are one type of classification adopted. The former is relevant to Electronic Health Records (EHR), text or data mining applications, while the latter is relevant to robots that assist in surgeries, such as physical aids and smart prostheses. There could be some hybrid systems, such as social robots. Adaptiveness, context awareness and interoperability are three important criteria that assist in their use in the health system. Depending on their assistive value to the surgeon, another classification is that of ‘assistive systems’ and ‘autonomous systems’ (Denecke and Baudoin 2022). From completely preprogrammed to semi-active systems wherein a surgeon can complement the system’s preprogrammed component, AI applications have helped in navigation, real-time tracking and determining three-dimensional position. Standard robotics and autonomous systems techniques include perception, localisation and mapping, system modelling and control and human–robot interaction (RAS).⁵ The robot’s “surgical skill” consists of its ability to first map its perception (i.e. sensory inputs) to an estimated environmental state and then map that estimate to future action (i.e. robotic outputs) in the most efficient way possible.

AI-incorporated robots are now used in several medical procedures, with a more significant interaction between surgeons and robots. There are various AI-based

⁵ “Application of Artificial Intelligence (AI) in Surgery | Imperial News | Imperial College London” (Imperial News, July 27, 2020). <https://www.imperial.ac.uk/news/200673/application-artificial-intelligence-ai-surgery/>. Accessed May 27, 2022.

surgical robots already available in the market. For instance, Moxi Robot, from Diligent Robotics, is a robotic assistant that delivers medicine and lab samples. Hanson Robotics, which introduced the popular robot Sophia, has developed Grace, a robot that interacts with patients. Laparoscopic surgery has become autonomous mainly due to the use of AI robots. MAKO, developed by Stryker Corporation, is a surgical robotic arm used to conduct hip and knee replacements. Medtronic has developed Mazor X Stealth robotic platform for spine surgeries. Expertise in advanced robotics and medical imaging has significantly impacted surgical procedures. CyberKnife, from Accurary Inc., is used for the radiosurgical treatment of neurological indications. Vdrive, developed by Stereotaxis, assists in remotely controlling diagnostic devices.

Hair transplants, kidney and cardiovascular surgeries are some areas where AI-assisted surgeries have been used. AI aims to boost the ability of robotic surgical systems to perceive complex *in vivo* environments, conduct decision-making and achieve precision, safety and efficiency. Perception, localisation and mapping, system modelling and control and human–robot interaction are the standard techniques used for robotics and autonomous systems (RAS) (Tsui 2020). The robot’s “surgical skill” involves in the first step mapping its perception (i.e. sensory inputs) to an estimated environmental state and then map that estimate to future action (i.e. robotic outputs) in the most efficient way possible” (Panesar et al. 2019). In Fig. 1.5, a few AI-based robots and their use is illustrated.

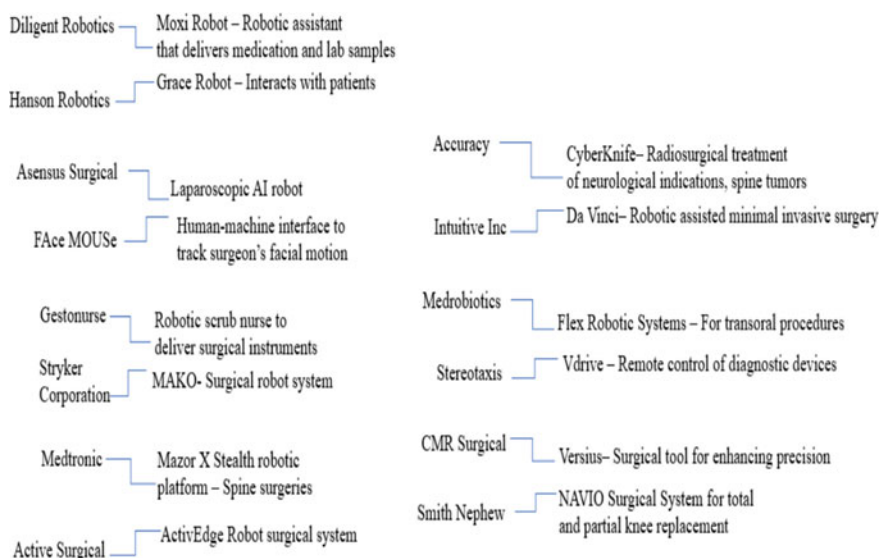


Fig. 1.5 Schematic representation of a few AI-based robots used in surgery. *Source* Composed by the authors

1.5.3 *Diagnosis*

The most prominent area of AI application is the area of diagnostic radiology. AI-based tools are used for biopsy, CT Scans, MRIs, Ultrasound, X rays, Eye tests and breast screening. Interpretation and analysis of images, generating reports and giving further inputs for consultation are a radiologist's three key work areas. AI is evolving radiology in a very rapid manner. This is generally proportional to the extensive growth of data and computational power. AI can solve problems of error, mental and visual fatigue, and tedious screening of large image datasets, which radiologists grapple with every day. AI algorithms can identify patterns and abnormalities and assist in diagnosis and treatment options.

Earlier attempts at utilising AI in radiology in terms of computer-aided detection focussed on single images. Two use cases of breast cancer screening and diabetic retinopathy have been studied to assess the relevance of computer-aided detection. In both cases, it was observed that computer-aided detection was helpful in large-scale screening programs through clinical adoption could be different. AI's role has been suggested to be promising, where CNN can be utilised to improve the performance of computer-aided detection as well as the productivity of services (Mun et al. 2021). The need for improving greater image sensitivity has been suggested in AI-based imaging analysis. Some studies suggest that identifying subtle structural and functional changes in the case of myocarditis, aortic stenosis, cancer, etc., would require refinement of AI tools that can distinguish between the abnormalities with clinical outcomes. To this end, using endpoints from non-patient-focussed radiographic and pathological aspects has been considered to improve sensitivity in medical imaging (Oren et al. 2020).

Several reports indicate that AI helps find diseases early and is also cost-effective. The AI systems are trained to detect minute observations that the human eye might overlook. A review of the applications of ML in the field of orthopaedics between 2015 and 2020 reveals that development of a 3D spine model based on ANN has been beneficial to identify fractures. Identification of specific manufacturer's implant through radiographic images is purported to save costs and reduce delays in care. The ML segmentation model developed is for assessing articular cartilage thickness from image-based pathology detection and prediction. ML has advanced applications of more patient specific and value-based care models (Helm et al. 2020).

Ezra, a New York-based start-up, has helped in early cancer diagnostics using AI-based MRI (Ezra 2022). RetinAI's AI platform detects glaucoma, age-related disorders and diabetic retinopathy. The use of AI-based devices increased and was frequent during the COVID-19 pandemic. The companies like Qure.AI have collaborated with non-governmental organisations/governmental health departments for COVID detection in remote locations for access to healthcare for everyone. Niramai has also used its devices to detect COVID through its various AI-based tools.

These are all examples of how different types of AI are utilised in multiple drug development and healthcare. Developers use ML, DL, NNs, and NLPs to augment healthcare practitioners. Many pharmaceutical companies and AI-based solutions

have already combined to use AI systems' potential in the pharmaceutical sector. The range of applications of AI in the healthcare sector is growing tremendously (Table 1.2).

Table 1.2 A representative set of healthcare AI-based tools

Healthcare area	Name of the AI system	Application
Smart hospitals	MUSA	It helps surgeons overcome human physical limitations
	DA Vinci	Minimal invasive robotic surgeries
	Logy.AI	Oral health
	Sense.ly	Smart virtual nursing assistance surgeries
	Zephyr Health	Customised care plans based on medical reports
	MONARCH	Robotic endoscopies
Tele-monitoring	Happify	AI platform for events regarding mental health
	Docty.ai	Digital health services like doctor consultations and symptoms checker
	BioBase	Tracking mental and physical health through BioBeam wearable
	Youper	Mental health assistant
	MDacne	Telemonitoring device for dermatologists
	ADA	Question answering and instant messaging for health monitoring
Administrative assistance	Appointment No-Shows (ClosedLoop.ai)	Predict appointments and no-shows and reduce costs
	Advata Smart AR™	Predicts clinical, financial and operational risk by analysing data
	Careskore	Tracker for patient's daily health records
	Binah.ai	AI tracker via light from through video for follow-ups
	AKASA AI Platform	Automated administrative tasks using AI
	Tempus EHR Integration	Analysing data and insights for better patient care

1.5.4 Administrative Assistance for Health

AI has various medical and non-core medical functions, one of which is administrative and operational applications (Table 1.3). AI is used strategically in organising hospital admission, discharge and other related functions. Once a patient has been discharged from the hospital, AI plans the medical prescription and sends reminders for follow-ups at regular intervals. Robotic process automation in hospitals can help automate functions from admissions to billing. This can significantly reduce the administrative burden. NLP-based programs help in administrative documentation and patient case management.

Further, AI-assisted physician documentation brings substantial efficiency in several hospital administrative assistance areas. Claims processing, clinical documentation, managing revenue cycles and medical records are some of the main application areas. A few research studies highlight the need for using AI to develop healthcare management systems to reduce administrative burdens. One such study suggests a five-step process involving the steps of identification of tasks, standardisation of events, uncovering interactions which are not apparent but help in understanding relationships of the components, assessing administrative burden and network optimisation. The study also reveals that there could be challenges in adopting such a framework due to public trust (Glover and Pachamano [2022](#)).

AI can also process insurance claims, manage revenue and keep track of medical records. Many companies are developing software that administers the insured's claims and medical insurance payments. For instance, Artivatic is an Indian insurance start-up company that assists insurance companies by providing an algorithmic platform for maintaining customers' profiles and tracking their financial journeys to develop real-time intelligence based on such activity. The company has streamlined its tools in healthcare and insurance.

1.6 Growth in Collaboration for Drug Discovery and Development and Healthcare

Several pharmaceutical companies collaborate with information technology companies to develop AI systems that can aid in drug discovery and development and in healthcare management. In Europe, USA, China and Japan, AI-based companies with the help of deep learning and machine learning techniques are developing different *de novo* drug design tools. Many AI companies collaborate with non-profit organisations and pharmaceutical companies to leverage technology in the drug-design process.

The Drugs for Neglected Diseases initiative (DNDi), a non-profit organisation and Atomwise Inc., a biotech company, announced discovery of drug-like compounds to develop first-in-class treatments for Chagas disease. Iktos, an AI-based company,

Table 1.3 AI systems/tools in healthcare prediction and management

Name of the AI system	Target solution(s)	Name of the institution/company	Reference
INTERNIST-I	Computer-assisted diagnostic tool	Pittsburgh University	Miller et al. (1982)
MYCIN	Diagnosis and treatment of bacterial infection of blood	Stanford University	Van Melle (1978)
CASNET	Diagnosis and treatment of eye disease	Rutgers Research Resource	Weiss et al. (1978a, b)
PUFF	Automatic interpretation of pulmonary test	Pacific Presbyterian Medical Centre	Aikins et al. (1983)
PRESENT-ILLNESS	Diagnosis of kidney disease	Massachusetts Institute of Technology	Pauker et al. (1976)
ABEL	Diagnosis for acid–base and electrolyte disorders	Massachusetts Institute of Technology	Patil et al. (1979)
DXplain	Program used inputted symptoms for differential diagnosis	University of Massachusetts	Barnett et al. (1998)
MUNIN	Diagnosis of neuromuscular disorders	Aalborg University	Andreassen et al. (2001)
CADUCEUS (expert system)	Blood poisoning	University of Pittsburgh	Banks (1986)
Pathology expert interpretative reporting system (PEIRS)	To generate pathology reports	University of Vienna	Edwards et al. (1993)
da Vinci [®] Surgical System	Robotic surgical system	Intuitive Surgical	https://www.intuitive.com/en-us/patients/da-vinci-robotic-surgery/about-the-systems
Lumiata	AI-powered health analytics	Lumiata	https://www.medigy.com/offering/lumiata-ai-platform/
Google Health	Repository of health records and data	Google	https://health.google/health-research/imaging-and-diagnostics/
IBM Watson	Data management	International Business Machines Corporation	https://www.ibm.com/in-en/watson

(continued)

Table 1.3 (continued)

Name of the AI system	Target solution(s)	Name of the institution/company	Reference
Microsoft Azure	Health cloud platform	Microsoft	https://azure.microsoft.com/en-us/solutions/ai
TensorFlow	Open-source software library for data	Google Brain	https://www.tensorflow.org/
Healthcare.ai	ML platform for healthcare data	Health Catalyst	https://healthcare.ai/
Siemens Healthineers Digital Ecosystem	A platform for data, applications and services	Siemens	https://www.siemens-healthineers.com/nl-be/healthineers-digital-ecosystem/digital-ecosystem
Infosys Nia TM	AI tool for predictability and solving complex problems	Infosys	https://www.infosys.com/newsroom/press-releases/2017/nia-artificial-intelligence-enterprise.html
IBM Genomics	Precision medicine	International Business Machines Corporation	https://research.ibm.com/labs/uk/computationalgenomics.html
Intellispace Discovery	AI data analytics in medical imaging	Philips	https://www.philips.co.in/healthcare/product/HC881015/intellispace-discovery
Amazon Comprehend Medical	Health data	Amazon	https://aws.amazon.com/comprehend/medical/
Lymph Node Assistant (LYNA)	Applying DL to metastatic breast cancer detection	Google	Liu et al. (2019)

announced collaboration with Merck KGaA, Darmstadt, Germany (a pharmaceutical company), to use Iktos AI Technology across three drug discovery projects. AstraZeneca, a pharmaceutical company, has entered into a long-term collaboration with BenevolentAI, a company providing an AI platform for the discovery and development of treatment for chronic kidney disease and idiopathic pulmonary fibrosis. Exscientia, a leading AI platform for drug discovery, collaborated with pharmaceutical giant Celgene for three years to speed up drug discovery for oncology and autoimmunity. WuXiNextCODE, the emerging global standard platform for genomic data, and Rhythm Pharmaceuticals, a biopharmaceutical company together are involved in the development and commercialisation of therapies for treating rare genetic disorders for obesity by employing deep learning capabilities to identify key genetic markers for rare metabolic syndromes. The collaboration between GNS

Healthcare, a leading precision medicine company and Genentech, a member of the Roche Group, is to use GNS REFS™ (Reverse Engineering and Forward Simulation) causal machine learning and simulation platform to leverage the development of different cancer therapies. Computational methods may be used for designing new drugs or to obtain newly discovered use of the same drug, also known as drug repurposing or drug redesigning. AI may provide solutions for tropical and rare diseases. ‘Eve’ has helped reposition several drugs against specific targets in parasites that cause tropical diseases (Williams et al. 2015). Data integration, with the help of AI software, also plays a crucial role in enabling cross-dataset analysis that will strengthen or fill gaps in our knowledge of biological, pharmacological, or clinical phenomena. Integrating sparse, highly dimensional and diverse data is considered a challenge. AI-based solutions will revolutionise data integration for drug discovery by converting complex data flexibly (Vijayan et al. 2019). A framework of Automated Synthesis and Purification Laboratory (ASPL) has been suggested which allows chemists to perform by remotely guiding chemical syntheses as a virtual extension of their library without their physical presence (Godfrey et al. 2013). However, it would be wrong to say that AI technologies have completely interchanged the role of human researchers. With the changing times and technological advances, drug discovery has ceased to be solely reserved for human researchers.

1.7 Widely Used AI Healthcare Tools

As discussed, the impact of AI on healthcare has been diverse. The expansion of the utilities in the case of AI tools has led to the development and deployment of AI platforms that deal with diverse aspects of drug development and healthcare. In this section, few prominent AI-based tools used for diversified areas encompassing drug development and healthcare are discussed. Some of the widely used AI platforms in the area are IBM Watson, GE Healthcare’s Edison, Benevolent AI’s Platform, etc. The information on these AI systems and their working model was identified from the relevant internet documents, web archives and company websites. The data was collated to understand the various facets of the collaboration and implementation of AI systems.

1.7.1 *IBM Watson*

The International Business Machines (IBM) Watson was designed purely for questioning and answering purposes, which ventured into healthcare with time. It was created as a question-answering computer system that utilises AI to compete with a human champion in real time (Ferucci et al. 2010). It is based on DeepQA architecture. There are three key aspects of the development; it understands natural language and human communication, generates and can evaluate evidence-based hypothesis

and adapts and learns from user selection and responses. Watson for Drug Discovery program was used by Barrow Neurological Institute to identify five new genes for a degenerative disease, amyotrophic lateral sclerosis (ALS) in which cells which control voluntary muscle movements die. This discovery would accelerate the development of drugs to treat ALS. Another collaboration with a company called Lundbeck was initiated for the treatment of psychiatric and neurological disorders such as schizophrenia and Parkinson's disease.

IBM's Watson Health is a digital platform facilitating medical, clinical research and medical services using data analytics, cloud computing and AI for intelligent health. The role of IBM Watson in healthcare is diverse. There are different tools in healthcare under Watson which helps build effective data-backed treatment strategies. Constant monitoring of the performance of the tools to enhance the efficacy and quality of the care provided.

The cloud-based platform of IBM Watson for Drug Discovery allows researchers to identify new drug targets and repurpose their drug discovery. Researchers in life sciences can create new hypotheses with the aid of NLP, which are supported by data and dynamic visualisations. The data collected can comprehensively be arranged in a tabular and unstructured format to get different insights that might not be possible manually. Keystonemab is a startup that is using IBM Watson to develop new treatments.

As reported, Watson has yet to be fully utilised to its potential. The leading areas where Watson has revolutionised healthcare are diabetes management, drug discovery, organisational performance management and oncological services. Watson has collaborated with Medtronic and launched Sugar.IQ is a data-driven application focussing on problems and providing solutions to patients to manage their diabetes. With the help of real-world data, it is proven to be an effective AI platform for managing diabetes among patients effectively.

IBM Watson is believed to be capable of analysing tens of millions of data in just a few seconds and identifying various therapies accordingly, which is not feasible for physicians. As per WHO data, cancer is the second largest cause of death. Around 12 cancer types are available for support on Watson Oncology. Watson Genomics also empowers precision cancer care in association with Quest Diagnostics, Baeal Pharmaceuticals Group, Illumina and so on. Watson's Clinical Trial Matching has aided by reducing the time of clinical trials by screening patients' eligibility. In the year 2016, the University of North Carolina's Linerberger Comprehensive Cancer Center has utilised Watson for Genomics to analyse more than 1000 patient cases. Some potential therapies could be identified as a result of this approach. Watson oncology platform is used in two hundred and thirty hospitals globally. Novartis collaborated with IBM Watson Health in 2017 to develop personalised therapeutic options for breast cancer to improve patient outcomes. In order to enhance immunotherapeutic approaches for the treatment of cancer Pfizer established collaboration to utilise Watson for the identification of drugs.



IBM Watson Health

- **IBM Clinical development**
 - Submission to support for clinical trials, clinical data management system
- **IBM Micromedex solutions**
 - Evidence based drug and disease insights
- **IBM Phytel**
 - Suite of solutions to enhance patient engagement through automated processes; works with electronic health records (EHR)
- **Merative Health Insights**
 - End to end analytics and data solution designed for population health management and health care program performance
- **Assistant for Health benefits**
 - Designed to understand the logic of health plan eligibility rules

The collaboration between Guerbet and IBM Watson Health was announced in 2019 for the co-development of innovative and clinical decision support solution. One of the diagnostic support tools, the Watson Imaging Care Advisor that was planned supports diagnosis of primary and secondary liver cancer. Another collaboration area has been in the area of prostate cancer where there is a need for rapid and accurate diagnosis. AI is expected to help radiologists and oncologists to diagnose and arrive at clinical decisions.

A large amount of traffic in healthcare, both of patients and their data, hinders proper care delivery. The use of cloud technology, AI like ML, and data-driven technology can help healthcare effectively. It integrates data from multiple systems into an automated platform for the organisation of patient-based data and other data. This data integration will help create personalised health plans, dose-error detection, preliminary diagnosis, fraud detection, cyber-security and many other issues related to healthcare.

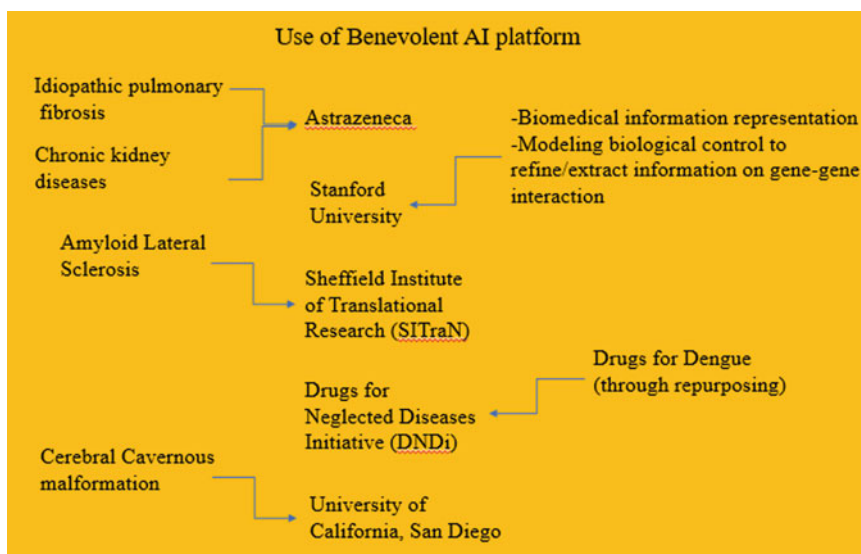
Researchers find dynamic visualisations helpful as it enhances data visibility by highlighting potential properties of interest, quick screening with supporting evidence, and visualised connections. The traditional drug discovery has been accelerated, and the process has been shortened with the help of Watson.

In 2022, IBM announced the sale of a part of Watson Health assets to Francisco Partners. IBM's Watson Health has been renamed Merative, which has been organised into six units for business: Clinical Decision Support, Healthcare analytics,

social program management, clinical development, real-world evidence and enterprise imaging. The University Hospital of Zurich in collaboration with IBM created an outcome prediction tool called Watson Trauma Pathway Explorer. This tool based on AU helps in the prediction of adverse outcome scenarios in polytrauma patients (Vetter et al. 2022).

1.7.2 Benevolent AI Platform

The Benevolent AI platform (hereinafter referred as Platform) was developed in 2013 that serves for two functions; technology and human health. It is an AI system whose activities cover an entire spectrum from drug discovery to clinical studies. It is being utilised for disease areas that include dermatitis, metabolic disorders, oncology, antivirals, nervous system, kidney and pulmonary diseases. BEN2293 is a target identified for atopic dermatitis and is currently in Phase 2 of clinical trials. For pulmonary fibrosis and chronic kidney disease, this platform is being used in collaboration with the company, Astrazeneca. The collaboration has been further extended to heart failure and autoimmune disorders. In addition to the collaboration, there are several exploratory programs being undertaken with the Platform.



Several collaborative agreements have been undertaken for target identification, molecule design and precision medicine development. The use of this Platform with Eli Lilly has led to the repurposing of Baricitinib, a rheumatoid arthritis drug, for COVID19 disease. The USFDA had given a EUA during the pandemic. Benevolent AI entered into collaboration with Novartis for the use of the Platform to utilise clinical trial and experimental data, personalised medicine and for the entire process

of target identification to clinical trials for oncology support. It is also collaborating with Janssen Pharmaceuticals to develop novel drug candidates. It has also several academic collaborations where the Platform is being utilised.

1.7.3 Atomwise

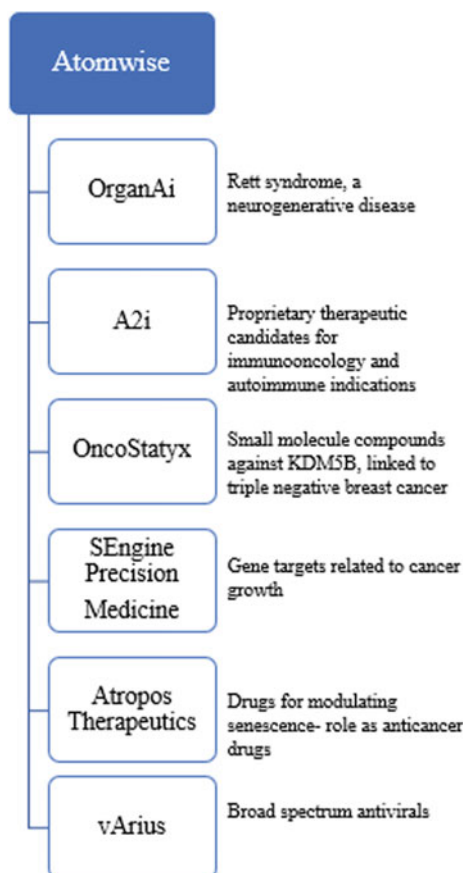
In the year 2012, Atomwise Inc. developed a deep learning AI technology for structure-based small molecule discovery. The AI platform named AtomNet platform is being used for in house programs as well as for collaborations with companies and academic institutes in various aspects of drug discovery and healthcare. The predominant collaborations are in the area of oncology (38%) and infectious diseases (26%). Atomwise has three main work areas; wholly owned pipeline, code-developed pipeline and academic collaborations. Immunology is the major area for development of leads from the in-house pipeline. In the year 2019, it cofounded a spin off, X37 with focus on two areas; development of two targets for oncology and one each for hematology and immunology, respectively. Its drug development programs with Theia Biosciences are in the area of age-related macular degeneration and antiviral drugs. It has collaborations with Sanofi and BioMotiv for identification of targets for small molecule discovery. The strength of the AI platform has been used to develop several joint ventures. Atomwise and Eli Lilly entered into a collaboration to develop up to ten drug targets. With the Chinese company, Hansoh Pharmaceuticals, Atomwise has entered into a collaboration to design and discover up to eleven target proteins in several therapeutic areas. Its research collaboration with a clinical stage biotech company, Bridge Biotherapeutics is for thirteen small molecule programs.

Through its AIMS program (Artificial Intelligence Molecular Screen) which started in 2017, it has funded several companies as well as academic institutes across the world. This program funds efforts to solve some of the complex health conditions by providing free access to academia and non-profit research institutes of the tailor-made virtual screening of millions of small molecules through the proprietary technology and a plate of as many as seventy-two small molecule compounds for functional testing. At the University of California, Santa Cruz the award is being used to develop therapeutics to restore the molecular clock of a person. In Canada, the University of Manitoba is screening and developing assays to identify compounds that can bind to netrin, a ligand, and block its interaction with cancer cell receptors. The award to the Graduate center of City College, New York, is to identify allosteric inhibitors for the protein tyrosine phosphatase, PTP1B, which is involved in diabetic signal pathway. At the Michigan State University, USA, the AtomNet platform is being used to decipher autophagy function in different cancer backgrounds. This platform is being utilised by University of Toledo in Ohio to identify compounds that can inhibit a defective enzyme that is encoded by a gene that results in Canaver disease, a genetic neurological disorder. These are few examples that demonstrate the

potential of AI platform technologies which are a bountiful resource for researchers (Fig. 1.6).

There are many joint ventures created for utilising the AI technology developed by Atomwise and combining strength of several organisations/research labs for drug development or healthcare. OrganAi is a joint venture created with Atomwise and Stemonix. Stemonix microorgan platform would be utilised for the development of solution for Rett syndrome. Along with FutuRx and Atomwise, a joint venture called A2i was created to develop proprietary drugs for immunoncology and autoimmune indications. In the area of breast cancer, a joint venture was formed with OncoStatyx to develop small molecule compounds. In order to utilise cellular senescence as a possible solution to develop anti-cancer drugs, a joint venture was formed with Atropos Therapeutics.

Fig. 1.6 Joint ventures of Atomwise for utilising the AtomNet platform. *Source* Composed by the authors



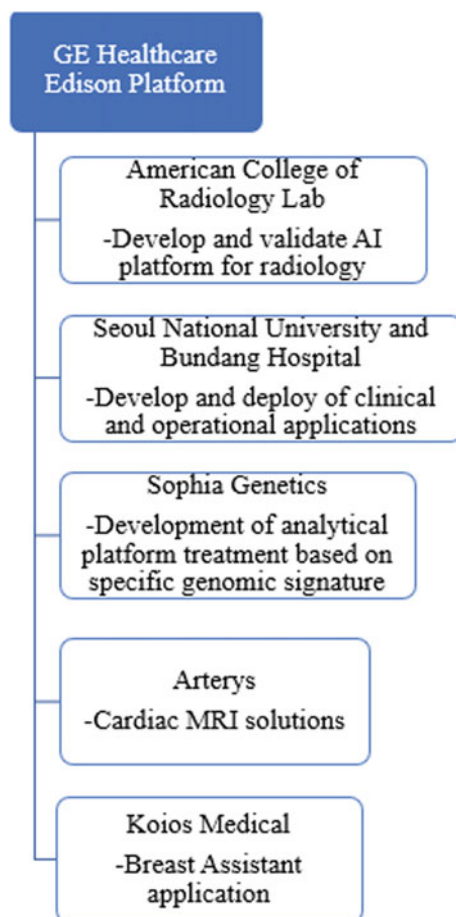
1.7.4 GE Edison Platform

The Edison digital healthcare platform was developed by GE in 2018 which is an AI platform that supports clinical applications for healthcare management. It is a data integration platform that helps collaborators to develop algorithms and develop applications. Some of the key applications of this platform are Critical Care Suite that is used for automated analysis of images especially lung related information, Air Recon DL which is DL based and used to improve signal to noise and image sharpness, Breast Assistant used for quantitative risk assessment, Embo Assist that helps clinicians simulate embolisation procedures and SonoCNS used in women healthcare applications and analysis of fetal brain images. In 2019, TH Edison Developer Program was announced to enhance the use of AI applications across the healthcare system. It has a suite of applications that have been designed and developed based on collaborations with several partners (Fig. 1.7). These tools have been implemented in the USA, UK and several other countries. The AIR Recon DL, Embo Assist, Auto Positioning (DL-based tool for hands-free positioning of patients), AW Fast Stroke (comprehensive work flow solution for reviewing all Computer tomographic scans acquired for acute stroke), AW Hepatic VCAR (DL tool for assessing complete liver anatomy), CardIQ Flow (PET Cardiac solution), PROView 2.0 (DL-based tool to automate prostate segmentation) are pending at the USFDA under 510(k) approvals.

Drug development and healthcare sector is one of the predominant areas impacted by AI technologies. The growth trajectory of the use of AI has been very extensive. The journey of the development of simple AI diagnostic tools, development of ‘software as medical device’ and currently AI expert systems indicates to the greater potential of AI in healthcare unlike any other domain. Evidently, AI is a disruptive technology, and to this end its extensive use is fulfilling requirements that were hitherto considered difficult to meet. It is expected that there will be further increase in the use of AI in the biopharma applications. The generation of data sets and data sharing platforms in this area has led to enormous collaborations not witnessed earlier in the industry. Academic research as well as industry research benefit from the large data sharing platforms. This not only has increased the propensity of licensing of tools but also the generation of intellectual property rights. In the last two decades, there is an increasing use of AI expert systems that has reshaped the work flow in the healthcare system. Diversified set of tools have been developed with a wide range of applications in the healthcare domain. Virtual nursing assistants, robots and AI platforms are now integral to healthcare interventions. More recently, the potential for use of robots in the pharmacovigilance process is being explored. The ChatGPT is a chatbot launched by the US-based OpenAI in the year 2022. Manual review of case reports through traditional methods of data analysis is not only labour intensive but also prone to errors. The use of ChatGPT can help in automated review of case reports and also identify relevant information from such reports. This is expected to be a significant improvement over manual review. The tasks based on NLP and text mining are envisaged to become easier due to the use of ChatGPT. While AI tools have evidently revolutionised drug development and healthcare, there is a need

Fig. 1.7 Schematic representation applications developed using GE Edison Healthcare AI platform.

Source Composed by the authors



for training, assessment of off types and possible adverse effects and accuracy in prediction. A responsible deployment and regular review of the use of the tools is a requirement to improve their use and patient acceptance in the healthcare sector.

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Chapter 2

Analysis of AI-Related Patents in Healthcare



2.1 Introduction

The healthcare sector has been growing in large proportions worldwide. Due to the large scale of operations healthcare monitoring and management is often a challenge. Meeting healthcare needs requires timely availability of technologies. Innovations in the medical sector are an ongoing requirement. Digital healthcare implementation is promising introduction of innovations that build sustainability and are data-driven. Healthcare innovations impact not only generalised healthcare but also specialised healthcare. The adoption of new technologies has been rapid in the healthcare sector. The emergence of the Internet as a worldwide communication medium and digital revolution of the late twentieth century has opened several applications. The use of AI/ML has pervaded in all sectors. From a global perspective, several forms of IP have become relevant for protecting AI. Understanding the intersection of AI and IPR is important to identify effective protection of the applications of AI. The value of IP is enormous as it not only incentivises the R&D process but also helps in building strategic alliances. Patents are the predominant form of IP rights relevant to the pharmaceutical area. The protection of innovation is an important requirement for growth in these industries. Patents are relevant not only to the prominent corporate giants but also provide economic value to big and small companies, including start-ups. With the growth of AI in healthcare technologies, there has been a drastic rise in patent filings in healthcare patents. Legal protection enhances the value of patent transactions. Patent protection helps pharmaceutical companies, start-ups or individual inventors to generate revenue through patent licensing. It also gives freedom to operate freely in the concerned market. The social cost of IPRs is the price to incentivise innovation. The review of national as well as IP policies has become pertinent for several countries in order to adequately promote AI in vital sectors. Further, it is important to understand how IP laws and rules provide for adequate protection of processes and products and incentivise innovation in AI.

The impact of policy and law would affect the growth of AI inventions. As a specialised UN Agency, the World Intellectual Property Organisation (WIPO) has discussed AI, digital technologies and IP aspects and the growth over the years. The WIPO 2019 Technology Trends report shows the growth of patenting and other IP concerning AI in several areas. The report is based on three aspects of AI; AI techniques, functional applications and application fields. The analysis includes information on geographical distribution, key players, acquisition and litigation information related to AI patents. Deep learning and neural networks have been identified as the fastest growing AI techniques based on patent filings. The worldwide relevance of the applications can be understood by the fact that PCT filings represent the fourth largest of the category of filings with the three patent offices of US, China and Japan accounting for seventy-eight percent of the total patent filings. Machine learning has been identified to be the dominant technique covering one third of the identified inventions. 12% growth in the life sciences and medical sciences was observed with distinct growth in medical informatics and public health. Machine learning co-occurred more frequently in the life sciences and medical sciences areas (WIPO Landscape Report 2019).¹ Automated diagnostic systems and drug personalisation are the areas that show tremendous growth in AI applications. Further, the amenability of the vast clinical data for rapid analysis by AI means that drug discovery process could be enhanced significantly thus reducing costs. According to the data analysed from 2016 to 2018, Asia accounts for around two-thirds of worldwide filing activity for patents and other IPs. 8.5% of the share of the global patent filings are from medical technologies and US ranks second in the filing number. The computer technology domain that is very relevant for developments related to AI was the dominant area of applications from US and China. The total number of PCT applications related to medical technologies grew by 6.9% in 2019 and pharmaceuticals by 4.0%, respectively. India has a large number of PCT applications concerning pharmaceuticals (WIPO IP Facts and Figures 2020). In 2021 WIPO IP Facts report shows that Asia increased its share of patent application filings. Data analysed from 2017 to 2019 indicates similar trends in the top technology fields as that of the 2020 report (WIPO IP Facts and Figures 2021). As a general-purpose technology AI is impacting several fields and the development of applications. Patenting data provides an analysis of the growth of technologies and information on innovations that have potential to the market. The analysis of the collaborative approaches in the AI application areas, the organisation information, filing trends by countries helps in drawing inferences related to patent quality, management and policy considerations for the future. In an analysis of the worldwide patent applications, it is evident that US, China and Japan are the most patent intensive in this domain followed by S. Korea, Germany and UK. US has been maintaining a lead since the past three decades. The forward citation relationship indicates the technological impact of innovations worldwide. Many leading companies such as Microsoft, IBM, Alphabet and Nuance have greater diffusion of technologies. It was observed that IBM had the highest technology absorptive capacity worldwide followed by Microsoft, Alphabet and Samsung (Liu et al. 2021).

¹ WIPO Technology Trends (2019).

The position of countries from their domestic strength (termed as National Breeding Ground) on extent to which market is perceived to be exploitable by inventors and companies and international strength (termed as International Breeding Ground) on their ability to attract applications for domestic filing was analysed to identify relative strength in AI domains. The categorisation of data was done based on seven AI techniques, i.e. neural networks, support vector machines, machine learning, expert systems, fuzzy logic, deep learning, supervised and unsupervised learning. The Revealed Technology Advantage Index calculation indicated the strength of each country in that area. This analysis provides an insight into how a leading IP developed for domestic growth of technologies can have relevance in the international context (Leusin et al. 2020). An analysis of the patent landscape in relation to AI and digital pathologies based on patent data from the patent offices of the US, Korea, China, Japan and EPO indicates that whole slide imaging, segmentation, classification and convoluted neural networks, training, detection and annotation are the major focus areas for most of the assignees. Maximum filings were from US and China. The largest representation of patent numbers is in the subject category of whole slide imaging followed by segmentation and classification, respectively (Ailia et al. 2022). Such is the disruptive nature of AI innovations that many countries have seen increased filings in its applications. A report released in October 2020 by the United States Patent and Trademark Office (USPTO) states that AI patent applications increased by more than 100% between 2002 and 2018, from 30,000 to over 60,000. The overall share of patent applications containing AI subjects rose from 9 to 16%. The patenting trend in AI technologies increased by over 400% over a decade at the United Kingdom Intellectual Property Office in 2019. Around 88% of first-filed AI patent applications seek protection in multiple jurisdictions.

The expanded scope of IP laws in view of new technologies has been witnessed at the patent offices and the courts. There have been several landmark judgements related to patents that have been pronounced by the courts. This has impacted patent prosecution on several fronts. Definitional considerations, substantive examination, application of patentability criteria, disclosure norms are the predominant aspects that need to be interpreted in the light of new technologies. The Device for the Autonomous Bootstrapping of Unified Sentence (DABUS) is an AI machine created and owned by Dr. Stephen Thaler (hereinafter Thaler) as part of the Artificial Inventor Project (Abbott 2019). It is when AI generated inventions were made by DABUS the question of inventorship became an important aspect to interpret under patent law. The justification of the patent rights to inventors or joint inventors is in the fact that it incentivises their effort to progress technology. AI assisted inventions are not a particular concern for inventorship. But AI generated inventions do not have a notion of natural person. It is when patent applications were filed in different countries with DABUS listed as the sole inventor the interpretation of inventorship became a dilemma. If DABUS independently developed the innovative technologies that are new and there was no human involvement, then the application of an objective standard of inventorship would mean DABUS is the inventor. As the declaration of an inventor is a requirement in patent prosecution at the patent offices, Thaler listed DABUS as the inventor in the patent application as he had no role in the conception

of the products developed by DABUS. The determination of inventive step, involves the person skilled in the art would assess the state of the art. The patent examiner utilises analogous art or distant art to determine whether an invention is obvious or not. If AI is granted inventorship, there is a possibility that such an AI would be the notional person skilled in the art in the case of AI generated inventions and will be on the level with human inventors. Three different levels of AI have been identified in a multilevel model system. Level 1 systems are semi-autonomous developments which still are controlled by human operations. Level 2 AI are fully autonomous and have both soft and hard AI parts. The soft AI component achieves a high-level task on its own without human intervention. The hard AI has cognitive ability enabling machines to think. They are creative and can make intelligent human like decisions. The Level 3 AI are neuro-autonomous that are a merger of biological intelligence and machine intelligence. It has been suggested that technologies such as serialisation and block chain technologies can help patent offices in identifying percentage of an autonomously created invention. This multilevel model is proposed to be *sui generis* framework for assessing the impact of AI on patent law from the patentability and inventorship standpoint (Chimuka 2019).

As discussed in the previous chapter, several developments in AI have resulted in healthcare applications and products in the market. The protection of the AI-based products and processes in the form of intellectual property rights helps leverage the position in market. The predominant areas in which AI is used in healthcare are radiology for interpreting X-ray images, clinical data for developing new medication and self-monitoring wearables. The USPTO and the EPO examine the AI applications to determine if the subject matter of the claim in AI application depends on the practicality of the innovation in a given technical field and if the identification of technical improvement is adequately described in the patent applications. In this chapter we discuss how AI-related inventions are being interpreted under patent law, evolution of patent office guidelines and the analysis of patents related AI technologies in healthcare. Further, the growth of patenting in India and patent prosecution aspects are also examined. The findings of the survey of selected Indian companies utilising questionnaire and/interviews survey are discussed. The patenting strategy of Indian companies in relation to product development in the area and the challenges involved are also discussed.

2.2 Cross-Country Legal Disputes on Inventorship of AI

In the year 2019, The UK Intellectual Property Office (UKIPO) rejected GB 1816909.4 and GB 1818161.0 applications filed by Thaler. Thaler submitted the application in his own name but mentioned DABUS as an inventor. As per Sections 7 and 13 of the Patents Act 1977, DABUS did not meet the definition of inventor. Only a natural person, not a machine, could be an inventor. Thaler appealed against the decision of the patent office based on three aspects that he did not receive an impartial hearing based on the IPO's Formalities Manual, the misinterpretation of the Patents

Act 1977 and wrong application of Section 13 of the Act to deny a patent grant. The High Court of Justice Business and Property Courts of England and Wales dismissed the appeal that Thaler did not advance the argument that could be interpreted under the fore of inventorship and noted “... *Even if an applicant honestly believed his or her cat to be the inventor, and identified the cat as such in his or her Patent Form 7, unless the IPO was satisfied that a cat was capable of being an inventor within the meaning of section 7, the applicant’s statement as to the identity of the inventor under section 13 would be deficient (no matter what the applicant’s state of mind.*” (emphasis added). The Court further mentioned “. *Equally, were the applicant to assert that the inventor had transferred the right the grant of a patent to him- or herself by reference to some form of transmission of ownership unknown in law (e.g. the applicant’s own assertion of right, without act, knowledge or acquiescence of the inventor), the IPO would be justified in treating the applicant’s statement under section 13 as deficient.*” (emphasis added). Thaler further appealed and in 2021 the UK Court of Appeal upheld the High Court decision.

In Australia, the Deputy Commissioner of Patents decided that the patent application number 2019363177 which names DABUS as inventor cannot be granted as Section 15 (1) of the Patents Act 1990 is inconsistent with an artificial intelligence system or device being treated as inventor. The Federal Court of Australia set aside this determination of the Deputy Commissioner of Patents. Judge Beach rejected it on four counts; first that an inventor may be an AI system in which case it could not be the owner, controller or patentee of the patentable invention, second that nothing in the Patents Act justifies the fact that if there is a patentable invention but no human inventor one cannot apply for a patent, third there is a need to interpret the purpose of the introduction of the Object 2 A clause and fourth that the Commissioner’s argument is based on dictionary definition of ‘inventor’. Judge Beach further stated that “... *I need to grapple with the underlying idea, recognising the evolving nature of patentable inventions and their creators. We are both created and create. Why cannot our own creations also create?*” (emphasis added)

Object 2A: The object of this Act is to provide a patent system in Australia that promotes economic wellbeing through technological innovation and the transfer and dissemination of technology. In doing so, the patent system balances over time the interests of producers, owners and users of technology and the public.

This decision was appealed by the Commissioner of Patents to the Full Court of Federal Court of Australia. An expanded five judge bench of the Court unanimously overturned the decision and held that DABUS cannot be given inventor rights. It concluded that an invention arises from the mind of a natural person and a human must be named as an inventor. There are four classes of persons who may be granted a patent under the Patents Act 1990. The High Court of Australia refused the special leave petition to Thaler to appeal the Full Court of the Federal Court of Australia.

Section 15 of the Patents Act 1990:

Who may be granted a patent?

- (1) Subject to this Act, a patent for an invention may only be granted to a person who:
 - (a) is the inventor; or
 - (b) would, on the grant of a patent for the invention, be entitled to have the patent assigned to the person; or
 - (c) derives title to the invention from the inventor or a person mentioned in paragraph (b); or
 - (d) is the legal representative of a deceased person mentioned in paragraph (a), (b) or (c).
- (2) A patent may be granted to a person whether or not he or she is an Australian citizen.

The South African Patent Office granted a patent for the patent application 2021/03242 titled 'Food container and devices and methods for attracting enhanced attention' in which Thaler and DABUS are mentioned as inventors. As there is no substantive examination of patent applications at the Patent office it was granted as it met the formal requirements. The application stands valid unless its validity is challenged in opposition proceedings.

In case of US, the USPTO rejected the non-provisional patent application 16/524350 titled 'Devices and Methods for attracting enhanced attention' as the application data sheet submitted with the application 'does not identify each inventor by his or her legal name'. The relevant provisions of the 35 USC, the US Patent Code, are Section 100 and 101.

35 USC 100—Definitions

- (f) The term "inventor" means the individual or, if a joint invention, the individuals collectively who invented or discovered the subject matter of the invention.
- (g) The terms "joint inventor" and "coinventor" mean any 1 of the individuals who invented or discovered the subject matter of a joint invention.

35 USC 101—Inventions patentable

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Thaler petitioned for the judicial review of the decision of the USPTO under the Administrative Procedure Act. The District Court in the case of *Thaler v Hirshfeld* ruled that an artificial intelligence machine cannot be considered as an inventor under the US Patent Code as inventors must be individuals. Individual will need to be a person. The Court cited several Supreme Court precedents that interpret inventor to a natural person. The Court noted *As the Supreme Court recognised, these definitions accord with “how we use the word in everyday parlance”:*

We say “the individual went to the store”, “the individual left the room” and the “individual took the car”, each time referring unmistakably to a natural person. And no one, we hazard to guess, refers in normal parlance to an organisation as an “individual”. Evidencing that common usage, this Court routinely uses “individual” to denote a natural person, and in particular to distinguish between a natural person and a corporation (emphasis added). In response to the arguments on the policy perspective, the Court noted *“As technology evolves, there may come a time when artificial intelligence will reach a level of sophistication such that it might satisfy accepted meanings of inventorship. But that time has not yet arrived, and, if it does, it will be up to the Congress to decide how, if at all, it wants to expand the scope of patent law”*. Thaler appealed against the decision of the District Court to the Court of Appeals of the Federal. Thaler argued on three aspects; first, the use of ‘whoever’ in 35 USC 101 to include corporations and other non-human entities, second, that AI software programs must qualify as inventors interpreted under ‘manner in which the invention was made’ and third, the term ‘inventor’ must be interpreted as a whole. The Federal Circuit affirmed the judgement of the District Court. The Court ruled

“When a statute unambiguously and directly answers the question before us, our analysis does not stray beyond the plain text. Here, Congress has determined that only a natural person can be an inventor, so AI cannot be”.

In a recent decision in March 2023, two patent applications filed by Dr. Thaler in Israel were rejected by the Commissioner of Patents. The Commissioner observed that until the legislature enacts different rules, only a human being may be named the inventor.

To discuss the impact of various domains in AI with IP, a conversation on AI and IP was first organised in the year 2019 by WIPO. It brought together different stakeholders on the same platform to discuss how patent offices practice would be impacted, data related aspects as well as policy. The first session of the WIPO conversation received submissions from individuals, corporate, organisations and countries. Based on the submissions received a draft issues paper in IP policy and AI

was published in the same year. The necessity for addressing issues concerning data, disclosure norms related to patents, the need for interlinking of WHO and WIPO on matters related to AI; and developing an AI clearing house mechanism have been the suggestions given by the authors (Submission for the First Session on AI and IP Conversation). The six panels that were formed discussed on definitional aspects, appropriateness of the current patent law and PTO guidelines, socio-economic and ethical impacts on AI on IP system, context of copyright and related rights, data privacy and AI and intellectual property office administration. The second and third sessions were conducted on the year 2020 (Revised Issues Paper on IP Policy and Artificial Intelligence 2020). The need to distinguish AI generated and AI assisted inventions was discussed. A broad consensus is that the existing patent laws are sufficient to evaluate AI assisted inventions and the existing disclosure norms for inventions are adequate. In order to build better certainty in the interpretation of patent laws a need for harmonisation in this area was suggested. WIPO has successfully conducted six conversation sessions so far.

2.3 Examining Artificial Intelligence Related Patents—PTO Practice

Several patent offices across the world have revised the patent examination guidelines in view of the greater increase in AI patent applications. While some patent offices included them into the existing guidelines on computer implemented inventions, other patent offices have provided a separate guidance.

The 2019 revised patent subject matter eligibility guidance document of the USPTO outlines examples that are in continuation with the earlier thirty-six examples previously issued. This has been updated with example from the AI area and the general guidance on the examination under 35 USC 101 based on the two-prong test. This revised guidance was applied in a PTAB case of *Ex parte* Hannun² decided in 2019.

The guidelines for examination practice at the EPO have included a separate guidance on AI and ML (under Part G, Chapter II 3.3.1 Artificial Intelligence and Machine learning).³ The use of terms in AI such as ‘support vector machine’, ‘neural network’ or ‘reasoning engine’ without any technical effect would be treated as abstract models or algorithms and render the related claim non-patentable. The guideline provides examples of list of subject matter that are technical contributions to a mathematical method. These could be representative when interpreting subject matter consideration for AI/ML-based patent claims.

² *Ex parte* Hannun <https://www.uspto.gov/sites/default/files/documents/Ex%20parte%20Hannun%202018-003323.pdf>.

³ EPO guidelines on AI and ML. https://www.epo.org/en/legal/guidelines-epc/2023/g_ii_3_3_1.html.

The UK IPO announced a guidance on examination of patent applications in relation to AI on 22 September 2022.⁴ Two types of AI inventions are recognised; applied AI and core AI. An ‘applied AI’ invention applies to AI technologies to a field other than the field of AI. It may be used in two different ways; either it performs processes outside the computer on which it runs or makes the computer work better. On the other hand, a core AI invention represents an advance in the field of AI itself.

Indian patent office had announced the revision to the computer related inventions (CRI) guideline in 2017. This is the currently applicable guidance for patent prosecution of claims related to CRI. It outlines the legal provisions related to these inventions. The terms/definitions used in relation to CRI such as algorithm, computer, computer network, computer program, computer system, data, firmware are defined as per the statutory definition under relevant laws in India and where there is no legal definition the ordinary use or dictionary meaning is provided. The examination of AI inventions is done as per these guidelines.

In 2021, China National Intellectual Property Administration (CNIPA) announced the draft revision of the guidelines for patent examination. Among the several changes, computer implementation invention examination practice changes were also suggested. For examination of AI-related inventions, in Section 6.1.3, Chapter 9 Part II, inventiveness is to be determined by two principles; overall consideration principle and relevance consideration principle. In the overall consideration principle, the contribution of both technical as well as non-technical features contribution should be considered. When the examination involves the use of the relevance consideration principle, mutual relation between the technical as well as non-technical features is considered and the interaction is analysed.

2.4 Applications of AI in Healthcare—Patent Analysis

Patents are the form of intellectual property rights which are given to inventions. In order to be patentable an invention must meet certain requirements as per the relevant patent law of a country. Inventions must clear eligible subject matter. The patentability criteria include novelty, non-obviousness and utility. Further, inventions need to be disclosed in written document form (called specification) as per disclosure norms. The right associated with the grant of a patent is a negative right, an exclusionary right that enables the patentee to prevent others from making, using, selling, offering for sale, importing and distributing the patented process or product. Any unauthorised use will amount to an infringement of a patent right. The TRIPS Agreement (Trade Related Intellectual Property Rights) has made IP a global obligation and member countries need to be compliant with the minimum standards of this Agreement (Padmavati 2019). There are several applications of the use of AI

⁴ UK IPO Guidelines on AI. <https://www.gov.uk/government/publications/examining-patent-applications-relating-to-artificial-intelligence-ai-inventions/examining-patent-applications-relating-to-artificial-intelligence-ai-inventions-the-guidance>.

in the healthcare. An initial pilot study of patents in this area indicates inventions related to use of AI in drug development, delivery, prediction, management and monitoring healthcare. The predominant innovations in this area are related to drug development and medical devices. The terms 'AI', 'ai', 'artificial intelligence' are used in patents. Further, there are patents related to animal health and plant health monitoring also. In order to identify patents related to use of artificial intelligence in healthcare in humans, a search was conducted in Orbit Patent Search tool (Orbit Intelligence version 1.9.8) using the keywords of 'AI', 'ai' and 'artificial intelligence' and 'health' in the abstract and title field categories. An alternate search was also done using the LENS patent search tool. Search strings were prepared for conducting the search in the patent search tool. The identification of patents was done based on the co-occurrence of terms related to AI and health in the title and abstract. This study considered the patents only related to human health. Therefore, the patents related to applications in AI related to plant and animal health were screened out by inputs strings that would not consider these patents in the generation of hits. The PRISMA approach was utilised to identify patent records for the analysis. The final patent set included 1067 patents which were analysed for qualitative as well as quantitative information.

There is a total of 680 simple patent families and 640 extended families. As per the legal status 322 patents are in force while 518 of them are pending at various patent offices.

2.4.1 Cross-Country Growth in Patent Filing

US, China and EU are the top jurisdictions for filing of patents in this area (Fig. 2.1). The number of PCT publications are 189 and in case of the European Union there are 37 EP patent applications. The count of patents as per application year indicates a major rise in the filings between 2015 and 2022. The peak year of the filings is in 2021 with 287 patents. The number of the patents for the year 2022 is 314. This may be indicative only as there could be a lag in the publication of patents (Fig. 2.2). Among the top 10 players who hold 11% of the patents, there are companies as well as academic institutes.

2.4.2 Technology Clusters and Patent Representation

A concept cluster helps in understanding the development of patent portfolios in a given area. The major domains that are represented by patents are computer technologies, medical technologies and Internet technologies for management (Fig. 2.3).

The cluster based on artificial intelligence is the largest in number. The patents surrounding the cluster provide the developments in relation to the area as well as

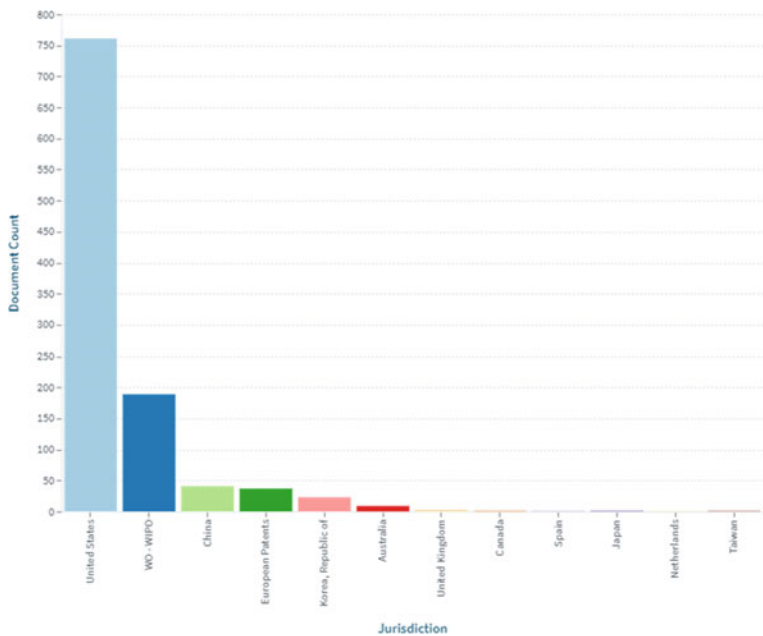


Fig. 2.1 Geographical distribution of patent filings in AI and healthcare

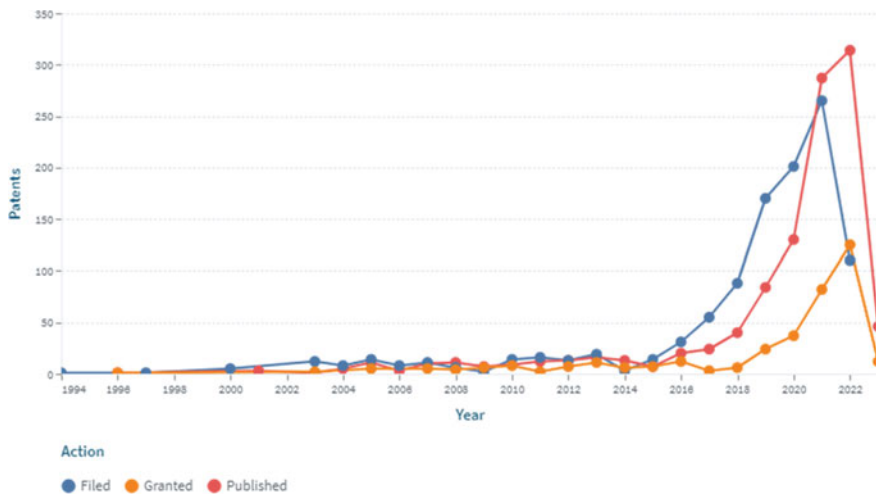


Fig. 2.2 Year wise global filings in AI and healthcare



Fig. 2.3 Cluster map of the technologies for AI and healthcare patents

main application areas. Analysis of the applicant information indicates to a multi-country prevalence of patents related to several technologies (Fig. 2.4). The categorisation of the technology areas as per the assignees provides an opportunity to identify complementarities with potential partners and development of various arrangement for further growth.

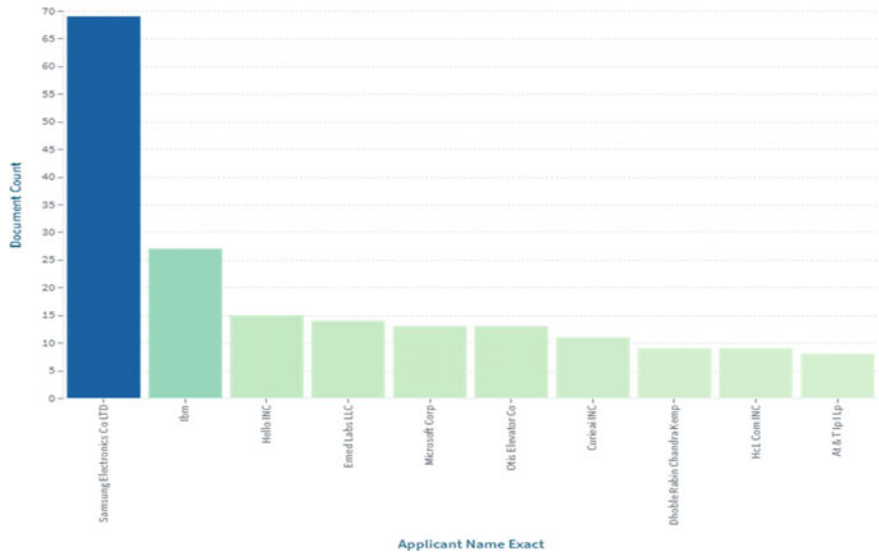


Fig. 2.4 Top applicants in the AI and healthcare area

Often, patents are organised into patent families. A patent family is generally regarded as a group of patent documents that are published with respect to the similar invention, or to many inventions sharing a specific common aspect, that are published at different times in the same country or published in different countries or regions. Priority dates are used in the classification of patent families. Patent families that are identified with respect to the same invention with each member having its reference to the same priority right marking its origin from the same application are known as simple patent families. Inventors have strong incentives to file a priority application at the earliest to protect them against imitators (Dechezleprêtre et al. 2017). Patent family data is often considered for analysis in economic and statistical studies. It may be used as the basis to build more refined patent indicators, to study different proxies for patent value or to investigate the motivations and strategies of patent applicants. The analysis of patent family data can reveal several aspects. It helps eliminate home bias, set an economic threshold in patent statistics, estimate patent value, monitor globalisation, facilitates comparison of different patent systems and analyse applicant filing strategies.

The number of patents per players provides an estimate of the growth of the company portfolio in certain areas. Absence of any opposition or litigation indicates the presence of strong patents. The top 10 owners of the technologies belong to the countries as shown in Fig. 2.5.

There is no dominant player as such and each player has patents that are unique to the company. It is interesting to note that a large number of the patents are pending and there is presence of patents that form a part of the standard which are held by the company, Samsung Electronics (Fig. 2.6).

The PCT published application WO202055172 which is related to an invention ‘Improvements in and relating to telecommunication networks’ is part of the standards ETSI-3GPP-TS-23-301, ETSI-3GPP-TS-23-502, ETSI-3GPP-TS-38-300

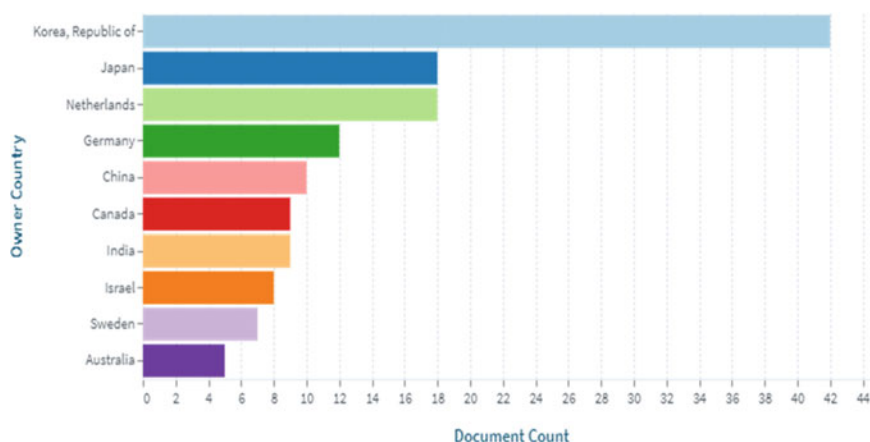


Fig. 2.5 Top owners and patent representation in the countries

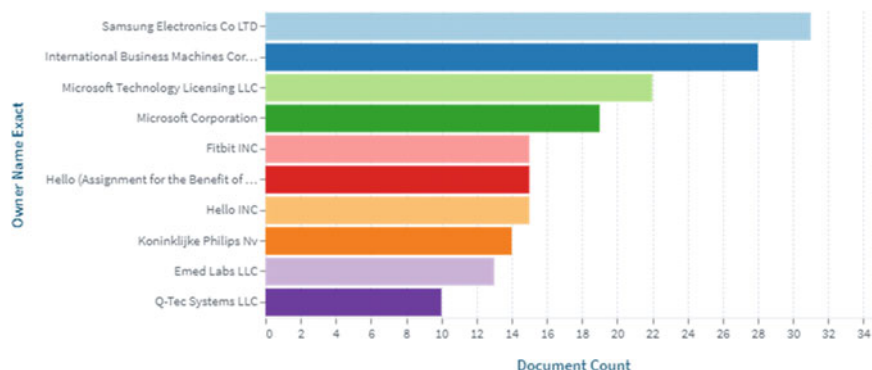


Fig. 2.6 Distribution of patents as per top 10 owners

and ETSI-3GPP-TS-38-331. This has been forward cited by several prominent companies in the sector. The identification of patent family members in the IP5 offices indicates including this application there are six members in the patent family (KR20210044826A, CN112673593A, US20220052915A1, EP3834374A1, EP3834374A4). The corresponding patent application in UK, GB2577055B, has been granted in the year 2021.

2.4.3 Cited Patents Analysis

Patents require a specialist attention to understand the scope and the extent of the technology expressed in them. Traditionally, patent attorneys and people who are specialised in the art have been helping legal and business entities. So, evaluation of patent of its quality, validity and scope requires attention from the patent attorneys or people specialised in the art. The market has approached patent valuation in a number of ways. First, brokers or sellers often evaluate patents using either a “heavy” or “light” version of a market-based approach. This involves standard factors such as the patent’s scope and quality, the industry and technology at issue, how easy it is to tell if the patent has been infringed, who the likely infringers are and a proposal of what licensees “should” pay the patentee for licenses. Further, many in the marketplace engage in a comparative analysis of the patent data (Kelley 2011). The key indicia of patent-specific value include number of citations to the patent by third parties and by the patentee, number of citations to prior art, remaining duration of the patent, number of times the patent has been transferred and number of claims contained within the patent.

The number of citations a patent receives is an index of the value of the technology and its diffusion. Cited patent information also marks the strength of the technology from its originality and relevance to a given area. Prior art citations are added in the patent prosecution by the patent examiners (as examiner citations). They are also

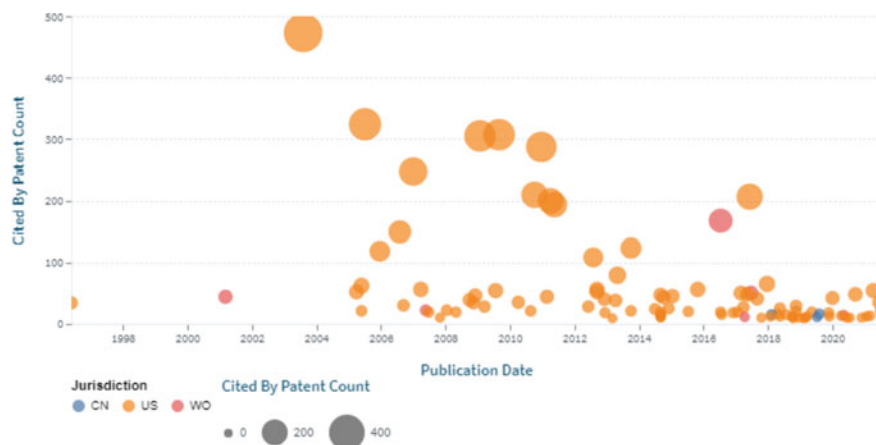


Fig. 2.7 Top cited patents

relevant to third parties when these are relied upon in opposition proceedings (Aristodemou and Tietze 2018). Technological impact of an invention can be assessed by its forward citation number. Hence, the analysis of forward citations of patents helps in identification of the growth of R&D and to what extent investment opportunities are available. In our analysis (statistics generated from the LENS database) we found that certain patents in our dataset have been cited more compared to others. The analysis of the citation index, i.e. the number of forward citations a patent received since its publication is shown in Fig. 2.7.

It is interesting to note that technologies covered by patents between the publication years of 2003–2010 have been cited the highest. These patents are related to the areas of health and disease management, diagnostics, real time medical event data collection, patient data monitoring, mobile healthcare (Table 2.1). The highest cited patent (Citation count = 473) is US 6602191 B2 titled ‘Method and apparatus for health and disease management combining patient data monitoring with wireless Internet connectivity’. The next highest cited patent (Citation Count = 324) is US 6915265B1 titled ‘Method and system for consolidating and distributing information’. The patents that have been cited ~ 250 and above times are shown in Table 2.1.

Often, highly cited patents also have several family members. The analysis of patent citation information and patent family information provides the potential global relevance of the technology area and also the stronger the portfolio of the patent the greater could be its value to create a barrier in the market.

Table 2.1 Top cited patents in AI and healthcare

S. No.	Title of the patent	Patent number	Patent family information (simple family; extended family)	Technology area
1	Method and apparatus for health and disease management combining patient data monitoring with wireless Internet connectivity	US 6602191B2	23; 23	Method and apparatus for a wireless health monitoring system
2	Method and system for consolidating and distributing information	US 6915265 B1	7; 7	A method and system providing consolidating and distributing information. The preferred embodiment of the invention provides an integrated healthcare system
3	Method and apparatus for entity search	US 7483894	3; 13	Method and apparatus that deliver a searching experience that is substantially akin to consulting with a human expert and that satisfies a user's information need (including healthcare)
4	Pharmacy management and administration with bedside real time medical event data collection	US 2010/ 0324936 A1	7;7	Methods and systems for automatically establishing an enhanced electronic health record

Authors compilation

2.4.4 IPC and CPC Spread of Patents

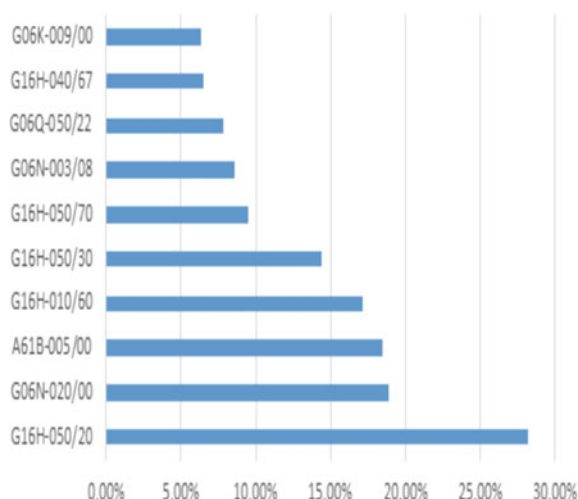
In the screened patent data that has been considered for the analysis there are greater number of filings seen in the past two years compared to that of earlier years. There is a total of one hundred and ninety patent applications. This is a highly significant number considering the fact that AI technologies have a distinct global relevance. The analysis of the patent applications reveal AI assisted inventions for healthcare management, medical image processing, predictive diagnosis and health monitoring in disease conditions. The earliest priority countries are predominantly US and China. Analysis of the International Search Reports reveal interesting insights into the related prior art and in most cases novelty and inventive step issues have been

raised. Assignee analysis reveals an even representation of universities, start-ups and companies.

The International Patent Classification (IPC) that has eight sections (A–H) with several thousand subdivisions is useful to classify patent applications and can help in understanding R&D in a given area. A search by IPC helps identify the spread of patents in the specific technology area. An analysis of the top IPCs in relation to patents provides a relative estimate of the abundance of patents in a given technology area. The analysis of the data as per IPC reveals that the largest AI patenting class is ‘healthcare informatics, i.e. information and communication technology specially adapted for the handling or processing of medical or healthcare data’—(G16H). G16H-050/20 has the largest representation in patents. This is followed by G06N-020/00 and A61B-005/00 which are the next most abundant in representation in patents (Fig. 2.8). The subclass G06N represents ‘computing arrangements based on specific computational models’ and A61B represents ‘Diagnosis; surgery; identification’ respectively.

The Cooperative Patent Classification (CPC) scheme jointly developed by the USPTO and EPO is divided into nine sections (A–H and Y) each with several subdivisions. There are approximately 250,000 entries in CPC. This is a major effort to convert the European Classification System (ECLA) and the US Patent Classification system (USPC) as per the IPC. The largest representation of patents is in the top CPC class G16H (Fig. 2.9).

Fig. 2.8 Top 10 IPC codes



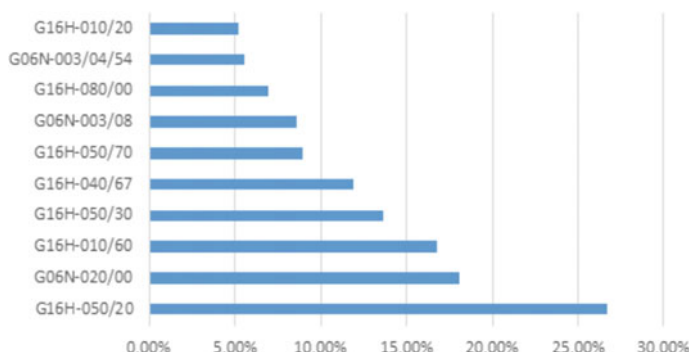


Fig. 2.9 Top 10 CPC codes

2.4.5 AI and Health Care Inventions in India—Patent Office Prosecution

Inventions must meet criteria stipulated under patent law to be patentable. According to Section 2 (1) (j) of the Indian Patents Act 1970, an ‘invention’ means a new product or process involving an inventive step and that is capable of industrial application. From the overall patent data that we collected (analysed till November 2022) the patents pertaining only to India were identified. Based on the application area, they have been classified into areas such as general health monitoring, disease specific health monitoring, health management and applications in predictive diagnostics. These inventions belong to the technical fields of biomedical engineering, communication technologies, electronics, physics and computer science. The largest number of patents are from the biomedical (with 81 patents) and computer science (with 47 patents) category. A large number of patents are awaiting request for examination. It is interesting to note that around 80% of the patents are a result of collaboration between at least two institutes. A few patents (upto seven) are a result of collaboration between an Indian university and another foreign university. As it is true of the multidisciplinary nature of AI applications, the patents that are a result of collaborative work represent the joint work of inventors from several domains such as computer science, biology, mathematics and medical science. Several AI applications that have been patented are from Indian start-ups that are fostered under the Start-Up India Initiative. Some of them have already introduced products into the market. The product mapping of some of the patents developed by the start-ups are shown in Table 2.2.

Patent grants help in enforcement of patents and provide monopoly to companies to leverage the market. An analysis of the patent prosecution provides important insights into how inventions are evaluated by the patent office. In the AI-related areas, the developments are related to use of AI methods for developing applications. A significant part of this is in relation to the use of algorithms to develop applications.

Table 2.2 Product mapping of the patents of start-ups in AI and health

S. No.	Name of the start up	Product	Patent application
1	Genic AI	GENIC.AI	IN201621023683
2	Artelus	Artelus LCHP	IN201841047063
3	DBNIX Systems Private Limited	AI data mining platform	IN201921024660
4	Mesbro Technologies Pvt. Ltd.	Credwatch platform	IN202021012729
5	Daijo Pvt. Ltd.	Daijo Lending Mobile App	IN202041042948
6	Atlamedico Techsolutions Pvt. Ltd.	Cloud AI application	IN201931031938
7	Cognitivecare India Labs LLP	Maternal and Infant Health platform, MIHIC Score™ Platform	IN201941042550
8	Life9 Systems Pvt. Ltd.	Data driven AI solutions	IN202041021088

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The First Examination Report (FER) reports serve as an important basis of understanding the application of provisions of the Patents Act 1970. In particular, substantive aspects such as patent eligibility, patentability criteria and disclosure norms affect the grant process. The FER reports in relation to the Indian patent applications were analysed to identify examiners investigation for restrictions to patent eligibility under Section 3, anticipation under Section 29 to Section 34, lack of inventive step under Section 2(1) ja and insufficiency under subsections under Section 10, respectively. In almost all cases, ineligibility of inventions under Section 3k has been raised by the examiner. In some other cases, the examiner has raised ineligibility jointly in relation to Section 3i or Section 3m or Section 3f. Further, the lack of patentability in relation to novelty and inventive step and lack of sufficiency in description of claim terms and invention description have been also raised. As such it is often observed that application amendments are imperative for the applicants. In the patent applications analysed, four applications belong with the PCT filing category with the earliest priority country as India.

2.5 Survey of the AI-Based Entities in India—Patent Protection and Strategy

Innovation index for an organisation is considered to be an important measure of the alignment of its intellectual property policy and the goals of commercial exploitation. The three major measures provided by an innovation index are alignment of science and technology policy with the solutions offered to real-world problems, major factors influencing the innovation index of the country and major organisations driving innovation in the country.

To obtain a real-world view into the developments of AI in healthcare in India we conducted interviews with a few start-ups as well as companies to understand the nature and scope of developments. The questionnaire consisted of modules related to developed/developing applications in AI related to healthcare, patenting activity of entities from a cross-country perspective, analysis of the collaborations between various entities to understand how AI-based products are developed and how regulations developed in different jurisdictions impact products in the market. The analysis of the regulatory impact is dealt with the next chapter of the book.

Patent analysis revealed that the companies had claimed patent protection based on their patent applications methods and systems. Cross-country filing of patent applications reveals filing countries, such as the United States of America, Europe, the United Kingdom, Australia, Germany, Japan, France, India, indicating companies' intention to expand the scope of products developed into multiple geographies. The questionnaire survey revealed that other than patents, the pharmaceutical companies, start-ups and individual inventors are equally interested in seeking copyright, trademarks on the brand name or device name and design protection on the product. We discuss below the findings of the interview with some of the companies and discuss a representative set of patents concerning certain areas of AI applications.

Niramai Health Analytix Pvt. Ltd. began as a start-up company in India. It has filed several patents, particularly concerning imaging. Twenty members are there in its patent family. Several patents have been filed in multiple jurisdictions, such as Japan, European Union, Singapore, Canada and China. At least six of its patents are about breast cancer and screening (Fig. 2.10). The patent filing started in 2014; by 2016, it had the highest filings. Computer Technology and Medical Technology are the major sectors of patenting. A small number of patents are related to measurement aspects and audio-visual technologies (Table 2.3).

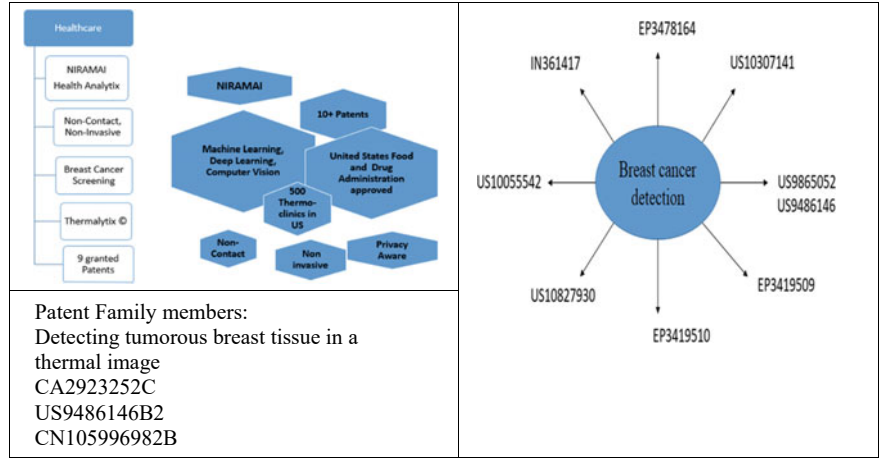


Fig. 2.10 Patent portfolio of Niramai application in relation to breast cancer

Table 2.3 Technologies covered in patent applications of Niramai and legal status

S. No.	Title	Patent family*	Jurisdiction	Legal status
1	System and Method to Generate Discretized Interpretable Features in Machine Learning Model	1s/1ex	US	Pending
2	System and Method for Adaptive Positioning of a Subject for Capturing a Thermal Image	1s/1ex	US	Pending
3	Classifying Hormone Receptor Status of Malignant Tumorous Tissue from Breast Thermographic Images	6s/6ex	US, EP, WO, JP	Active
4	Blood Vessel Extraction in Two-Dimensional Thermography	7s/7ex	JP, US, WO, EP	Active
5	Thermography-Based Breast Cancer Screening Using a Measure of Symmetry	3s/3ex	US, WO	Active
6	Contour-Based Determination of Malignant Tissue in a Thermal Image	5s/5ex	WO, JP, US, SG	Active
7	Privacy Booth for Breast Cancer Screening	5s/5ex	JP, SG, US, WO	Active
8	Software Interface Tool for Breast Cancer Screening	7s/7ex	CA, US, CN, DE	Active
9	Automatic Segmentation of Breast Tissue in a Thermographic Image	7s/7ex	US, WO, EP, SG, JP	Active
10	Software Tool for Breast Cancer Screening	8s/8ex	SG, EP, WO, JP, US	Active

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* 1s/1ex refers to 1 simple patent family/1 extended patent family

One of its popular products is that of early diagnosis of breast cancer. In this area, it has patents for various subject matters like enabling privacy for patients undergoing breast cancer screening in a non-clinical setting (WO2017145127A1), classifying the hormone receptor status of malignant tumorous tissue identified in a thermographic image of a breast (WO2018002862A1) for breast cancer screening which determines whether hot spots, as seen in a thermal image of both breasts, can be classified as possibly malignant based on a measure of symmetry, for isolating blood vessels in a thermographic image of a patient's breast (WO2018002863A1) or any other muscular region of the body and for automatically segmenting a breast from surrounding tissue in a thermal image (US20170249734A1).

More recently, Niramai has developed FeverTest, which uses computer vision and AI to screen infected people for COVID-19. This has been deployed in public places to screen those infected with the disease effectively. Its XraySetu is an AI-based service that has been freely available for rural doctors to screen chest X-rays. The company received CE mark approval, the ISO 13485 certification, and the Medical Device Single Audit Program certification. These would enable the expansion of its product market to Europe and other countries. One has been objected to among the two-word marks applied at the Indian Patent office.

Sigtuple, a health-tech start-up founded in 2015, has thirteen members overall in its patent family. Further, eight patents are pending. The filing of patents started in 2016, and the US and India are the major filing countries. Computer technologies are the predominant sector for filing patents. A few patents have been filed in optics, measurement, medical technologies and lab material analysis. The patents are developed on various subjects matters such as determining the quality of semen samples (IN201847008380), acquisition of optimal images of the object in multi-layer samples (IN201641033732), generating a structure map for retinal images, Peripheral Blood Smear that determines an area to be scanned in PBS for analysis (IN201741014502), for detecting disorders in retinal images (IN201847000803).

It is interesting to note that Sigtuple has several innovations in the field of microscopic determination, where AI has been utilised to improve accuracy in measurements. Several patents have been filed in this area, and the company has used the PCT mode for patent filing (Table 2.4).

Table 2.4 Technologies covered in patent applications of Sigtuple and legal status

S. No.	Title	Patent family	Jurisdiction	Legal status
1	Method and System for Generating a Structure Map for Retinal Images	2s/2ex	WO, US	Discontinued
2	Method and System for Acquisition of Optimal Images of Object in Multi-layer Sample	3s/3ex	US, WO	Active
3	Method and System for Determining Quality of Semen Sample	5s/5ex	US, WO	Active
4	Calibration Slide for Calibration of an Automated Microscope	1s/1ex	US	Pending
5	System and Method for Digitising Samples Under a Microscope	2s/2ex	US, WO	Discontinued
6	Method and System for Acquisition of Optimal Images of Object in Multi-layer Sample	3s/3ex	US, WO	Active
7	A Method and System for Evaluating Quality of Semen Sample	5s/5ex	US, WO	Discontinued
8	Method and System for Auto Focusing a Microscopic Imaging System	3s/3ex	US, WO	Active
9	Method and System for Reconstructing a Field of View	3s/3ex	WO, US	Active

Authors compilation

Qure.ai is another healthcare start-up that has filed various patents for its healthcare technologies. The patent family of the company consists of five patents. It has recorded patent filings since 2018. The major jurisdictions for filing patents are the US and India. Computer Technologies are the major area for patenting. Few patents are found to be related to medical technologies and measurements. Some patents have been filed in multiple jurisdictions, such as Japan, China, the US and European Union. The patents granted to them are for different subject matters like processing electronic data obtained from imaging or other diagnostic and evaluation in medical procedures, for the development of deep learning algorithms that perform machine recognition of specific features (US10504227B1) and conditions in imaging and other medical data (W02020099940A1), for detecting and localising medical abnormalities on medical imaging scans by a deep learning algorithm (US10733727B2). One of the AI and ML-based applications called qXR technology has been used to interpret digital X-rays and has been helpful in the rapid diagnosis of COVID-19. The qXR is a CE approved product and it is used in the detection of findings in relation to lungs, bones and heart. It can detect up to thirty critical lung abnormalities. It has been used for the detection of tuberculosis, lung cancer and heart failure. The qER is an AI-based application which aids in the detection of eleven findings and is used for head CTs. The qVH is a ultrasound tool which is used only for investigation and research purpose only. It is used in early detection and monitoring of atherosclerosis. The qMSK is used for musculoskeletal diagnosis. qRemote application is a telehealth solution that uses qER and others tools. Additionally, a qTrack app was developed to help quickly process X-ray images, which has been utilised overseas in some countries. Their main areas of work are lung diseases. It is used in comprehensive case management in cloud or non-cloud settings (Fig. 2.11).

Some of the recent patents related lung cancer risk prediction are given in Table 2.5.

Innoplexus is a leading global AI-based platform for drug discovery and development, which has now filed more than a hundred patents in its account, and more than twenty patents have been granted to them so far. The growth in the filing of patents has been observed since 2017. Major jurisdictions of filing are the US, China and European Union. Patents are predominantly in the Computer Technology domain. Some patents are related to digital communication and IT methods of management. It has developed an AI-based platform for drug discovery called Ontosight. It utilises several global standards and certifications, including the ISO/IEC 27001.2013 certification (Table 2.6).

They have claimed patents on various subject matters for methods of extracting information related to a product, extracting user-specific content, presenting information related to a search, creating entity records (US10614136B2), executing access transactions of documents related to drug discovery (US20200004771A1). Several patents are in the area of data processing.

Philips has included AI in its medical innovations. Its IntelliSpace Discovery is an integrated AI solution for developing solutions, data integration and use in research. Innovations in healthcare based on AI have been an area of expansion. Predictive healthcare technologies are a prominent area of growth for the company.

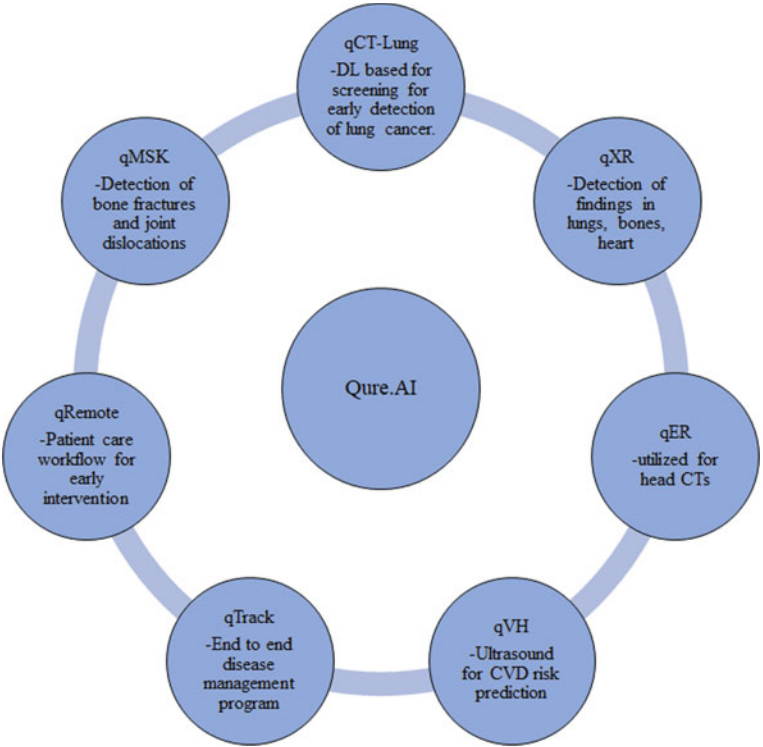


Fig. 2.11 Qure.AI applications based on AI

Table 2.5 Representative set of patents of Qure.AI and legal status

S. No.	Title	Patent family	Jurisdiction	Legal status
1	Systems and Methods for Detection of Infectious Respiratory Diseases	2s/2ex	US	Active
2	Application of Deep Learning for Medical Imaging Evaluation	4s/7ex	JP, CN, WO	Pending
3	Methods and Systems for Detecting Acquisition Errors in Medical Images	1s/1ex	US	Active
4	Systems and Methods for Detection of Infectious Respiratory Diseases	2s/2ex	US	Active
5	Predicting Lung Cancer Risk	1s/1ex	US	Active
6	System and Method for Automating Medical Images Screening and Triage	1s/1ex	EP	Pending
7	Acquiring Ultrasound Image	1s/1ex	US	Active
8	Monitoring Patient’s Health	1s/1ex	US	Active

Authors compilation

Table 2.6 Representative patents of Innoplexus and legal status

S. No.	Title	Patent family	Jurisdiction	Legal status
1	System and Method for Interpreting Contextual Meaning of Data	2s/2ex	US	Active
2	Method and System for Performing Topic-Based Aggregation of Web Content	2s/2ex	US	Active
3	System and Method for Language-Independent Contextual Embedding	2s/2ex	US	Active
4	System and Method of Documenting Clinical Trials	2s/2ex	US	Active
5	System and Method to Identify Entity of Data	2s/2ex	US	Active
6	System and Method for Name Entity Disambiguation with Latent Topic and Deep Graph Analysis	2s/2ex	US	Active
7	System and Method of Crawling Wide Area Computer Network for Retrieving Contextual Information	3s/3ex	GB, US	Active
8	Determining Drug Combinations, Synergistic Drug Combination and Use Thereof in Pancreatic Cancer Treatment	1s/1ex	US	Pending
9	System and Method for Restrictive Clustering of Datapoints	2s/2ex	US	Active
10	System and Method for Selecting a Set of Candidate Drug Compounds	1s/1ex	US	Pending
11	Method and System for Evaluating Potential Drug Compositions for Target Disease	1s/1ex	US	Pending

Authors compilation

The company has a sizable portfolio of patents related to AI/ML. The major areas of patenting are computer and medical technologies. The company has participated in the development of standards. Some areas of importance are clinical decision support systems, medical image data processing and acquisition methods. Many patents have family members across several countries, such as Japan, European Union, China, the US, Brazil, Korea and Germany.

Philips has various patents related to medical technologies like machine learning on a system based on machine learning on raw medical imaging data for clinical decision support (EP3631808A1), a system for pre-processing medical image data for machine learning (EP3570249A1), a system and method for providing model-based predictions of the quality of life implications of treatment via individual-specific machine learning models (EP3791397A1) (Table 2.7).

Stryker is a medical technology company. It has been using AI to develop applications in several healthcare areas. Recently, it has developed an e-tool that deals with stroke problems. This tool enables the scanning of brain images, rapid diagnosis by physicians and thereby, early treatments that could open based on these aspects. The

Table 2.7 Representative patents of Philips and legal status

S. No.	Title	Patent family	Jurisdiction	Legal status
1	Salient Visual Explanations of Feature Assessments by Machine Learning Models	5s/5ex	WO, CN, EP, US, JP	Pending
2	Feature Detection Based on Training with Repurposed Images	1s/1ex	WO	Pending
3	A Computer-Implemented Method of Structuring Content for Training an Artificial Intelligence Model	2s/2ex	WO, EP	Pending
4	Systems and Methods for Incorporating Multimodal Data to Improve Attention Mechanisms	1s/1ex	WO	Pending
5	Late-Onset Neonatal Sepsis Predictions	1s/1ex	WO	Pending
6	Methods and Apparatus to Integrate Systematic Data Scaling into Genetic Algorithm-Based Feature Subset Selection	10s/10ex	WO, EP, RU, CN, JP, US	Active
7	Waveform-Based Hemodynamic Instability Warning	3s/3ex	CN, WO, US	Pending
8	Artificial Intelligence-Based Clinician Worklist Implementation	1s/1ex	WO	Pending
9	Magnetic Resonance (Mr) Image Artefact Determination Using Texture Analysis for Image Quality (Iq) Standardisation and System Health Prediction	3s/3ex	EP, CN, WO	Pending

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major area of patenting is computer technologies and medical technologies. Some patents represent family members in multiple jurisdictions, such as the US, Europe, Canada, Japan, Korea. Its technology related to wearable cardioverter defibrillator (US2020/0398065A1) has been acquired by West Affum Holdings Corporation (Table 2.8).

Theranosis Life Sciences is a personalised medicine start-up using AI-powered technologies for cancer diagnostics, prognostics and theranostics. It has been developed lab-on-chip medical devices that can help in the treatment of cancer. It has

Table 2.8 Representative patents of Stryker and legal status

S. No.	Title	Patent family	Jurisdiction	Legal status
1	Systems and Methods for Classifying and Annotating Images Taken During a Medical Procedure	2s/2ex	WO, US	Pending
2	Patient Support Apparatus Systems with Dynamic Control Algorithms	1s/1ex	WO	Pending
3	Thermal Control Systems with Dynamic Control Algorithms	1s/1ex	WO	Pending
4	Systems and Methods for Controlling a Surgical Pump Using Endoscopic Video Data	3s/3ex	WO, US	Pending
5	Patient Support Apparatus with Automatic Display Control	2s/2ex	WO, AU	Pending
6	Systems and Methods for Generating a Three-Dimensional Model of a Joint from Two-Dimensional Images	2s/2ex	US, WO	Pending
7	Wearable Cardioverter Defibrillator with ai-Based Features	1s/1ex	US, WO	Pending

Authors compilation

filed patents for a cell population enriched in a targeted cell subpopulation of a heterogeneous cell population.

There are a multitude of ways in which organisations can derive value from a patent portfolio. The foremost among it is to develop new products and services and gain patent rights. The term ‘disruptive innovations’ was coined by Prof Christensen to indicate business models that help products and processes to be successful in market. In his theory on disruptive innovations, he examines why leading technologies are not necessarily relevant to the market for very long. The impact of disruptive technological innovations and sustainable technologies has been compared based on product performance with respect to time. It was observed that disruptive technological innovation may be relevant to high end market as well as low end market. Five principles of disruptive innovations were proposed. The first principle is that companies depend on customers and investors for resources. In order to succeed in implementing disruptive technologies companies will need to orient their work keeping this resource dependence. The second principle is that small markets do not solve the growth needs of large companies. As resource allocations can be large, rather than large companies enter small markets it is useful to identify smaller organisations who can fit well into such markets. The introduction of disruptive technologies in such cases becomes the responsibility of small organisations. Prior to product introduction market surveys are conducted to forecast the value of technologies. In the case of disruptive technologies, no market data exists. Analysis of the size and growth in markets is hence not possible. This forms the third principle. The fourth

principle is that an organisation's capabilities define its disabilities. Contrary to the general notion, the existing skillset in the organisation may not be adequate in developing disruptive technologies. The fifth principle is that technology supply may not equal the market demand. Disruptive technologies are not introduced initially in main mainstream markets and tend to be used only in small markets (Christensen et al. 2015).

Improving existing products with newly developed technologies helps expand the patent portfolio. The continuous focus on using the patent portfolio to create new and improved products provides the organisation with a competitive edge it might not otherwise possess. An effective patent portfolio can help deter competition in the marketplace. It is a valuable asset that can generate revenue through technology sharing and patent licensing agreements. Strategic reasons for building a patent portfolio can be categorised as offensive, defensive or both. Patents offer an offensive stance when they help prevent product copying, create barriers to entry, build company assets, attract investment capital and generate revenue through patent licensing or litigation. On the other hand, patents may provide a defensive shield against a competitor's patents and may confer bargaining leverage in developing cross-licenses or other business deals (Kramer 2007).

While patent portfolio can be built in relation to a company's own products, it is necessary to keep in mind the patents of a competitor who may be also working in the area. In addition to existing patents, strengthening R&D developments can be helpful in generating know-how that could provide a market leverage. This leverage can be utilised across a breadth of business relationships including those associated with a supply chain. The key to maximising the portfolio's effectiveness lies in identifying and balancing the company's business plan and objectives against the costs associated with obtaining patents. Such informed decisions can ensure the use of patent portfolio to strengthen the company's position. The collaborative ecosystem consists of several participants/stakeholders. Patients are at one end of this ecosystem who utilise healthcare provided and in turn companies utilise patient data. At the other end are the pharmaceutical companies which are involved in promoting innovations for better therapies and medicines. The disruptive nature of AI facilitates the collaboration of the companies with several partners for such development.

2.5.1 Collaborative Aspects

The implementation of AI in the healthcare sector involves several partners involved in various stages of development and deployment of the technology. The collaboration model is necessary as AI-based tools are very data-intensive. Collaboration in healthcare helps to reduce medical errors and deliver an efficient patient experience. In the entire value chain, healthcare professionals and health authorities are present between the patients and the pharmaceutical companies. For instance, the UK National Health Service (NHS) has a breast screening program which comprises a huge amount of high-quality imaging data across different population types. The

associated metadata is of great potential to AI developers. A significant number of patients approved the sharing of data to enable the development of new medicines and treatment methods. Understanding ownerships in such use of data sets is necessary in any collaborative study (Sidebottom et al. 2021). The John Hopkins University Hospital in the US collaborated with GE Healthcare to use predictive analytics based on AI to manage patient movement and volume and the management of healthcare. The collaboration between San Diego University in the US and Guangzhou University Medical School in China resulted in the development of AI solution for the diagnosis of the eye diseases, macular degeneration and diabetic macular oedema (Lee and Yoon 2021). In the past two years there has been an increase in the collaboration in the biopharma area and several AI tools are being utilised/developed further.

In the questionnaire survey, we observed that companies collaborate with start-ups, doctors, hospitals and big pharmaceutical companies to advance the research and development of products and services in the healthcare industry. The primary collaboration is among hospitals, healthcare start-ups and companies. The parties generally enter into two types of collaborative agreements.

2.5.1.1 Service Agreements

Healthcare companies and hospitals enter into a service agreement to provide patient products and services through tools or devices. Companies offer a wide range of AI-based solutions like automated medical diagnosis, automated analysis of medical tests, wearable sensor-based medical devices, detection and screening of diseases, patient management systems, predictive healthcare diagnosis and disease prevention.

The companies interviewed collaborate with leading hospitals in different parts of India like Bangalore, Mumbai, Gurugram, Delhi, Kolkata, Hyderabad and foreign countries. Innoplexus has established a collaboration with the Regional Cancer Centre, Gwalior to share its IPlexus platform. The IPlexus platform has more than 300 terabytes of data related to scientific data, clinical trial databases, biological data, several patent office data, regulatory agency information and patient data. SigTuple and Krsnna Diagnostics collaborated together for the use of Sig Tuple's AI100 tool. This tool is used in digital pathology and is deployed in several states of India. In collaboration with Silicon Valley Bank, the AI100 tool has been implemented in tribal hospitals of Tamil Nadu. Qure.ai has developed six tools for various applications. Its AI bot is helpful in swift triaging for COVID-19. One of its tools, the qXR that is used in radiological applications has been introduced in ten primary care clinics in Malaysia with the help of a medical group. In order to make the qXR deployable in fifteen states of India, funding support has been given by SAMRIDH Healthcare Blended Financing Facility. This support is expected to enable dual screening of COVID-19 and lung diseases such as TB in remote location. Qure.ai has collaborated with the health ministry in India to deploy its deep learning techniques for tuberculosis screening. NIRAMAI's device, Thermanalytix, has already been used in hospitals and clinics, including HCG Hospital, Apollo Clinics, HealthSpring Diagnostics, etc. In a joint partnership with Roche Pharma and the Government of Punjab,

it is accelerating the screening of the breast cancer in the state of Punjab in India. This project is called the Punjab Breast Cancer AI digital project or the Pink Project.

2.5.1.2 Data Agreements

The data agreements are for data sharing between the companies that might be between two start-ups or a start-up and pharmaceutical companies or companies collaborating with start-ups/companies for data sharing; this arrangement enriches and improves the research and development of both parties. The questionnaire survey revealed that there are several considerations that need to be considered. While the start-ups had data agreements and non-disclosure agreements with top pharmaceutical companies like AstraZeneca, Discoveric Bio Group, NovImmune, Nanox, etc., they also collaborated with hospitals such as Apollo, Columbia Asia, Narayana. The implementation of AI tools is over a distributed network and customised use of tools brings in a new for not only modifications but also could involve development of innovations. The collaborative network is not limited to pharmaceutical companies and hospitals and it is observed that several governmental agencies as well as non-governmental organisations are also involved. This is essential to maximise the outreach and provide aid to the patients at large. Our work deals with only a general understanding and not the in-depth aspect of collaborations.

Increasing economic value gained from innovation is not only an objective for large companies but also start-ups in the area of AI developments. There is a significant increase in applications of AI for developing novel processes and products. Several jurisdictions allow software applications to be patentable but there remain fundamental questions that continue to be debated on eligible subject matter and the interpretation of the patentability criteria. The issue of autonomous AI and inventorship has been discussed from a cross jurisdiction perspective. As patents continue to be filed at various patent offices, international organisations and patent offices have identified rules for examination of AI related patents, the applicability of disclosure norms, need for an AI clearing house etc., Identification of global trends in patentability not only provides a general picture of the growth but more specifically could lead to greater collaboration and diffusion of technologies. The growth in patent family as well as extended patent family information indicates to the global relevance of the technologies. The Indian industry is also developing unique applications that are not only relevant from the domestic but also in the international context.

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Chapter 3

AI-Based Medical Devices and Regulations: A Cross-Country Perspective



3.1 Introduction

The development and commercialisation of products in the market is subject to regulation. New technologies are also impacted by existing regulation. Regulatory changes also happen due to the development of many different types of technologies. Regulation of technology includes compliance with technical requirements/specification, standardisation, taxes, information disclosure and market regulation. On the one hand, regulation can incentivise innovation, and on the other hand, it may create an entry barrier. The evolution of regulatory processes is governed by political, economic and social imperatives (Weiner 2004). There are different standpoints in understanding regulatory design. Regulatory assessments are key for policy and implementation. Diffusion of new technologies is affected by regulation. Governments develop regulations as a reactive response to the introduction of new technology-based products by the industry. Hence, initially it is the industry which develops compliance procedures that are reviewed by the regulators. Companies tend to be in an advantageous position with respect to market in cases where there is no or very little regulation of new technology products. This is in contrast to companies that introduce products when there is not only a full-fledged legislation but also has been implemented for years. So, the flexibility or stringency of a regulation depends on these considerations as well. Regulation is also jurisdiction specific and has several components. It is not static and is dynamic and is influenced by the growth of social regulation. The development of the risk regulatory framework involves the study of the impact of new technologies on the health, safety and environment. Prof. Alfred Kahn in his seminal work on the economics of regulation noted that it is the responsibility of legislatures and regulatory commissions to find ‘the best possible mix of inevitably imperfect regulation and inevitably imperfect competition’ (Khan 1988). Technological developments that are disruptive are widely utilised on the global front. Emerging technologies present a huge challenge to regulatory authorities. Further, the implementation of technologies on the digital medium has brought

several challenges. Just as in the case of other technologies, digital healthcare has necessitated a relook at whether or not the traditional regulatory system is effective. While digital medium helps in decentralising and providing greater flexibility and public convenience, there are adequate concerns on monitoring and assessment of safety of the digital technologies. Building soft-law approaches has been observed to be an alternative to enhance regulatory governance. The introduction of industry guidance, best practice recommendations, white paper reports and advisory circulars help in stakeholder engagement as well as drive public policy mandates. These build flexibilities yet ensure that industry is accountable. Regulatory authorities, unlike in earlier times, engage in multi-stakeholder discussions to identify and adopt consensus-based standards (Hagemann et al. 2018).

The transformative nature of technologies has necessitated a need for a co-evolution of regulatory approaches. In the traditional set up, the regulators would not know the risks and expect companies to know the risks and ways to mitigate them. To this end, the regulators would be tasked with the need to elicit information from the companies on what are the standards and rules and specify plans that are already/proposed for risk assessment and mitigation. This is a prerequisite to then set an institutional process of event reporting, tracking and measures to be implemented for public safety. Such regulatory systems have been termed recursive as changes in regulation are based on incomplete understanding of the risks and shared experiences are necessary for an effective regulation (Sabel et al. 2018).

Drug regulation as it exists today has undergone expansion in nature and scope largely due to the complexity of the pharmaceutical sector that has grown in vast proportions. Pharmaceutical industry varies in the type of production and size. The greater the size of the pharmaceutical industry, the greater are the number of registered products generally. From a historical perspective, the response to the crisis due to hazardous consequences of drug use, government's own initiatives of setting standards and introducing more processes under the ambit of drug regulation are suggested to be some aspects that necessitated a relook at drug legislation (Temin 1985). Drug laws provide the basis of drug regulation. They lay the foundation to the substantive and procedural aspects of approvals for drug development and commercialisation. Drug regulatory functions may be with either a single agency or may be fragmented. Drug regulatory authorities in different countries may have similar or different approaches as mandated under the law. Public health and safety are the primary mandate of drug legislations. Certain countries have an elaborate drug regulatory system such that there are individual divisions to deal with specific type of drugs. Standards and guidelines are developed by drug regulatory authorities.

As discussed in Chap. 1, AI has impacted the drug discovery and development and the healthcare areas. There is greater impact of AI in the healthcare area. This chapter will examine the regulatory changes concerning AI-based medical devices in the cross-country context of USA, EU and India. AI has seen a transition from being previously reserved for rare occasions to now being used quite frequently. Doctors, physicians, and even consumers can now use these devices for anything from simple calorie tracking to high-priority tasks like surgery. AI-based medical devices are being used actively to track patient data and provide regular updates on their health.

All AI-based software may or may not be considered as medical devices. The need for their regulation is realised as these devices could affect the people who use them, such as doctors, patients and consumers. As has been the case with introduction of any new technology-based products into the market, the efficacy and safety of such devices are common concerns. In this chapter, the analysis is limited to drug regulatory process. The scope of the work does not include regulation of data as it is outside the scope of this study.

Innovation in healthcare is very rapid but regulation changes are slow. The drug regulatory authorities have to fast-track the changes in regulation relating to such new technologies in healthcare. The USFDA and a few other countries such as Canada, Australia, Singapore and the European Union have been ahead of the curve in regulating AI-based medical devices. The problem with regulating such technology is that it is widely adopted in healthcare and has a vast application area. In the following sections, we analyse the context of AI-based medical devices under drug regulation and how they are subject to a different regulatory framework.

3.2 Need for Regulation on Artificial Intelligence Tools in Healthcare

As national digital health strategies continue to be announced, it is evident that digital interventions for patient diagnosis, care and comfort would play an essential role in the overall healthcare system. Many countries have included digitalisation as one of the pillars to be achieved in digital healthcare. By the end of the year 2018, two-thirds of the world's population subscribed to mobile devices. Mobile devices became the digital health platforms. New approaches have helped to connect AI, cloud computing and big data together. The working group on digital and AI in healthcare, which was part of the Broadband Commission for Sustainable Development established in 2010, sought to work on digital health solutions that are fully integrated, scalable and financially viable. Based on interviews with hundred different digital health leaders from twenty countries and international organisations, they identified some common aspects. One of the aspects identified is the lack of common regulatory standards due to inoperable or inflexible policy and regulatory systems. The need for three categories of regulation was identified: data management regulation, device regulation and regulation of delivery care (Aerts and Bogdan-Martin 2021). The goal of digital healthcare is to combine information technology and medical knowledge to make solutions that are better and more efficient. The use of digital technologies in research and development of drugs and devices and the maintenance and management of data or electronic health records are some instances of healthcare digitisation. Digital healthcare has been used in different ways in many countries, including the USA and some African countries.

In the post-digital era, the concepts of distributed ledger (blockchain), artificial intelligence, extended reality and quantum computing (DARQ) are gaining much importance. Under “high performance medicine,” digital patient records are expected to accentuate the ability to correct errors, improve workflow and permit the accurate predictability of clinical trial information (Kavita and Padmavati 2020). Clinical decision support, diagnosis, screening and system efficiency are the four areas recognised in the UK, USA, Israel, EU, Singapore, China and Saudi Arabia. AI as a technology used in a medical device can be only software or a software application with hardware. It might be both hardware and software components and so may refer to a robot, a program running on a single computer, a program running on networked computers or any other set of components that hosts an AI. Foreseeability, autonomy and assisted decision-making aspects of AI could go beyond prediction to integrate various areas. The use of AI in multiple fields, which is different from standard computer software, comes with various liabilities. As there is no specific law to govern the liability of AI software, which is self-learning and makes decisions based on experience, it becomes more complex and vital. “Flying robots” and “living robots” show that there are limits and risks when accidents happen on purpose or by accident. As computer intelligence, to a certain extent, outgrows human intelligence, the extensive implementation of AI could have undesirable effects, thereby necessitating to regulate it. The “*RoboLaw Project*” by the *European Commission*, which investigated the legal implications of robotics, led to the development of “*Guidelines on Regulating Robotics*” (Palmerina et al. 2016).

As an emerging technology that cannot be limited to a particular jurisdiction, AI needs to be regulated worldwide. Technology regulation has a broader meaning than just creating and applying technical standards. Technological regulation mostly depends on how the regulators perceive the new technology. Software medical devices must be regulated parallelly with hardware medical devices due to their capability to interpret medical data, make predictions, aid in diagnosis and prognosis, monitor health and perform many other similar functions in healthcare.

In the first part of this chapter, the definitional aspects and classification of these devices under the existing medical device categories are discussed. The eligibility criteria for approval of the devices and the different pathways for approval are discussed from the US standpoint. The development of allied laws with respect to regulation of these devices is also analysed. In the case of the EU, the development of the medical device’s regulation and country considerations are discussed. The chapter also compares and contrasts the analysis of developing norms and guidance with respect to software medical devices being developed by the US and the EU drug regulatory agencies. From an Indian perspective, the approval pathway under the existing drug legislation is discussed.

International Medical Devices Regulators Forum Definition for SaMD:**Key Definitions****1.1 Software as a Medical Device**

The term “Software as a Medical Device” (SaMD) is defined as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.

Notes:

SaMD is a medical device and includes in-vitro diagnostic (IVD) medical device.

SaMD is capable of running on general purpose (non-medical purpose) computing platforms.

“without being part of” means software not necessary for a hardware medical device to achieve its intended medical purpose;

Software does not meet the definition of SaMD if its intended purpose is to drive a hardware medical device.

SaMD may be used in combination (e.g., as a module) with other products including medical devices;

SaMD may be interfaced with other medical devices, including hardware medical devices and other SaMD software, as well as general purpose software.

Mobile apps that meet the definition above are considered SaMD.

1.2 Medical Purpose

The following two terms as defined in GHTF/SG1/N71:2012 (*italicized below*) identify medical purpose applicable to SaMD:

1.2.1 Medical Device

‘Medical device’ means any instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

diagnosis, prevention, monitoring, treatment or alleviation of disease,

diagnosis, monitoring, treatment, alleviation of or compensation for an injury,

investigation, replacement, modification, or support of the anatomy or of a physiological process,

*supporting or sustaining life,
control of conception,
disinfection of medical devices,
providing information by means of in vitro examination of specimens derived from the human body;
and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means.*

Note: products which may be considered to be medical devices in some jurisdictions but not in others include:

*disinfection substances,
aids for persons with disabilities,
devices incorporating animal and/or human tissues,
devices for in-vitro fertilization or assisted reproduction technologies.*

Source: Software as Medical Device- IMDRF/SaMD WG/N10FINAL: 2013. <https://www.imdrf.org/documents/software-medical-device-samd-key-definitions>.

3.2.1 Software As a Medical Device

In the earlier part, we explained what medical devices are. We also talked about why regulating AI is important. In order to understand how AI-based medical devices are regulated, it is essential first to know what constitutes *software as a medical device*. Conventionally, medical devices were only considered to be hardware products, but in more recent decades, software is also considered to be a type of medical device. In this regard, the International Medical Device Regulators Forum (IMDRF) has a specific working group that has been identified to develop the guidance to support innovation as well as access to safe and effective software as medical device (SaMD) globally. This group has developed several technical documents. These documents deal with key definitions, risk categorisation, application of quality management system and clinical evaluation. It developed a definition of the term “software as a medical device” (SaMD). The definition of SaMDs states that “*it is a software intended to be used for one or more medical purposes that performs these purposes without being part of a hardware medical device.*”¹ SaMDs may have additional

¹ Software as a Medical Device (SaMD) (International Medical Device Regulators Forum) (2013).

considerations. The IMDRF identifies three aspects in which SaMDs may also be used. They may provide means and suggestions for disease mitigation, providing health information or treating physiological conditions, health state, illnesses or congenital problems and be an aid for diagnosis, screening, monitoring, prediction, prognosis, identification of physiological status and predisposition.

‘Intended use’ is defined as

The term “intended use/intended purpose” is the objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer (GHTF/SG1/N70:2011—Label and Instructions for Use or Medical Devices).

As with any other sector, healthcare also needs updated regulation that involves modern technologies and the way it should be moderated. Different regulatory frameworks had been set up by the countries for a vigil on the deployment and premarketing approvals of SaMDs. We will analyse the general regulation on medical devices first and then move to the medical device regulation of the SaMDs.

In Vitro Diagnostic (IVD) Medical Device

‘In Vitro Diagnostic (IVD) medical device’ means a medical device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.

Note 1: IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status.

Note 2: In some jurisdictions, certain IVD medical devices may be covered by other regulations.

Source: Software as Medical Device—IMDRF/SaMD WG/N10FINAL: 2013. <https://www.imdrf.org/documents/software-medical-device-samd-key-definitions>

In the year 2014, the IMDRF published the technical documentation on the possible framework for risk categorisation. It identified the principles that you could be utilised for categorisation of SaMDs. In the first instance, categorisation is based on SaMD definitional aspects. Further, information on SaMD and healthcare decision are considered together for determining the categories. Four categories, Categories I to IV are identified based on the levels of impact on the patient or public health. Category IV has the highest and Category I has the lowest impact respectively. A SaMD that is used across multiple healthcare situations is categorised under Category IV.

If there is a change in the SaMD leading to change in definition, the manufacturer is suggested to re-evaluate the categorisation. Even if the SaMD is used as an interface with other systems or as a module, it will nevertheless have a separate categorisation.

Criteria for Determining SaMD Category

Criteria for Category IV

- i. SaMD that provides information to treat or diagnose a disease or conditions in a critical situation or condition is a Category IV and is considered to be of very high impact.

Criteria for Category III

- i. SaMD that provides information to treat or diagnose a disease or conditions in a serious situation or condition is a Category III and is considered to be of high impact.
- ii. SaMD that provides information to drive clinical management of a disease or conditions in a critical situation or condition is a Category III and is considered to be of high impact.

Criteria for Category II

- i. SaMD that provides information to treat or diagnose a disease or conditions in a non-serious situation or condition is a Category II and is considered to be of medium impact.
- ii. SaMD that provides information to drive clinical management of a disease or conditions in a serious situation or condition is a Category II and is considered to be of medium impact.
- iii. SaMD that provides information to inform clinical management for a disease or conditions in a critical situation or condition is a Category II and is considered to be of medium impact.

Criteria for Category I

- i. SaMD that provides information to drive clinical management of a disease or conditions in a non-serious situation or condition is a Category I and is considered to be of low impact.
- ii. SaMD that provides information to inform clinical management for a disease or conditions in a serious situation or condition is a Category I and is considered to be of low impact.
- iii. SaMD that provides information to inform clinical management for a disease or conditions in a non-serious situation or condition is a Category I and is considered to be of low impact.

Source: “Software as a Medical Device”: Possible Framework for Risk Categorization and Corresponding Considerations IMDRF/SaMD WG/ N12FINAL:2014

The general regulatory considerations for SaMDs are classification, design, whether it is a general software or third-party software, cybersecurity, use of the device and the type of AI. SaMDs have changed in healthcare settings in different ways, the way in which healthcare professionals practice medicine, interaction with patients and how patients address their own health.

3.3 Regulation of Medical Devices in the USA

The USFDA is the agency that reviews the process of approval for drugs and devices in the USA. The 1976 *Medical Devices Amendment* in the *Federal Food, Drug, and Cosmetic Act* created a new body known as the Center for Device and Radiological Health (CDRH). This Center deals with the protection and promotion of public health with regard to application of medical technologies. It regulates medical device manufacturing, repackaging, relabelling and importing. Medical devices are used to diagnose, prevent or treat a bodily condition or disease without chemical insertion into the body. Before a medical device can be placed on the market, it has to go through a long process of regulatory approval. Unlike the EU and India, the USA has a central system for approving medical devices, which is available at the USFDA's database of all approved medical devices. The daily updated rules and proposed rules are published in Federal Register (FR). Once the FR is finalised and codified, the Code of Federal Regulations (CFR) is published. Title 21 CFR Part 800–1299 relates to medical devices and radiation emitting products. The updated version of CFR is eCFR which is an electronic version.

3.3.1 Definition and Classification of Medical Devices

Section 201(h) Federal Food, Drug and Cosmetic Act (FFDCA) defines medical device as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or any other similar or related article”, which meets several requirements and is intended for diagnosis, cure, mitigation, treatment or prevention of medical conditions.

About 1700 different categories of devices have been categorised by the FDA and placed in sixteen panels of medical specialties. Based on the degree of regulatory oversight required to ensure the device's safety and efficacy, each type of devices is categorised into one of three regulatory classes. These medical device classifications

are based on two things: the intended use of the device and the risk associated with it to the user and patient. According to USFDA, there are three classifications that the USA follows:

- (1) Class I devices are low to moderate-risk devices like bandages, surgical instruments, non-electric wheelchairs, etc.
- (2) Class II devices are intermediate-risk devices like CT scanners, infusion pumps, etc.
- (3) Class III devices are high-risk devices that are very important to health or life-sustaining, like pacemakers, deep brain stimulators, etc.²

The first step by a manufacturer is the identification of the class of the medical device, then the regulation citation under 21 CFR Parts 862–892. But if the manufacturer is not identifying any specific class, consultation with the FDA’s CFR Device Classification Panel can be done. Medical devices must meet the definitional criteria outlined in the classification Section 21 CFR.³

Once the medical device class and regulation citation have been decided, the manufacturer must implement the other basic requirements that the FDA has prescribed for all medical devices. Some of the basic requirements to be fulfilled by medical devices are included in the list that follows:

3.3.2 Basic Requirements

The regulatory requirements for each class depend on how they are categorised and under which regulation citation a device has been accepted. The basic requirements that medical device manufacturers of medical device in the USA must confirm with are establishment registration, listing of medical devices, premarket approval, quality and labelling. The details of the same are described below.

3.3.2.1 Establishment Registration

The first important aspect of the requirements is that initial distributors (importers), domestic and foreign manufacturers of medical devices must register their establishments with the FDA in the electronic form under 21 CFR Part 807. This will not be a requirement if there is a waiver granted. For instance, those who are private label distributors are not required to register. The verification of the establishment registration is done on an annual basis. The manufacturers will need to renew their establishments on an annual basis. In case of foreign manufacturers, there is a need to appoint a US agent. If there is a current US entity registration already done, the same could be utilised to add several foreign manufacturers. Once the details are entered,

² U.S.C. Title 21-FOOD AND DRUGS (2022).

³ Device Classification Panels (FDA) (2018).

the FDA site would indicate submission acceptance information is validated. There is no separate registration certificate. Establishment registration fees must be paid which is uniform whether or not a given entity is a large business or a small business.

3.3.2.2 Medical Device Listing

Manufacturers must list their devices with FDA under 21 CFR Part 807. An update to listing of information is imperative in the effort to improve patient health. Since the 2021, the listing unit has been renamed as Drug Registration and Listing Branch (DRLB) under the Division of Labeling, Registration and Unapproved Drugs and Labeling Compliance. It is important to note that National Drug Code (NDC) Directory would show whether a drug is listed or not. The submission of information should comply with the Structured Product Labeling (SPL) format, and the FDA site has the guidance available on the same. So, establishments involved in production and distribution of medical devices for commercial distribution in the USA would require to also list the devices and activities performed on those devices at a particular establishment.

3.3.2.3 Premarket Notification or Premarket Approval

Depending on the type of medical device, the next step that is relevant after establishment registration and listing is either a premarket clearance or a premarket approval. A premarket clearance comes under the purview of 510(k) clearance and is an authorisation given to market a medium risk medical device. On the other hand, premarket approval is required for the high-risk medical devices.

A premarket notification or the 510(k) clearance comes under 21 CFR Part 807 subpart E. If a device is due for submission of commercialisation, it cannot be commercialised without receiving a letter of substantial equivalence from FDA. A 510(k) needs to show the predicate device availability in the market before 28 May 1976 or a device that has been determined as substantially equivalent by the FDA.

The premarket approval process is under 21 CFR Part 814. Class III of medical devices requires premarketing approval submission which are high risk, and no predicate device is found in Classes I and II through the 510(k) process.

Substantial Equivalence

A device is substantially equivalent if, in comparison to a predicate it:

- has the same intended use as the predicate; **and**
- has the same technological characteristics as the predicate; **or**
- has the same intended use as the predicate; **and**

- has different technological characteristics and does not raise different questions of safety and effectiveness; **and**
- the information submitted to FDA demonstrates that the device is as safe and effective as the legally marketed device.

Source: [fda.gov/medical-devices](https://www.fda.gov/medical-devices)

If FDA ascertains that a device is not substantially equivalent, the applicant may have the option of resubmitting another 510(k) application with new data, request for a Class I or II designation through the De Novo classification process or file a reclassification petition or submit a premarket approval application.

3.3.2.4 Investigational Device (IDE) for Clinical Devices

Under Section 812.3 (g) an ‘investigational device’ means a device, including a transitional device, that is the object of an investigation. Further, investigation means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

An investigational device exemption (IDE) under 21 CFR Part 812 lets the investigational device be used in a clinical study to collect safety and effectiveness data needed to support a Premarket Approval (PMA) or a Premarket Notification 510(k) submission to FDA. Hence, before a clinical study with a device that could pose a risk can start, the FDA and an Institutional Review Board (IRB) must give their approval. IRB approval is only needed before starting a study with a device that does not pose a significant risk.

Investigational Device Exemption (IDE):

- Clinical research
- Collection of safety and efficacy data
- Approval from Institutional Review Board is a requirement

3.3.2.5 Quality System Regulation (QSR)

The quality system regulation under Title 21 Code of Federal Regulation Part Sub-Chapter H includes requirements for the methods, facilities, and controls used in medical device design, purchasing, manufacturing, packaging, labelling, storing, installing and servicing. The FDA checks manufacturing facilities to make sure they meet the QS requirements. The ISO 13485 is the quality standard for devices that is used by many regulatory authorities. Current good manufacturing practices (CGMP)

requirements for devices were authorised under Section 520(f) of the FFD and C Act. A revision of the CGMP regulation was effected in 1990 by the addition of design controls authorised under the Safe Medical Devices Act. This regulation called the Quality System Regulation of QS regulation, that became effective from 1 June 1997, applies to finished device manufacturers who intend to commercially distribute medical device in the USA. This was harmonised with the international standards of ISO 9001 and ISO 13485.

Key Definitions for Quality System Regulation Under Code of Federal Regulations (CFR) Title 21 Volume 8

- 21 CFR 820.3 (k)—Establish—Define, Document and Implement
- 21 CFR 820.3(l)—Finished device—any device or accessory to any device suitable for use or capable of functioning, whether or not it is packaged, labelled, or sterilised.
- 21 CFR 820.3 (c)—Component—any raw material, substance, piece, part, software, firmware, labelling or assembly which is intended to be included as part of the finished packaged and labelled device
- 21 CFR 820.3 (o)—Manufacturer—design, manufactures, fabricates, assembles or processes a finished device, includes contract sterilisation, installation, relabelling, remanufacturing, repackaging or specification development, and initial distributors of foreign entities performing these functions.

3.3.2.6 Labelling Requirements

General device labelling requirements are provided under 21 CFR Part 801. Labelling includes labels on the device as well as informational and descriptive materials that come with the device. The label of a device must clearly specify the name, place of business of manufacturer, packer or distributor. In case the device is manufactured, packed or distributed at a place other than the principal place of business, then the label may have the principal place of business written instead of the actual place.

Label Requirements-Definitions

- Section 201(k) of Federal Food, Drug and Cosmetic Act defines ‘label’ as a: ‘display of written, printed, or graphic matter upon the immediate container of any article...’.
- The term ‘immediate container’ does not include package liners. Any word, statement, or other information appearing on the immediate container must also appear ‘on the outside container or wrapper, if any there be, or the retail package of such article, or is easily legible through the outside container of wrapper.’

- Section 201(m) of Federal Food, Drug and Cosmetic Act defines ‘labeling’ as:

‘all labels and other written, printed, or graphic matter

- (1) upon any article or any of its containers or wrappers, or
- (2) accompanying such article’ at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce.

The term ‘accompanying’ is interpreted liberally to mean more than physical association with the product. It extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, etc. ‘Accompanying’ also includes labeling that is brought together with the device after shipment or delivery for shipment in interstate commerce.

As per ‘intended use’ requirements (under 21 CFR 801.4), there is a need to furnish adequate labelling in cases there are uses other than the intended ones. Further, ‘adequate directions for use’ part of the label provides statements that enable a layman use a device safely and for intended purposes. Such directions include conditions of use of the device, frequency of and time of administration, route or method of application, duration of application, etc.

Labelling Regulation for Medical Devices Under Federal Food, Drug and Cosmetic Act:

- 21 CFR 801—General Device Labelling
- 21 CFR 809—In vitro diagnostic products
- 21 CFR 812—Investigational Device Exemptions
- 21 CFR 830—Unique Device Identification
- 21 CFR 820—Good Manufacturing practices
- 21 CFR 1010—General Electronic Products

3.3.2.7 Medical Device Reports

Under the USFDA, the Medical Device Reporting Program comes under 21 CFR Part 803. This is one of the post-marketing surveillance tools to monitor device performance, detect device-related safety issues and help in the risk assessment of the products. Incidents in which a device may have caused or contributed to a death or serious injury must be reported to the FDA. Voluntary reports may be submitted by healthcare professionals, caregivers, patients and consumers. The MDR regulation is a way for the FDA and manufacturers to find and keep track of serious problems with medical devices. Reports on significant adverse events or product problems are submitted to MedWatch which is the FDA’s safety information and adverse event reporting program.

3.3.3 Approval Pathway for Marketing

General controls apply to all three classifications of medical devices unless exempted by any other regulation. The manufacturer must first determine the class of the medical devices. According to the class to which they belong, medical devices have two different types of safety controls: general and special controls. After the class is established, the regulatory procedure will be chosen, and as a result, the regulation number will be determined. Prior to the discussion about the regulation number and safety controls, it is relevant to know what are the different ways medical devices can get marketing approval. There are two main routes for medical device approval by the FDA's CDRH which are described below.

3.3.3.1 510(K) or Fast-Track Approval

Most of the products have 510k or premarket notification process (PMN) clearance at the moment. Manufacturers are only required to provide the CDRH with evidence that the subject device is “substantially similar” to another predicate device in the USA as part of this process. There are no requirements for clinical or laboratory studies to show that the product is safe or effective. The premarket notification, or 510(k) process, is used for low- to medium-risk devices. The intent to market a medical device must be notified at least 90 days before the FDA. Four types of parties must take 510(k) approval as shown in Fig. 3.1.

Upon examination, if the FDA finds that the submitted device is not substantially equivalent, the applicant may resubmit another 510(k) application with new data, request a Class I or II designation through the De Novo classification process, file a reclassification petition or submit a premarket approval application. The FDA can ask a company to submit clinical data to support clearance or approval, regardless of whether a device must go through the 510(k) or PMA pathway.

3.3.3.2 Premarket Approval

Premarket approval (PMA) is a process the centre employs to assess and approve medical devices that are both genuinely novel and carry a significant risk to the patients who use them. This involves scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. PMA is the CDRH's most stringent and detailed method to check out new medical devices. It is made for devices that could cause the most harm, and it has prerequisites for clinical trials and laboratory tests. The FDA imposes specific requirements on the manufacturing procedure and has the authority to ask for additional information to confirm the device's effectiveness and safety. During this process, the agency asks the manufacturer for information about everything from the drug's shelf life to its microbiology and immunology, as well as any side effects or problems found in clinical studies.

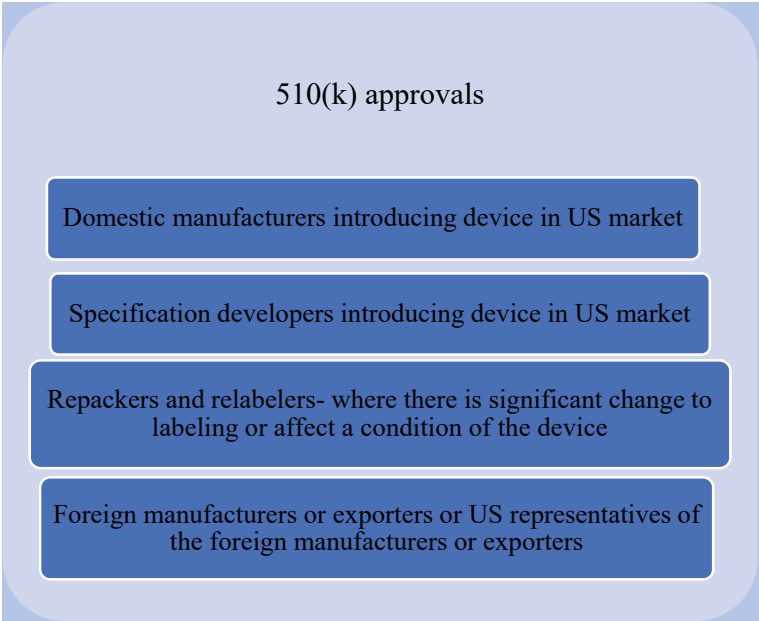


Fig. 3.1 Section 510(k) approval at USFDA (Authors Compilation)

Such approval is governed by 21CFR 814. In case a Class III device fails to meet the premarket approval requirements, it is considered as adulterated under Section 501(f) of the Act and may not be given.

Premarket Approval Application (PMA)

- Applicable for highest risk devices
- Evaluation of safety and effectiveness
- Specific evidence requirements

3.3.3.3 De Novo Pathway

The *De Novo* process allows for the classification of novel medical devices for which general controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use, but for which no legally marketed predicate device exists. In addition to the two pathways above, the *Food and Drug Administration Modernization Act* (FDAMA) of 1997 introduced the *De Novo* classification option as an alternative classification pathway for novel medical devices

that were automatically placed in Class III after receiving a “not substantially equivalent” (NSE) determination in response to a premarket notification [510(k)] submission. *Section 513(f)(2) of the FD&C Act* was amended by *Section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA)* on 9 July 2012 to permit a sponsor to submit a *De Novo* classification request to the FDA without first being required to submit a 510(k) application. There are two options for *De Novo* classification for a novel device of low to moderate risk. First, anyone who gets an NSE determination in response to a 510(k) submission has 30 days to ask the FDA to do a risk-based evaluation to decide whether the device belongs in Class I or Class II. Second, if a person decides that there is no other predicate device on the market for the FDA to use to classify the device into Class I or II based on risk without first submitting a 510(k) and getting an NSE determination. *De Novo*-classified devices may be marketed and used as predicates for subsequent 510(k) submissions. *De Novo* is a classification system that is based on risk and evidence. In 2021, the FDA released a final guidance document ‘De novo classification process’ (Evaluation of Automatic Class III designation). This provides guidance to the manufacturer and the FDA on the process for the submission and review of a *De Novo* classification request under Section 513(f)(2) of the FD and C Act. The review of the *De Novo* request submission is done within 15 days by the FDA.

De Novo Pathway

- No classification regulation
- Applicable for marketing novel devices
- Alternative to premarket approval application
- Lower regulatory control

The similarity between the 510(k) and *De Novo* process is that they are relevant for medical devices with low to moderate risk. The difference is that the former process requires the substantial equivalence part to be proven unlike the latter process.

3.3.3.4 Humanitarian Device Exemption (HDE)

A HDE is a type of premarket application that is described under the Safe Medical Devices Act 1990. Devices approved as an HDE are referred to as a Humanitarian Use Device (HUD). A HUD is intended to treat patients with rare diseases or conditions (i.e. affects fewer than 8000 individuals per year in the USA). The definitional criteria under Section 3052 of the 21st Century Cures Act must be met to be a HUD. The definition of a “rare drug” is to be in accordance with the 1984 Orphan Drug Act (ODA). The eligibility requirement for HDE is to first get designated as HUD by applying at the FDA’s Office of Orphan Products Development (OOPD). For marketing an HUD, application must be filed under Section 520 of FD&C Act;

the device is exempted from the effectiveness requirements under Section 514 and 515 of the said Act but it will be subject to certain profit and use restrictions.⁴ The request for HDE must be approved by the FDA's OOPD over a period of forty-five days. This application is similar to a premarket approval in general form and content but is exempt from the need to demonstrate safety and probable benefit. While the application is not required to include clinical investigation results to substantiate the effectiveness of the device, it must contain sufficient information for the FDA to determine that there is no unreasonable or significant risk of injury or illness from its use. A HUD can only be used under the supervision of an Institutional Review Board that must be set up in the facility.

Humanitarian Device Exemption:

- Represents premarket submission for Humanitarian use of devices
- Intended to 8000 individuals per year in the US (rare or specific conditions)
- Effectiveness determination is exempted
- Reasonable assurance of safety and probable benefit

In the foregoing section, the regulatory pathways that must be followed for each type of medical device, based on its classification, have been discussed. A 510K will be needed for marketing if a device falls under Class I or II and does not qualify for an exemption. For all devices that are designated as exempt, the restrictions on exemptions apply. In accordance with CFR 21, exempted device limitations are listed (862–892). Class III devices must submit a premarket approval application unless they were on the market before the 1976 medical device amendments were passed or are essentially equivalent to such a device, and PMAs have not been requested. The product will then be released to the public via a 510(k). This is about the regulatory approval pathways of medical devices. In addition to the above criteria, all medical devices must also go through regulatory controls. The *De Novo* is very new form of regulatory approval. The Humanitarian device exemption is used in very rare conditions of medical devices.⁵ In the following section, regulatory controls that are applied by the FDA are discussed.

⁴ Humanitarian Device Exemption (FDA) (2022).

⁵ Jill (2014).

3.3.3.5 Regulatory Controls for Medical Devices

Along with the regulatory pathways for the different class of medical device, safety controls are required for medical devices. Each of the medical devices class is based on the level of control needed to provide a reasonable check on safety and efficacy. The regulatory control increases with the risk associated with the medical device.⁶

- Class I medical devices with low to moderate risk need general control.
- Class II medical devices with moderate to high risk need general and special controls.
- Class III medical devices with high risks need general and premarket approval (PMA).

General Control

Section 501, 502, 510, 516, 518, 519 and 520 of the FD&C Act authorise the requirement for general controls. The general controls apply to all medical devices, i.e. Classes I, II and III unless they are exempted by a different regulation. If a device is exempt from the general control, it will be mentioned in the classification regulation for that device.

The general controls are enlisted in following sections of *FD&C Act*:

501: Adulterated devices.

502: Misbranded devices.

510: Registration of producers of the device

- Establishment registration and device listing.
- Premarket notification (510k).
- Reprocessed single-use devices.

516: Banned devices.

518: Notifications and other remedies

- Notification.
- Repair.
- Replacement.
- Refund.
- Reimbursement.
- Mandatory recall.

519: Records and reports on devices

- Adverse event report.
- Device tracking.
- Unique Device Identification System.
- Reports of removals and corrections.

⁶ How to Study and Market Your Device (FDA) (2022).

520: General provisions respecting control of devices intended for human use

- Custom device.
- Restricted device.
- Good manufacturing practice requirements.
- Exemptions for devices for investigational use.
- Transitional provisions for devices considered as new drugs.
- Humanitarian device exemption.

Special Control

Special controls are regulatory requirements for Class II devices where general controls alone are inadequate. Special control measures include:

- Performance standards.
- Post-market surveillance.
- Patient registries.
- Special labelling requirements.
- Premarket data requirements.
- Guideline.

Unique Device Identifier (UDI) Labelling Requirement

In July 2021, the FDA announced a final detailed guidance on form and content requirements for Unique Device Identifier labelling. The regulation for establishing a UDI system fulfils the statutory requirement prescribed under Section 519(f) of the FD&C Act. It also fulfils the requirement under Section 614 of FDASIA Act. This is necessary from the manufacturing through distribution to patient use. The labeller/manufacturer needs to submit product information about the device to FDA's Global Unique Device Identification Database (GUDID), unless any exception is stated.

The labelling guidelines of UDI requirements are as follows:

- The information must be presented in two forms on device labels and packaging; first, it should be easily readable in plain text so that it is easily understandable for entering into patients' records for stakeholders like healthcare providers, patients and regulators. Also, it should have automatic identification and data capture (AIDC) technology, which allows a fast, accurate process of recording and retrieving UDI data.
- UDI content shall incorporate a device identifier (DI) segment and a production identifier (PI) segment. In some cases, only DI is required.
- Data delimiters shall be used to identify specific data elements within the UDI device that helps in supporting the effectiveness of both plain text and AIDC UDI format.

The UDI data given in plain text format must be presented as DI data; afterwards, PI data only in cases applicable.

The guidance document has also clearly distinguished the UDIs from Universal Product Codes (UPCs). UPCs are the product identifier codes which are sold in retail outlets in USA. The manufacturer of Class I medical device may avail the UPC criteria for the purpose of meeting the UDI requirements on condition that the device labellers “have proper control over the UPC assignment and use advance the goals of the UDI system.”⁷

3.3.4 The Food and Drug Administration Safety and Innovation Act (FDASIA), 2012

Congress enacted the FDASIA in July 2012 to empower the FDA to protect and improve public health in numerous ways, such as by allowing it to collect user fees, encourage innovation, involve stakeholders and make the drug supply chain safer. FDA was mandated to post the number and type of medical devices reclassified in the previous calendar year under *Section 608(c)* of the said Act. The act has reclassified medical devices into two categories: pre-amendments and post-amendments.

Pre-amendment devices were on the market before 28 May 1976 when the *Medical Device Amendments* to the FD&C Act became law. If the FDA decides to reclassify a medical device *suo moto* or in response to a petition, new information regarding the medical device is required. This requires publishing a proposed order in the Federal Register mentioning proposed reclassification and supporting valid scientific evidence. Further, the device classification panel meetings need to be conducted to consider comments from relevant public dockets. The scientific evidence for each medical device class is different, and hence compliance with general and special controls is also different.

Post-amendment devices are those that did not exist prior to the Medical Devices Amendment and are generally classified as Class III medical devices under Section 513(f) (1).⁸

The FDA created the Breakthrough Device Program (hereinafter referred as the Program) to implement Section 515B of the FD&C Act created by Section 3051 of the 21st Century Cures Act and amended by Section 901 of the FDA. Reauthorization Act of 2017. This Program is voluntary for specific medical devices or device-led combinational products that aim to provide effective treatment or diagnosis of severe or irreversibly debilitating diseases or conditions. It also aims to get medical devices to patients on time by speeding up the development, assessment and review processes not compromising on the regulatory standards under various regulatory pathways.

This Program has superseded the Expedited Access Pathway (EAP) and the Innovation Pathway, both designed to facilitate the development and review of Breakthrough Devices. Due to its consistent vision and designation criteria, the devices previously approved under these programs are now part of the Breakthrough Devices

⁷ Unique Device Identification System (UDI System) (FDA) (2022).

⁸ Food and Drug Administration Safety and Innovation Act (FDASIA) (FDA) (2018).

Program. Under Section 515B of the FD&C Act, Breakthrough Devices will receive priority review. Several Breakthrough Devices have been granted to CDRH and the Center for Biologics Evaluation and Research (CBER). There are eight hundred and twenty-eight Breakthrough Device designations so far. The maximum number granted are in the areas of cardiology and neurology. A total of fifty-six marketing authorisations have been given which include fifty-four CDRH devices and two CBER devices respectively.

Under this Program, a few AI devices also got approval as Breakthrough Devices; one example is Paige. AI. It has a device called Paige Prostrate, an algorithm software device used to assist in digital pathology. The device also got approval through a novel regulatory pathway, i.e. De Novo (DEN 200080).⁹ Vicarious Surgical becomes the first to get designation of Breakthrough Device in the category in surgical robots. The device is intended to help “surgeons perform the surgery through a single micro-incision.”¹⁰

3.3.5 *The 21st Century Cures Act (Cures Act)*

The Cures Act was signed in December 2016 to speed up the process of development of medical devices and new innovations and to provide faster and efficient technology to patients. The Act has established programs for facilitating faster product development through recruiting expert scientific, technical and professional experts. One such program is Breakthrough Devices Program, which is already discussed in paragraph above. At the end of 2016, the 21st Century Cures Act clarified the scope of FDA regulatory jurisdiction over software used in healthcare, specifying that a medical device is an instrument or other tool “*intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals, or intended to affect the structure or function of the body of man or other animals.*” Every AI system that falls under this definition will be regulated by the USFDA (Pesapane et al. 2018).

Section 3060 of the Cures Act exempts five categories of software functions from the definitional aspect of device under FD&C Act, and the type of software excluded from the definition of “device” is as follows:

- Software providing administrative support of a healthcare facility.
- Software used in transferring, storing, formatting conversion or displaying certain electronic medical records.
- Software used for maintaining healthy lifestyles, which are not related to diagnosis, cure, mitigation, prevention or treatment.

⁹ Breakthrough Devices Program—Guidance (FDA) (2018).

¹⁰ About Vicarious Surgical | Revolutionizing Robotic Surgery (*Vicarious Surgical*) (2022).

- Software tools for transferring, storing, converting formats or displaying clinical laboratory test or other device data and results as long as it is not intended for the purpose of interpreting or analysing the clinical laboratory test or other data.
- The term ‘medical information’ means information that supports or provides recommendations to a healthcare professional about prevention, diagnosis or treatment of a patient. It does not mean that such information should be relied upon solely for the purpose of making individual clinical diagnosis or treatment decisions.¹¹

Devices which meet all the requirements under this section will be exempted from the definition of “device” in Section 520 (o) (1) (e) of FD&C Act. 3.2.6 Approval of AI-Based Medical Devices.

As discussed above, the basic requirements for a medical device have been elaborated. These requirements are general and apply to all AI-based medical devices in the USA.

The USFDA has classified software as medical devices and approved several over the last few decades. It has adopted the definition of SaMD provided by IMDRF, which has been mentioned earlier in this chapter. For any software to be governed as “software as medical device,” it has to be in line with the prerequisites mentioned in the definition of SaMD. Any software intended to “*treat, diagnose, cure, mitigate, or prevent disease or any condition*” will be considered a medical device and regulated by the FDA. In some cases, the software is manufactured using AI/ML, so they are also classified as SaMD. Sometimes, the device may not be an AI medical device but can incorporate AI technology. Manufacturers often fail to follow the definitional criteria of SaMD.

Once a product has passed the “definition test,” the manufacturer has to look into other eligibility aspects for regulatory clearance. The next step is identifying the class of medical device. Depending on the class regulatory controls will apply. Software medical devices also go through the same essential preconditions as non-software medical devices. The only difference is in their regulatory pathway or any other provision that might be mentioned in any other US Act relating to SaMD. FDA routinely updates its database of approved SaMD with all the particulars. As per the available data on the FDA website, five hundred and twenty-one SaMDs have been approved by 15 January 2023. Analysis of some of the trends has been done by the authors based on the available data. First is the yearly growth of approval of SaMD by the USFDA in Fig. 3.2. Interestingly there has been a growth in the approval of AI-based medical devices post-2010. Before that, a few devices were approved under various other simultaneous programs the FDA has carried out.

¹¹ 21st Century Cures Act 2016, 114 Congress, H.R.34 (USA) <https://www.congress.gov/bill/114th-congress/house-bill/34>.

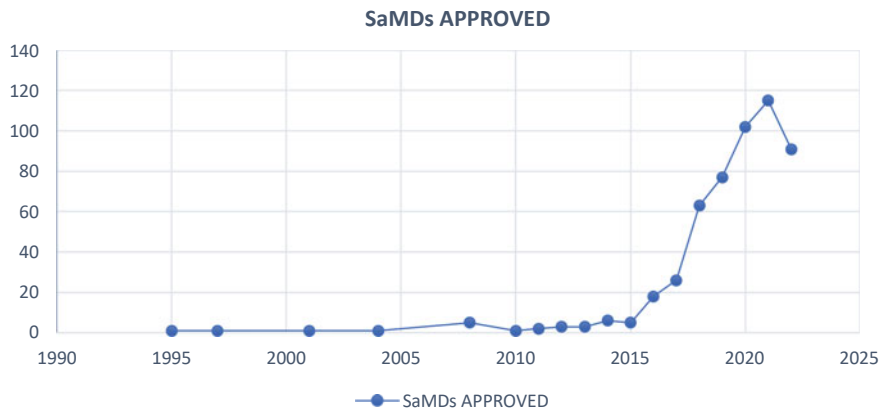
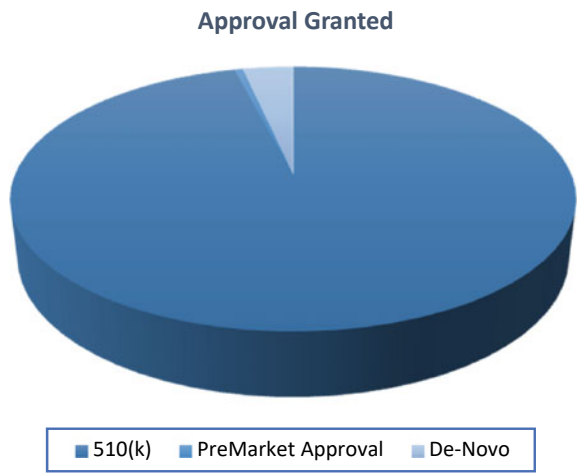


Fig. 3.2 Year-wise SaMD approvals by USFDA (Authors Compilation)

In the preceding sections, the various regulatory pathways have been discussed for medical device regulation. It is observed that 510(k) approval route is the most predominant route of application for marketing approval (Fig. 3.3).

There are various domains of application of approved SaMD devices under various product classifications. It is observed that broadly there are at least fifteen different areas in which SaMDs have been approved. Among these, the area of radiology is the top category with three hundred and ninety-two approvals so far (Fig. 3.4.).

Fig. 3.3 Regulatory pathways for approval of SaMDs by FDA (Authors Compilation)



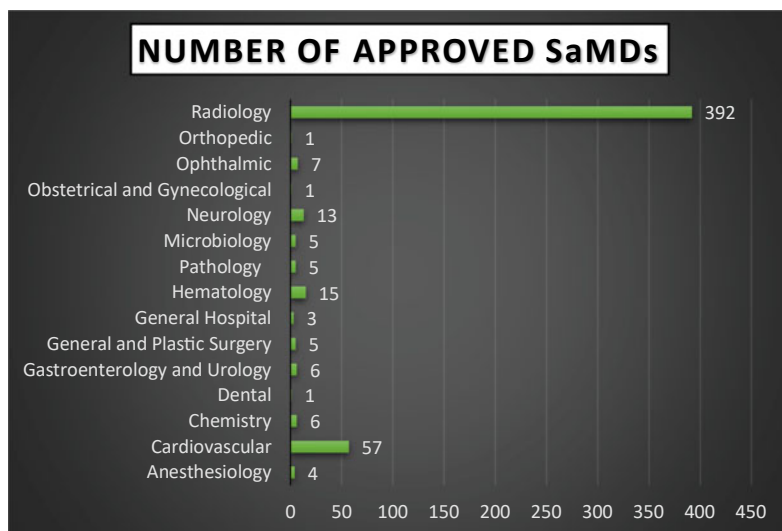


Fig. 3.4 SaMDs approval in various medical device categories by FDA (Authors Compilation)

The manufacturer has to identify the medical device classification for its devices; generally, AI devices are placed under Class I or II. For Class I, the SaMD is the software that displays the readings, e.g. smart watches and glucometers. Class II SaMD is a device used for diagnosis and scans that analyses medical images. A few devices approved in Class III got approved through PMA, like Guardian Connect System and Continuous Glucose Monitoring System. In this category, SaMD must undergo a strict approval process and submit clinical evidence, by listing all the risks and benefits of the device. After the classification, regulatory controls standards are applicable on that device, if it comes under Class I. Only general controls will be applicable on SaMD. General and special regulatory control will be applicable if it comes under Class II. For Class III SaMDs, general and PMA will be applied. As described earlier with regard to regulatory controls, SaMD has to fulfil all the criteria according to the regulatory control provisions. After this comes regulatory pathway selection. In the case of SaMD, it is observed that mostly these devices go through the 510(k) regulatory pathway. In some cases, the PMA and De Novo pathway have been implemented.

Example of a 510(k) approved SaMD

Device Classification Name	stethoscope_electronic
510(k) Number	K220766
Device Name	eMurmur Heart AI
Applicant	CSD Labs GmbH Nikolaipplatz 4 Graz, AT 8020
Applicant Contact	Andreas Reinisch
Correspondent	RQM+ 2251 San Diego Ave, Suite B-257 San Diego, CA 92110
Correspondent Contact	Allison Komiyama
Regulation Number	870.1875
Classification Product Code	DQD
Subsequent Product Code	DQC
Date Received	03/16/2022
Decision Date	05/31/2022
Decision	Substantially Equivalent (SESE)
Regulation Medical Specialty	Cardiovascular
510k Review Panel	Cardiovascular
Summary	Summary
Type	Special
Reviewed by Third Party	No
Combination Product	No

Source: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K220766>

Under 510(k) approval, the manufacturer has to establish the pre-existing predicate device with the same technological characteristics in the matter. Premarket approval is granted for Class III medical devices based on AI algorithms. Class III medical devices pose a great risk to human health, and for that reason, their approval process is extensive compared to the other two classes. The FDA only verifies medical devices when the safety and efficiency of the medical device is corroborated by valid scientific evidence.

Example of a PMA approval of SaMD

Search for ‘pacemaker’ in the PMA database:

Premarket Approval (PMA)

FDA Home Medical Devices Databases

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.

[Learn more...](#)

Search Database

Help Download Files

Applicant

Product Code

PMA Number

Device

Expedited Review

Docket Number

Decision Date

to

Advisory Committee

Cleared/Approved IVD Products

Supplement Type

Combination Products

Sort by

Center

Quick Search

Clear Form

Search

New Search

Export to Excel Help

Device	Applicant	PMA Number	Decision Date
Pacemaker/Icd/Crt Non-Implanted Components Psw 210...	BIOTRONIK, INC.	P100009 S100	01/12/2023
Pacemaker/Icd/Crt Non-Implanted Components Psw 210...	BIOTRONIK, INC.	P150023 S169	01/12/2023
Pacemaker/Icd/Crt Non-Implanted Components Psw 210...	BIOTRONIK, INC.	P170008 S143	01/12/2023
Pacemaker Devices	Boston Scientific Corp.	N170003 S277	12/20/2022
Pacemaker Devices	BOSTONSCIENTIFIC	P150012 S131	12/20/2022
Drug Eluting Permanent Right Ventricular (Rv) Or R...	BIOTRONIK, INC.	P150037 S243	12/16/2022
Non-Mri Pacemakers	Boston Scientific Corp.	N970003 S278	12/12/2022
Accolade Family Of Devices Pacemakers And Cardiac...	Boston Scientific Corp.	N970003 S280	12/12/2022
Cardiac Resynchronization Therapy - Pacemaker /Crt ...	GUIDANT CORP.	P130005 S223	12/12/2022
Accolade Family Of Devices Pacemakers And Cardiac...	GUIDANT CORP.	P130005 S225	12/12/2022

Upon such approval by the USFDA, the applicant can move to market the product. A 510(k) clearance is granted to an AI algorithm when it has been established that it is as effective and safe as another similar, approved and legally marketed SaMD or AI-based device. The applicant must show that the product is very similar to the one that is already on the market in terms of safety and effectiveness. De Novo pathway clearance is used to classify those classes of medical devices that do not have their legally marketed counterparts. Still, those advanced medical devices fulfil safety and efficacy criteria with general controls. For this class of AI-based medical devices, or SaMDs, the FDA performs a risk-based assessment of the device before legally

Table 3.1 Types of 510(k) approval (Authors Compilation)

Premarket notification 510(k)	Traditional 510(k)	Special 510(k) program	Abbreviated 510(k) program
	This Program can be used in any condition to seek approval for a device. There is no PMN form for this. There is the only concept of “substantial equivalence (SE)” with the device already marketed legally or predicate device. A comparison is made between the prospective and predicate device	Special 510(k) can be submitted by the manufacturer if he wants to make changes to his existing device in the market or changes like labelling or design	The manufacturer can apply for this Program if the submission is based on guidance documents, there are voluntary consensus standards, or if you follow any special controls for the type of device

allowing it onto the market.¹² In some cases, the manufacturer of SaMD has also applied for the reclassification request and has been granted the provisions mentioned in the FDSAI Act.

Based on an analysis of the approved SaMD details on the FDA website, SaMDs have three types of premarket notification 510(k) approvals.¹³ We found that though the application has been under the 510(k) regulatory pathway, most of the applications filed by manufacturer for SaMD approval are under the traditional 510(k) program. A few of the applications are under abbreviated or special 510(k) program (Table 3.1).

Once the AI device has passed through the regulatory process, the FDA uses a risk-based method to decide if any changes made by the developer will need to be reviewed. If the product is updated in a way that changes how it performs in a significant way, the FDA will review it again. The extent to which changes were made to the device will determine what kind of review it will go through. According to a study, FDA has only approved AI devices based on “locked algorithms.” These devices only frequently change if the developer makes some changes. Adaptive algorithms, on the contrary, learn in real time and are more susceptible to risk and changing performances.

21 CFR 801.50 states that the UDI rule is applicable for standalone software devices regulated by the FDA. As per 21 CFR 801.50 (a) and (b), the labelling rule differs for standalone software devices, depending on their packaged distribution.

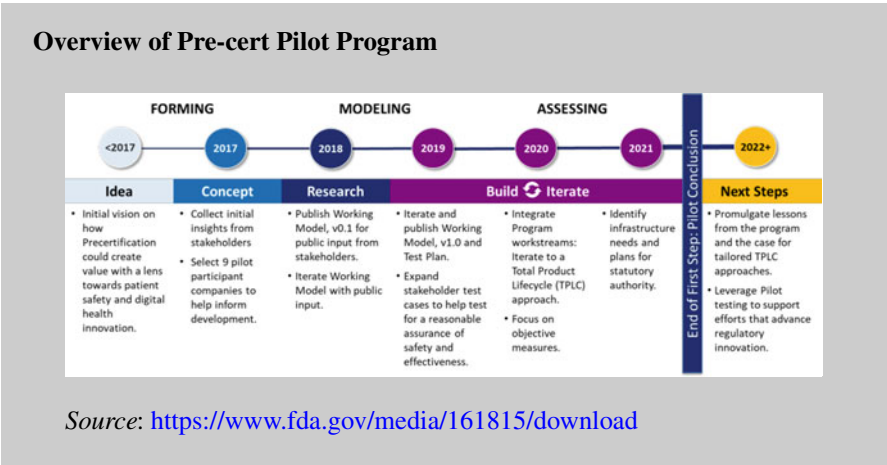
For devices not distributed in packaged form, the labelling requirements can be met by fulfilling either or both criteria, and the version number must be conveyed in its production identifier (PI). The two standards are: first, it should be a plain text statement displayed at the start of the software, which is easily understandable, or a simple text statement which can be displayed through the menu command of the software. For devices that are distributed in the packaged form must adhere to the standard mentioned above and bear a UDI in both easily readable formats, i.e. plain text and AIDC format.

¹² Benjamins et al. (2020).
¹³ 510(k) Submission Programs (FDA) (2019).

All the approvals by the USFDA are under the Digital Healthcare Innovation Action Plan,¹⁴ which consists of the Software pre-certification (pre-cert) Pilot Program under which many AI-based digital health projects have already been completed.

AI healthcare data is governed by data protection law in the USA and other medical device legislation and rules. Software-based medical devices are also subject to post-marketing surveillance. The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule says that patient information must be kept private in the USA. HIPAA creates a relatively complex set of permitted and restricted uses of protected health information, and all the developers and manufacturers must comply with all the relevant rules regarding AI medical devices.¹⁵ The registration and listing, labelling, medical device reporting or post-marketing safety reporting are also applicable to SaMD but are not limited to only these provisions. So, these standard rules apply for AI-based medical devices in the USA.

When discussing regulations for artificial intelligence in healthcare devices, there are a few documents and guidance that are noteworthy. While some of these are not binding, they are still relevant for regulatory oversight in some aspects of AI medical devices. The pre-certification pilot program should also be mentioned when we discuss regulation and AI. The pre-certification program (Developing a Software Pre-certification Program 2019) is a USFDA initiative to assist SaMD developer access to the product’s safety and efficacy and provide more streamlined and efficient regulatory insights.



It has a provision of evaluating the developer first before reviewing the devices. The developer needs to show the adoption of a rigorous process to develop a safe and

¹⁴ Digital Health Innovation Action Plan | FDA (2022).

¹⁵ Health Insurance Portability and Accountability Act of 1996 104 Congress H.R. 3103 (USA). <https://www.congress.gov/bill/104th-congress/house-bill/3103>.

effective device. Under the pre-cert program, the FDA has shortlisted some companies, and the SaMDs developed by these companies are continuously evaluated to be supported by an enhanced regulatory decision.¹⁶ Compared to computer-aided detection systems (CADE), FDA clearance is even harder to obtain for an AI system that does not need a radiologist's supervision and cannot be compared to predicate medical devices used as replacements for radiologists. The USFDA has categorically differentiated the algorithms designed to automate the performance of clinical tasks as medical devices by either being embodied in traditional medical devices or under SaMD. The USFDA published its views on the use of AI in healthcare in "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning-Based Software as a Medical Device (SaMD)" in 2019. The USFDA goes through continuous modification to permit any software as a medical device, depending on the risk factor involved. FDA notes that unlike other medical devices AI algorithms used by software devices in healthcare are self-learning. They need to be scrutinised from time to time.

The USFDA has mentioned various objectives in its report to decide on the need for new submissions in the case of AI-based medical devices. Improvements to clinical and analytical performance.

- I. Modification of the "input data".
- II. Change of intended use.

There are a few best practices followed by the FDA irrespective of the use of AI in medical devices, which all manufacturers must conform to as given below:

- I. Planning and initial evaluation regarding the performance and safety of the device.
- II. Approach for modifications after initial release.
- III. Quality management systems and Good Machine Learning Practices.
- IV. Transparency and real-world performance monitoring.

FDA's proposed regulatory framework on a "Pre-determined Change Control Plan" (PCCP) is a significant development for manufacturers. This document outlines how the manufacturer expects and intends the algorithm or smart medical device to act, function and evolve when in use. In 2019, a white paper was developed in which FDA answered some potential questions of adoptive learning based on four general principles:

1. The first aspect is about standards. FDA expects SaMD developers to comply with Good Machine Learning Practices (GMLP). These are the best practices a developer would need to follow when making an algorithm. This set of standards is still being worked on and may need to be added to the GMP requirements for devices in future.
2. As part of the initial review, before putting an AI/ML-based SaMD on the market, developers would have to submit a plan for possible future changes. This is called

¹⁶ Digital Health Software Precertification (Pre-Cert) Pilot Program (FDA) (2022).

- a “pre-determined change control plan.” This plan would enumerate the changes that are likely to happen and how the developer anticipates making those changes.
3. If a SaMD product needs to be changed, the developer will likely need to file a new premarket submission. If changes are made within the limits of a pre-determined change control plan already set, developers would only need to record those changes. However, if the changes lead to a change in how the product is meant to be used, the FDA would likely need to do another premarket review.
 4. Developers would have to closely watch their products’ progress over time and report back to the agency with regular updates on their development status.¹⁷

Types of Anticipated Changes Under Pre-Determined Change Control Plan

SaMD Pre-specifications: A SaMD manufacturer’s anticipated modifications to “performance” or “inputs,” or changes related to the “intended use” of AI/ML-based SaMD. These are the types of changes the manufacturer plans to achieve when the SaMD is in use. The SPS draws a “region of potential changes” around the initial specifications and labelling of the original device. This is “what” the manufacturer intends the algorithm to become as it learns.

Algorithm Change Protocol: Specific methods that a manufacturer has in place to achieve and appropriately control the risks of the anticipated types of modifications delineated in the SPS. The ACP is a step-by-step delineation of the data and procedures to be followed so that the modification achieves its goals and the device remains safe and effective after the modification.

Source: <https://www.fda.gov/files/medical%20devices/published/US-FDA-Artificial-Intelligence-and-Machine-Learning-Discussion-Paper.pdf>

Beginning 1 January 2023 the FDA aims to streamline the development of medical devices to increase predictability and to bring down the time from concept to commercialisation by the introduction of the TAP Pilot program. The Program is called the total Product Life Cycle (TPLC)¹⁸ Advisory Program (TAP) Pilot. The expedited process will focus on the expeditious development of safe, effective and high-quality medical devices for consumers. During the COVID-19 pandemic, FDA has utilised it to evaluate and authorise medical device quickly. TAP Pilot has a specialised team to provide feedback and advice according to the case-to-case device developer in the Program. This will be helpful for the developers for improvement and submission process.¹⁹ USFDA has approved some machine vision imaging applications. In Table 3.2, a representation of some AI-based medical devices supported for marketing in the USA from the year 2017–2022 is provided.

¹⁷ Artificial Intelligence and Machine Learning in Software (FDA) (2021).

¹⁸ The Total Product Life Cycle (TPLC) database integrates data pertaining to medical devices from premarketing and post-marketing.

¹⁹ Total Product Life Cycle Advisory Program (TAP) (FDA) (2022).

Table 3.2 Representative approved SaMDs by FDA (Authors Compilation)

Name of the tool/device	Target area	Year
Arterys	AI-based tool on MRI to hear the interpretation and CT diagnostics of lung and liver cancer	2017
Alivecor	AI-based tool on atrial fibrillation detection via Apple Watch	
MaxQ-AI and Icometrix	CT brain bleed diagnostics and MRI brain interpretation	2018
Bay Labs (Caption Health)	Echocardiogram EF determination	
Neural Analytics	Paramedic stroke diagnosis	
Zebra Medical	Coronary calcium scoring	
ProFound AI™	Digital breast tomosynthesis	
Recursion Pharmaceuticals	Investigational new drug application (a Phase I study of REC-994) in cavernous cerebral malformation	
Aidoc	AI solution for flagging large vessel occlusion (LVO) in head CTA scans, pulmonary embolism, cervical spine fractures and intracranial haemorrhage	2019
Apple Watch Series 4	For capturing rhythmic heart irregularities using electrodes	
Tokyo-based start-up AI Medical Service	Analysis of endoscopy images for potential diagnosis of gastric cancer	
Eko	The first digital stethoscope to identify AFib and murmurs	
HealthJOINT	Orthopaedic medical image device	
Quantib Prostrate	Radiology solution for reading MRI reading	2020
EyeArt	Software for detecting diabetic retinopathy	
HALO	Medical image diagnosis device	
CINA CHEST	Medical imaging radiological device	
EnsoSleep	Automatic event detection software for polysomnograph with electroencephalograph	2021
<i>RetinAI</i>	Ophthalmology	
Plaque Analysis	Diagnosis of coronary artery disease	2022
FreeStyle Libre 3	Glucose monitoring app	
ONO Retrieval System	Surgical tool for removing devices from patient's vascular system	

(continued)

Table 3.2 (continued)

Name of the tool/device	Target area	Year
Anumana	Detects signs of pulmonary hypertension (PH) in electrocardiogram results	
Viz PE Solution	Automated right ventricle/left ventricle ratio algorithm for identifying potential RV dilation	

In 2021, the FDA introduced the Q-submission program or ‘Q-Sub’ for medical device submissions. Participants may share information with the FDA on pre-submissions, submission issue requests, study risk determinations, informational meetings and other Q-submission types. Such meetings are in person or through videoconference modes only and are helpful to orient with the FDA before the costly testing procedure and also appraise it with the designs developed by the company. The Q-submission program can help companies make an early determination on their commercialisation strategies. Each of the Q-sub types varies in the method of feedback as well as the time frame for feedback or scheduling meeting. It should be noted that the guidance is non-binding and not legally enforceable (Fig. 3.5).

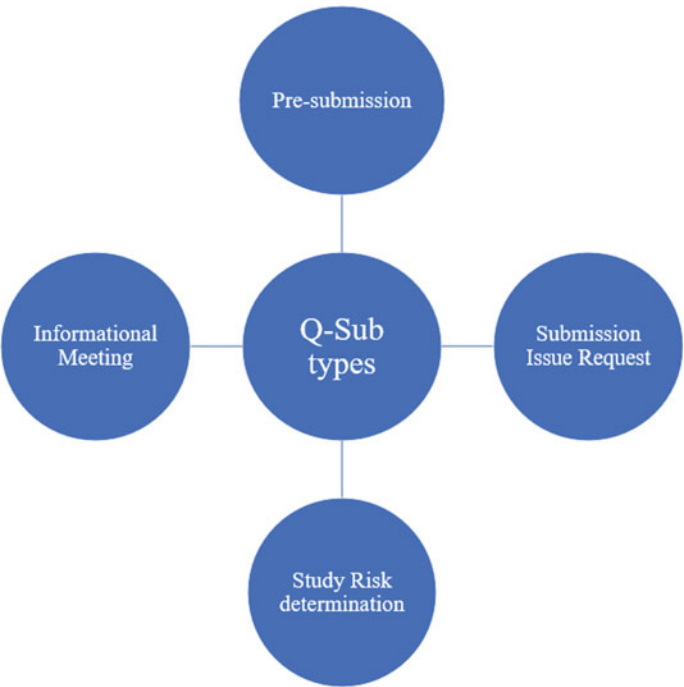


Fig. 3.5 Q-sub types for medical devices

Emergency Use Authorisation (EUA) has been given to certain AI/ML-based devices by the USFDA. In 2021, the USFDA gave EUA for the first ML-based device, the Tiger Tech COVID Plus Monitor, that identifies certain biomarkers indicative of SARS-CoV-2 infection. It is suggested to be useful in blood clotting conditions or in severe allergic reactions. The COViage (COViage Hemodynamic Instability and Respiratory Decompensation Prediction System) is a software that utilises two algorithms: one to measure the risk-level determination for hemodynamic instability and the other to calculate risk-level determination for respiratory decompensation.

3.4 Regulation of Medical Devices in the European Union

The European countries joined together to create a common marketplace known as the European Union. The EU legislation lays a consistent foundation across the Union for unified standards. Previously there were directives relating to medical devices, which were adopted by the Member State, but they had a degree of flexibility and depended on the domestic interpretation. The regulation is directly effective without any flexibility in each Member State, outlining the objective it needs to achieve and the way it must be met. The European Medicines Agency (EMA) is the drug regulatory authority in the EU. EMA is responsible for evaluating the quality, safety and efficiency of applications for marketing approval that undergo the centralised procedure. This includes evaluating a medical device's safety and performance when combined with a drug.

Prior to the Medical Device Regulation (MDR) directive, the EU had a Medical Device Directive (MDD). The MDR replaces the Medical Devices Directive (93/42/EEC) and the active implantable Medical Devices Directive (90/385/EEC). In 2017, the MDR was published providing a four-year transition period from the MDD to the MDR applicability. This transition period ended on 26 May 2021. The MDR retains the aspects of MDD but is more expansive and has several newer aspects. With the introduction of the new MDR, a harmonised medical devices regulation has come across all the Member States with no variation or flexibility of implementation. Recently the EU *In-vitro medical devices directives (IVDD) 98/79* have been replaced with *In-vitro diagnostic medical regulation (IVDR) 2017/746*, and *Medical Device Directives (MDD) 93/42* have been replaced with *Medical Device Regulation (MDR) 2017/745* which govern all the medical devices.

Key Changes from MDD to MDR

- Enhanced aspects of safety
- Changed requirements for Notified Bodies
- Classification of device with wider scope

- Recognition of internet sales of medical devices and remote use of diagnostic and therapeutic services
- Introduction of clinical evaluation consultation procedure for some Class IIb devices and for implantable Class III devices by an independent expert panel
- New UDI system with enhanced traceability and post market safety
- New database for increasing transparency as well as a single repository—the development of EUDAMED.

3.4.1 Definition and Classification of Medical Device

According to Article 2 of MDR, a medical device is defined as:

*“any instrument, apparatus, appliance, **software**, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:*

- *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
- *investigation, replacement or modification of the anatomy or a physiological or pathological process or state,*
- *providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,*

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.”

Article 51 of EU MDR 2017/745 classified medical devices based on their inherent risks²⁰ and intended purpose²¹ in four classes. EU follows the rules-based approach for classification of its medical devices which are listed in Annex VIII.²²

- i. Class I is the low-risk medical devices like manual wheelchairs, glasses, frames, etc.

²⁰ According to Article 2(23) of MDR “risk’ means the combination of the probability of occurrence of harm and the severity of that harm.”

²¹ According to Article 2(12) of MDR ‘intended purpose’ means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation.”

²² REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL [2017] OJ 2 117/01.

- ii. Class II (a) is medical devices with low to medium risks, like dental fillings, surgical clamps and tracheotomy tubes.
- iii. Class II (b) is a medical device with medium to high risks, like condoms, lung ventilators and bone fixation plates.
- iv. Class III is medical devices of high risk, like pacemakers, heart valves and implanted cerebral stimulators.

Once the medical device manufacturer is assured of its definition and class, it must adhere to all the general requirements listed in Article 10 of MDR. The general requirements are not limited to risk management, clinical evaluation, technical documents, etc. Once general requirements are complied with, then the manufacturer (other than custom-made and investigational devices) shall comply with Article 19 declaration of conformity and Article 20, affixing the CE mark.

3.4.2 *Authorised Representative*

According to Article 2(32) of MDR Authorised Representative has been defined as “any natural or legal person established within the Union who has received and accepted a written mandate from a manufacturer, located outside the Union, to act on the manufacturer’s behalf in relation to specified tasks with regard to the latter’s obligations under this Regulation.”²³

The Article 11 of MDR states that “before obtaining a CE marking, non-EU manufacturers must appoint an Authorized Representative. Authorised Representatives must operate within the EU and will continue to serve as the primary point of contact between manufacturers, notified bodies, and competent national authorities. The authorised representative’s contact information must also be visible on all packaging and labelling.”²⁴

3.4.3 *Notified Bodies*

The notified bodies are responsible for the assessment of the medical devices in the medium and the high-risk category devices before they are marketed in the EU. They are private organisations designated by the national health authorities to review and assess whether the documentation submitted is in compliance with the regulation. A certificate is issued by the notified body if the requirements are met allowing the manufacturer to place a CE mark on the products and market them. Regular compliance is monitored by the notified body. Before a new certificate is issued it

²³ REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL [2017] OJ 2 117/01.

²⁴ REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL [2017] OJ 2 117/01.

will audit the manufacturer's compliance on the legal requirements. Manufacturers of all classes of a medical device must take approval from notified bodies (NB) before applying for CE mark except Class I devices. Class I devices are self-certified. The only exemption from this is for those that include sterile products or a measuring function.

Each Member State of the EU will designate accredited notified bodies; these bodies will be responsible for conformity assessments of the devices. In the case of high-risk devices, they can approach the EMA or seek an expert's opinion from expert panels. Presently, there are 37 NB under EUMDR.

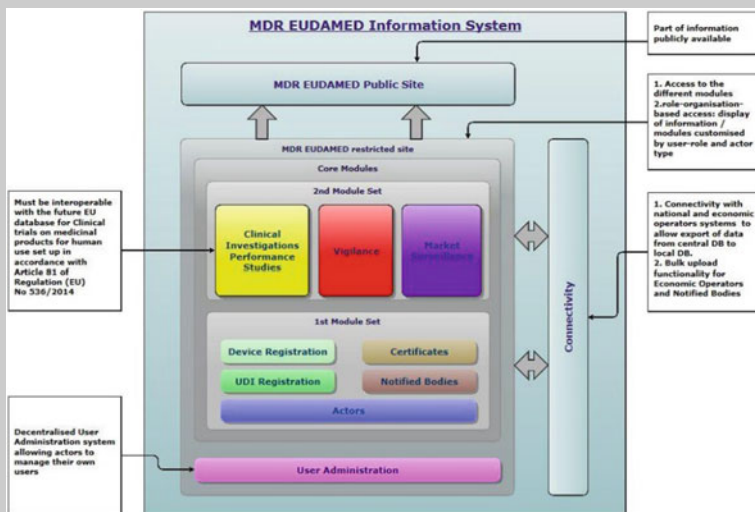
3.4.4 European Database on Medical Devices

European Database on Medical Devices (EUDAMED) is an existing EU database for medical devices. EUDAMED was initially created per *MDD 94/42 EC Article 14(a)*. It is due for a thorough update following the full implementation of the new MDR. *Article 33 of MDR* mentions about “*EUDAMED is a central repository for information relating to marketing surveillance activities within each member state. The current database is only accessible to the competent authorities (CA) and the EU Commission. It will be publicly available only after the full implementation of MDR.*”²⁵ It has comprehensive information about the manufacturers, notified bodies, clinical investigations, certificates, medical devices as well as details on the impact of the use of medical devices (injury/malfunction/failure information). It provides access of information to healthcare professionals, authorities and patients. Out of the six modules that are part of the EUDAMED, the three modules of ‘Actors registration’, ‘UDI/Device registration’ and ‘Notified Bodies and Certificates’ have been released. By the last quarter of 2023, it is expected that all the six modules will be fully developed. This would result in the application of EUDAMED Minimum Viable Product (MVP) compliance. The MVP compliance means that the system developed implements at least the minimum Medical Devices Regulations requirements. This would assist the competent authorities and stakeholders in legal compliance. Currently, the EUDAMED use is voluntary. The EU Commission has planned that by the second quarter of 2026, its use will become mandatory.

In the last quarter of 2022, the functional specifications for the EUDAMED were released. As per Article 34 of the Regulation 2017/745 the European Commission is obliged to announce the functional specifications for EUDAMED in collaboration with the Medical Device Coordination Group (MDCG).

²⁵ REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL [2017] OJ 2 117/01.

Overview of the Modules in EUDAMED



Source: https://health.ec.europa.eu/system/files/2022-12/md_eudamed_fs_v7_2_en.pdf

3.4.5 Quality Management System

Quality guidelines under the EMA are provided for active substances, manufacturing, impurities, specifications, excipients, packaging, stability, pharmaceutical development, quality by design, specific type of products and lifecycle management. On 1 January 2022, the guideline on quality documentation for medicinal products when used with a medical device was adopted (EMA/CHMP/QWP/BWP/259165/2019). The guideline introduced three terminologies: ‘Integral’ medical devices, ‘co-packaged’ medical device and ‘referenced’ medical device.

Three Configurations of Medical Devices

Integral: a medical device (part) that falls under the second sub-paragraph of Article 1(8) or the second sub-paragraph of Article 1(9) of Regulation (EU) 2017/745, where the action of the medicinal product is principal.

Co-packaged: A medicinal product and a medical device are packed together into a single pack (e.g. carton), which is placed on the market by the marketing authorisation holder.

Referenced: The product information (SmPC and/or package leaflet) of the medicinal product refers to a specific medical device to be used (e.g. identified by its brand name and/or specific description), and the specified medical device is obtained separately by the user of the medicinal product.

“The quality management system must include all parts and elements of a manufacturer’s organisation that deal with the quality of processes, procedures, and devices. The system includes the structure, responsibilities, procedures, processes, and management resources needed to put the principles and actions needed to meet the requirements of this Regulation into action.”²⁶

3.4.6 Declaration of Conformity

According to *Article 19 of MDR*, the declaration of conformity will have all the fulfilled specified requirements of the MDR concerning the device. It must be continuously updated and minimally contain the information mentioned in Annex IV and translated into the official language of each Member State. In case of devices subject to any other Union legislation, the declaration conformity will be such information relating to that Union legislation to which the declaration relates. This declaration will prove that the manufacturer is assuming responsibility for compliance with the requisites of the MDR and all other Union legislations applicable to that particular device. The commission has the power, as per Article 115, to amend the minimum content of the declaration of conformity as per Annex IV.²⁷

Declaration of Conformity

Manufacturer needs to sign an EU Declaration of Conformity which has the following information:

- Name, full business address or that of the authorised representative
- Product’s serial number, model or type identification
- Statement for full responsibility
- Means of product identification

²⁶ REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL [2017] OJ 2 117/01.

²⁷ REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL [2017] OJ 2 117/01.

- Notified body details
- Name and signature
- Date of declaration issued
- Supplementary information (if applicable)

3.4.6.1 CE Mark

The notified bodies that conduct conformity evaluations are assigned by the EU Member States. In order to receive the CE mark for medical devices, every medical device in the EU must first pass a conformity assessment. When a product is approved to be sold on the market for public use and satisfies the relevant directive's fundamental requirements, it receives the CE mark.

Article 20 of MDR states that “All devices other the custom-made or investigational devices having a declaration of conformity will bear the CE marking as per Annex V. The device or its sterile packaging must bear the CE marking in a clearly visible, legible, and permanent manner. Additionally, all usage instructions and sales packaging bear the CE marking. The CE marking will be affixed to the packaging in cases where such affixing is impossible due to the nature of the device. Where applicable, the CE marking will be followed by the device identification number responsible for the conformity assessment procedures in Article 52 of the legislation. Where devices are subject to other Union legislation which also provides for the affixing of the CE marking, the CE marking shall indicate that the devices also fulfil the requirements of that other legislation.”²⁸

3.4.7 UDI System

The European Medical Device Nomenclature (EMDN) is utilised by manufacturers to register in the European database on medical devices (EUDAMED). This nomenclature is applicable to both medical devices and in vitro diagnostic medical devices (as per Article 26 of Regulation 2017/745 on medical devices and the Article 23 of the Regulation 2017/746 on in vitro diagnostic medical devices, respectively). The EMDN is necessary activities such as device documentation and technical documentation, post-marketing surveillance, vigilance and post-market data analysis. Each device has a unique device identifier—Device Identifier.

As the chair of the International Medical Device Regulators Forum (IMDRF), EU has been instrumental in the development of the international guidance on unique device identification system that was adopted in December 2013. A common framework for the same was announced for identification and tracking devices. Article 27

²⁸ REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL [2017] OJ 2 117/01.

of the Regulation 2017/745 and Article 24 of Regulation 2017/746 identify the UDI system. The key aspects in this are as follows:

- Production of a UDI that comprises a UDI device identifier (UDI-DI) specific to a manufacturer and a device providing access to the information on a UDI production identifier (UDI-PI) which is for identification of device production and packaging.
- Use of UDI on the label of the device or on its packaging.
- Storage of the UDI by healthcare professionals, healthcare institutions and marketing entities.
- Establishment of an electronic system (UDI database).

The new regulation has developed a Unique Device Identification (UDI) requirement for every medical device and in vitro device, which will be helpful in the traceability of devices. Part VI of EU MDR specifies that UDI will consist of UDI-Production Identifier (PI) and UDI Device Identifier (DI). UDI-DI will be unique at each packaging level, and UDI-PI will consist of lot number, serial number, software identification or expiry on the label.

3.4.8 Software Medical Devices Approval

In the case of AI-based medical devices, the concerned devices have to meet the requirements of the EU Medical Devices Regulation 2017/745. The point 19 of the Regulation indicates *‘It is necessary to clarify that software in its own right, when specifically intended by the manufacturer to be used for one or more of the medical purposes set out in the definition of a medical device, qualifies as a medical device, while software for general purposes, even when used in a healthcare setting, or software intended for life-style and well-being purposes is not a medical device. The qualification of software, either as a device or an accessory, is independent of the software’s location or the type of interconnection between the software and a device’*. (Emphasis added).

Under Article 2 (1), ‘medical device’ means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes. (emphasis added).

The Medical Devices Regulation and its certification process, as they currently exist, according to the European Commission, are able to keep up with AI-based medical devices in the healthcare industry. Regulations currently in place must be followed by AI-based devices. Medical device evaluation is carried out by the EMA and relevant competent authorities.

Unlike the USFDA, the MDR does not have a different definition for software-based medical devices in MDR, but it has defined software as medical device in a guidance document. According to Medical Device Coordination Group (MDCG) which is established under Article 103 of EUMDR defines medical software device

as “*Medical device software is software that is intended to be used, alone or in combination, for a purpose as specified in the definition of a “medical device” in the medical devices regulation¹⁵ or in vitro diagnostic medical devices regulation.*”²⁹

For software to be regulated under MDR as a device must meet the following criteria:

- (1) Intended use should be related to medical purposes.
- (2) It must meet the definition of a medical device under *Article 2 of MDR*.

The inventor needs to clearly and carefully mention the device’s intended use and risk involved. Manufacturers of software medical devices must be highly cautious when drafting the product’s intended use and public description since they will have to support their claims with concrete evidence. The ‘Intended Use’ is generally sorted into various elements like name, model, device description, safety classification, principles of operation, exact medical indications, stage and severity of medical conditions, intended purpose, intended use environment, intended patient population, intended users, risk of use, intended outcome limitations and conditions of normal use.

The next consideration is whether the product meets the definition of a medical device. Some AI devices may not properly be considered medical devices or may not have the intended purpose that they should. To figure this out, the manufacturer can also look at other aspects of the software medical device, such as whether it has a medical purpose on its own, is a standalone product or adds value. For e.g. any device that alerts patients based on the tracking of their health records. It will also cover the system that allows remote consultations and provide care in any way by highlighting important information to consumers.

According to MD Regulations, these are applicable on software medical devices along with other general requirements:

- Developing a Quality Management System (QMS)—*Article 10* outlines that various proviso relating to QMS which have been mentioned above. “*A medical device’s use is associated with certain risks, which must be identified, analysed, mitigated, eliminated, and the results of these processes must be drawn. This process is known as risk management is also a part of QMS. All medical devices come with inherent risks. For quality management systems for medical devices, specific requirements are outlined in the harmonized standard ISO 13485:2016, which was created in relation to the MDD.*”
- Implementing a post-marketing (PMS) system for tracking the performance of the product—*Article 83 of MDR* outlines that “*the new regulatory framework’s requirements for Post-Market Surveillance systems. Each medical device must have a PMS that is carefully thought out, established, documented, implemented, maintained, and updated by the manufacturer. A PMS plan must be created to document the system’s design and subsequent updates, which are made based on*

²⁹ Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745—MDR and Regulation (EU) 2017/746—IVDR.

a systematic evaluation of the system's efficacy and an ongoing analysis of the data it generates."

- Designing post-market clinical follow-up and vigilance systems as components of PMS—Article 87-90 of MDR outlines *"the rule for Vigilance. Medical equipment the process of establishing and maintaining a system to gather and report information on serious incidents, Field Safety Corrective Actions (FSCAs), and the observation of trends of anticipated side effects is known as vigilance. Under the MDR, it is a key part of all Post-Market Surveillance (PMS) systems. It is a reactive process."*
- Performing a clinical evaluation of the product and submitting a clinical evaluation report (CER)—According to Article 61 of MDR, an important technical document that *"summarizes the clinical evaluation of a medical device is called a Clinical Evaluation Report (CER). Effective clinical evaluation reports outline a systematic appraisal and analysis of all available clinical evidence to rate the performance and safety of a medical device."*

Currently, most AI-based medical devices are used for predictive use, which helps doctors in decision-making; they are also Clinical Decision Support (CDS) Software and are considered Class II under current rules and regulations. Moreover, the Class II classification of Medical Devices in the EU has been further subdivided into Class II a and Class II b, under which CDS devices whose outputs can be overridden by humans are considered under Class II a, and those that are autonomous are considered under Class II To obtain a CE mark, each product must meet specific requirements based on its class.

The CE mark, which stands for "Conformité Européenne" in French, had been granted to the company for the marketing of its AI-based medical devices, which is valid for five years. The riskier the devices are, the greater the level of regulatory scrutiny. However, manufacturers must still undergo random audits from notified bodies, maintain technical documentation on an ongoing basis and conduct extensive post-market surveillance for the period of five years that the CE marking is in effect. UDI is required for software commercially placed on its own or software that constitutes a device in itself (standalone). A new UDI-DI is needed whenever there is modification and for minor revision like bug fixes UDI-PI will be suffice.

The General Data Protection Regulation (GDPR) of the EU, which "protects fundamental rights and freedoms of natural persons, and in particular their right to the protection of personal data," provides a general and obligatory framework for the processing of any individual's personal data within the EU by any data processor (party) within the EU. Data is the main component of modern technology, such as AI. Discussing about AI and healthcare also raises concerns regarding data regulation. In the case of the EU, each Member State and organisation outside of the European Union that processes data concerning EU citizens must comply with the General Data Protection Regulation (GDPR). This recognises four areas of compliance:

1. Checklist interpretation: automating a compliance checklist and offering guidance on critical sections.

2. Risk analysis: identifying high-risk, medium-risk or low-risk activities according to the GDPR's criteria and taking compliance measures accordingly.
3. Giving adequate replies to requests for information about automatic profiling.
4. Identification and risk analysis of potential or actual data breaches.³⁰

According to a study, till now more than 240 software medical devices have been approved, according to data collected by governmental and non-governmental sources (Muehlemaier et al. 2021).

EU has also approved various AI medical devices by accrediting them with a CE mark, and the number will be certainly higher than mentioned in the previous study. Below are a few of the devices that have a CE mark and are successfully marketed in EU and global markets (Table 3.3).

One of the cases of the rulings by the Court of Justice of the European Union (CJEU) on medical devices, the C-329/16 SNITEM, pertains to use of software. The discussion of the case is relevant here to understand the scope of software as medical device from the statutory interpretation. While the case was decided in the year 2017, it is relevant from the medical device regulation perspective. Philips France, an undertaking of SNITEM (Syndicat national de l'industrie des technologies médicales) marketed the drug prescription assistance software 'Intellispace Critical Care and Anesthesia' (ICCA). This software is used for resuscitation and anaesthesia and provides the doctor with relevant information for the correct prescription of drugs. Thus, it helps in assessing contraindications, interaction between different drugs and excessive doses. The ICCA bears a CE marking. SNITEM and Philips sought to annul the third heading of Article 1 and Article 2 of Decree 2014-1359 before the Conseil d'Etat (Council of State). They submit that this Decree requires certain software to be certified by the national authority which is incompatible with the EU law. The Conseil d'Etat (Council of State) sought the interpretation of the Article 1(2)a of the Directive 93/42 from the CJEU.

The question it raised is as follows:

'Must ... Directive [93/42] be interpreted as meaning that software, the purpose of which is to offer to prescribers practising in towns, a health establishment or a medico-social establishment support for determining a drug prescription, in order to improve the safety of prescription, facilitate the work of the prescriber, encourage conformity of the prescription with national regulatory requirements and reduce the cost of treatment at the same quality, constitutes a medical device within the meaning of that directive, where that software has at least one function that permits the use of data specific to a patient to help his doctor issue his prescription, in particular by detecting contraindications, drug interactions and excessive doses, even though it does not itself act in or on the human body?'

In the hearing that was held on 26 March 2017, oral arguments were presented by Snitem, the French Government and the European Commission. The CJEU ruled that *'Article 1(1) and Article 1(2)(a) of Directive 93/42 must be interpreted as meaning*

³⁰ REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL [2016] OJ L 119/01.

Table 3.3 Medical software devices approved for CE mark at EU (Authors Compilation)

Name of the tool/device	Target area	Year
TIETO INTELLIGENT WELLBEING	Healthcare data	2018
QURE.AI	Radiology	2019
VUNO	Diagnosis and radiology	2020
Behold.ai	Diagnosis	
GE Healthcare	Diagnostics	
IBM Watson Health	Oncology	
Varian	Radiology	
Varian	Radiotherapy	
IBM Watson Health	Decision support	
GE Healthcare	Radiology	
Siemens Healthineers	Medical imaging	
Halologic, Inc	Breast cancer screening	
Varian	Radiotherapy	
Siemens Healthineers	Decision support	
GE Healthcare	Decision support	
Siemens Healthineers	Decision support	
GE Healthcare	Decision support	
ITU/WHO Focus Group	Diagnosis	
ITU/WHO Focus Group	Decision support	
Aidence	Radiology	
Niramai	Radiology	2021
Biobeat	Patient monitoring	
Exini Diagnostics	Diagnosis	
Abbott	Imaging	
ActivSight Intelligent Light	Imaging	2022
C2inform	Minimal residual disease cancer test	

that software, of which at least one of the functions makes it possible to use patient-specific data for the purposes, inter alia, of detecting contraindications, drug interactions and excessive doses, is, in respect of that function, a medical device within the meaning of those provisions, even if that software does not act directly in or on the human body’.

3.5 Regulation of Medical Devices in India

The regulatory authority in India is the Central Drugs Standards Organization (CDSCO). All the notified medical devices in India are regulated under the Drugs and Cosmetics Act, (D&C Act 1940³¹ and the Medical Devices Rules (MDR), 2017. In India, new Medical Devices Rules came into force in January 2018, clearly distinguishing drugs and devices. The new rules are formed to favour the goals of the National Health Policy 2017, which aims at addressing the changes in Indian health-care that focus on bridging the accessibility and affordability gaps. According to the new Medical Devices Rules, 2017, India covers more than 300 medical devices and more than 250 in vitro medical devices.

However, there is no mention of AI-based medical devices or software as medical devices in the current Medical Rules.

According to *Section 3 (zb) of Medical Device Rules, 2017* medical device has been defined as:

India follows risk approach for classification its medical devices. It has classified medical devices into four types under Section 4 of MDR, 2017:

4. Class A is low-risk, like a nasopharyngeal catheter, surgical dressings, tongue depressors, etc.
- ii. Class B has low, moderate risk like intravenous catheters and hypodermic needles, disinfectants, etc.
- iii. Class C is with moderate to high risk like bone cement, lung ventilator, bifurcation stent, etc.
- iv. Class D is high-risk devices like copper-T, heart valves, implantable defibrillators, cardiac patches, etc.³²

The D&C Act only regulates those medical devices as drugs that the government notifies from time to time. There are various medical devices forms available on the CDSCO website where an applicant can get the certificate of registration, import licence for a device, permission to conduct a clinical performance evaluation for new in vitro diagnostics medical devices, etc. All the importers/manufacturers/sellers of notified medical devices must get a licence from the appropriate licencing authority before placing the product on the market. All the manufacturers/importers have to register their medical devices compulsorily. Compulsory registration with the Drug Controller General of India (DGCI) through the online portal “Online System for Medical Devices.” A person must have a manufacturing licence to manufacture or sell an MD. In the case of foreign manufacturers, they need to appoint a local agent with CDSCO. The agent must have proper qualifications and licences under Form 20B and 21B/21C. Section 19 A, 19B, 19C, 19 D, 19 E and 19F are related to registration of medical devices.

Provide all relevant information in the device application (Form MD-14), such as the manufacturing facility’s details, the device’s technical specifications, the ISO

³¹ The Drugs and Cosmetics Act. 1940 (Act 23 of 1940).

³² The Medical Devices Rules, 2017.

13485 certificate, the device's directions for use, the results of any testing conducted, any clinical data (if applicable) and evidence of device approval in any foreign country like the USA and the European Union. The rules were amended in 2020 to require medical device importers and manufacturers to seek certification from the International Standards Organization.

3.5.1 Approval of Software Medical Devices

In the Indian healthcare sector, many AI-based devices are already in use. Currently, there is no separate guideline or directive that can guide the principles of AI-based medical devices, or SaMD, in India. The software medical devices in India comply with the definitional aspects, QMS standards, the medical devices rules and some standards relating to medical devices like ISO 13485:2016 and ISO 14971:2019. For registering new novel device, CDSCO may ask the manufacturer for meeting with subject matter expert. The validity of import licence is valid as long as fees are paid every five years.

Most Indian start-ups have begun commercialising their products in the Indian healthcare market, with regulatory approval from the US Food and Drug Administration and CE marking from the European Union. India follows the rules of the International Medical Devices Regulations Forum when it comes to clinical trials, clinical evaluation of medical devices, documents, licencing and safety standards. The other aspect that must be adhered to by the manufacturers is the standard laid down by either the Central Government or the Bureau of Indian Standards (BIS).

The AI-based medical devices should meet the standards set by the International Organization for Standardization, the International Electro-Technical Commission and many others. When it comes to SAMDs or AI-Based Medical Devices, the Indian Medical Device Rules are still in their early stages.

Based on the questionnaire analysis, most of the companies that were interviewed have filed their applications under 510(K) in the USA and companies got CE mark approval in EU. As mentioned by one of the interviewees, clinical validations and regulatory certifications are the keys to getting regulatory clearance. The companies also focus on the quality management system before proceeding for regulatory approval. The ISO 13485 certification is an important standard used by organisations involved in the designing, producing, installing and servicing of medical devices and related services. This standard is also applicable to AI-based medical devices. Most of the companies were hardware and software solution providers, so they also needed hardware verification, including tests like temperature, biocompatibility, electromagnetic interference (EMI), etc. And lastly, for validation, the clinical studies done by the company are very important, which may be divided into clinical studies and usability testing.

These are the regulatory compliance checkpoints every company has to go through to get regulatory approval for their AI-based medical devices. There has to be post-marketing submissions at regular intervals. The manufacturers need to be updated

with the regulation in case of any new update. The common problem among the interviewers was being informed about the latest guidelines and regulations relating to the devices market and following different regulatory compliances in individual jurisdictions. Also, the manufacturers must comply with drug regulations and all allied legislations like data protection laws relating to software medical devices. One of the discouraging.

To summarise the above analysis, it is evident that software medical devices are being used, developed and placed in the market for public use. The software medical devices and their intended use are identical in all jurisdictions, but their regulation is the only difference. The primary contention of regulatory difference is the definitional aspect and the intended use of these software medical devices. Although the software uses AI/ML to track health records, it might not be considered a medical device. AI-based devices have been regulated differently in all three countries. The AI regulation in the USA and the European Union is more detailed, elaborative and accommodating, whereas it is still at a nascent stage in India.

The USA's regulatory approach is very progressive because it has discussed the recent technologies through various guidance documents, which might not be binding but build a strong base for manufacturers. Regarding the EU, it has tried to be extensive concerning software in its recent MD Regulations. It also discusses software medical devices through Medical Device Coordination Group through guidance documents on various issues relating to software medical devices. In the case of India, it has very recently 2020 inserted the word "software" in the definition of medical devices. The rules are no different for software medical devices; only requirements under import licence must be fulfilled. For regulatory comparison, the few basic things must be uniform, and the definition of software medical devices is the foremost.

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Chapter 4

Artificial Intelligence and Policy in Healthcare Industry



4.1 Introduction

A healthcare policy of a country enables accessible, equitable and affordable healthcare infrastructure to an individual irrespective of social and economic disparity among the population. In addition, the healthcare policy serves to keep in check the quality and cost-control mechanism of healthcare services in a country. It has other key functions such as promoting awareness about diverse vaccinations programs, health and related awareness campaigns. This has relevance for all the stakeholders in healthcare area. A sound and robust policy relating to healthcare can assist a country in its initiatives at the national and international level. Regulatory and policy considerations help in addressing challenges and the aligning with global healthcare standards. Ethical compliance can help reach a nation to its highest potential for effective delivery of healthcare services. Artificial intelligence has impacted several areas as discussed in the earlier chapters. And will continue to have the potential to transform various sectors of healthcare.

The transition from the use of erstwhile technologies to using AI in healthcare decision-making involves several considerations. The implementation of new technologies presents challenges from several perspectives that includes the lack of capacity building, skill set, extent of control, extent of assistance, etc. The analysis of the research studies on the ethical and legal aspects of AI provide an important background to the current perspectives and considerations. The extent of the use of AI in healthcare studied in the low- and middle-income countries (LMICs) identified broad range of health issues. The studies are largely focussed on communicable diseases. In the case of non-communicable diseases, signal processing methods for disease detection are used. Diagnosis, mortality and morbidity risk assessment, disease outbreak prediction and surveillance and health policy and policy planning are the four AI interventions deployed. While the study suggests the use of digital principled for development and deployment of AI, the additional need for the role of institutional structures has been emphasised. The need for establishing global systems

for assessing and reporting efficacy and effectiveness of AI driven interventions in global healthcare has been suggested (Schwalbe and Wahl 2020). For developing responsible AI in healthcare, AI principles have been examined. From the AI principles proposed by several organisation, the ones that are relevant for AI development have been identified. Principles that relate to alleviation of health disparity, clinical outcome, overdiagnosis, reduction of overtreatment, addressing high priority healthcare, relevance of biographic drivers of health, features relevant for local population, enhancing learning outcomes and shared decision-making are considered necessary in AI development (Badal et al. 2023). The relevance of ethics and governance in AI applications has been studied. From an ethical standpoint, the analysis of the trustworthiness of medical AI has been examined. Data quality, algorithmic bias, opacity, safety and security and responsibility attribution are the five factors that were developed. High quality data is a prerequisite for AI development. When algorithms are used in the development, two types of bias; human induced bias and data induced bias can arise. The data source can differ as it can be from a high-level medical facility setting or from a low-level medical setting. Greater data representativeness and diversity are essential to address these issues. Proprietary nature of the algorithm, lack of skill to understand the program and algorithmic techniques and the complexity of algorithms are considered as reasons for opacity. Second generation AI has opacity related issues. This makes it difficult to translate the explanation of health conditions in a meaningful manner. The increase in incidence of harm by surgical robots brings to light the need for implementation of safety aspects. Further, data breach can pose serious security concerns (Zhang and Zhang 2023). The role of governance framework in the context of AI technology has been discussed. The role of government was analysed by a review of forty-nine AI policy documents for the context, role of state, public engagement and dialogue. Benefits and the risks of AI and the potential to increase social and economic inequality has been analysed in view of the concentration of power among few companies. The role of state has been observed to be that of a promoter. The extent of involvement of various stakeholders with respect to AI activities by the state was identified. There is a change in the unitary role of the state to that of a facilitator has been observed. Public engagement for the governance of AI helps in understanding challenges related to AI. Most of the policy documents that were reviewed emphasise on multi-stakeholder engagement. A broad range public engagement is expected to not only align the policy to societal needs but also remove inequalities (Ulnicane et al. 2021). Besides the issues of privacy and security related to AI, data governance is also a key issue. The nature and scope of health data has increased beyond the bounds of hospitals. Collection of personal health data through purchase decisions, social media platforms, fitness trackers is increasing in an uncontrolled manner as this does not come directly under the existing health data regulation. Further some of the data that is collected does not come under the data protection regime such as HIPAA in the case of US and GDPR in the case of EU, respectively. As the use and movement of data is not transparent it is difficult to enforce compliance. There have been widespread concerns of how social media-based enterprises are violating norms by using personal health data for profits (Winter 2021). There is a possibility of inaccuracy in the results of the use

of AI as well as breach of data. The ethical considerations such as informed consent for use of data, safety and transparency, algorithmic fairness and biases and data privacy need to be addressed. With the extensive spread of AI data sets, traceability problems are expected to limit the fixing of liability. AI models indicate that there are underlying social and human biases. There are no guidelines or standards in this area as yet. From the legal standpoint, confidentiality, decision-making, governance and accuracy and liability aspects are important to build accountability (Naik et al. 2022).

The use of AI tools (IBM Watson) in the public healthcare system in China was reviewed from the perspective of various stakeholders. The opinion of different stakeholders such as hospital managers/doctors, IT firm managers and government policymakers was obtained in interviews utilising semi-structured questionnaire. Several findings were identified based on the analysis of social, economic, ethical, political, legal and policy related, organisational and managerial, data related and technological challenges. The use of IBM Watson in the setting of Chinese medical patients and health practices presents different considerations when compared to that of a Western medical healthcare. Lack of trust towards AI-based decisions and rules of accountability, lack of data integrity and continuity have been also identified as some of the important challenges. The study identifies four recommendations for the public healthcare system in China; need for a holistic approach and prevent vendor lock-in when establishing partnership with AI firms, use new forms of governance for adapting to new technologies, develop AI management guidelines and data interpretation prior to AI applications (Sun and Medaglia 2019). The need for an agreed standard for AI-health ethical evaluation has been proposed. Based on the review of existing studies the eleven considerations identified were attributed categories such as level of abstraction, individual, interpersonal, group, institutional, sectoral and societal aspects and the key authorities were mapped to them. The need to update specific policies/guidelines of relevant authorities in the English National Health System was suggested. The findings of the study are a representative of the current debates on the ethical aspects of AI (Morley et al. 2020).

4.2 Setting the Context

For the implementation of innovations and use of emerging technologies on the global front international organisations engage in stakeholder discussions and come up with action plans in the forms of policy, discussion paper, consultation paper, etc. from time to time. Several countries participate either as a member or non-member in this process. The discussions are not only on the development and deployment of technology in concerned sectors but also in identifying the framework for the risks and liabilities. Many countries like Singapore, China, Switzerland, Japan, France, the UK, South Africa, South Korea, United Arab Emirates, the USA and the EU have announced their AI policies and strategies lately. India has also developed AI policies

and strategies in different sectors. The applications are seen in various sectors like education, agriculture, healthcare, finance and transportation.

Before discussing the AI and Ethics frameworks proposed by various international forums, first look into the meaning of a few terms for better understanding. The term AI system denotes “machine-based system is a system capable of influencing the environment by way of predictions, recommendations or decisions for a given set of objectives, using machine and human-based inputs to perceive the environment, abstract perceptions into models and formulate probable outcomes” (Holmes et al. 2021). Each AI system has a lifecycle which can be defined as “a phase of an AI system which consists of planning and designing; collecting and processing data; building and using the model; verifying and validating; deployment; and operating and monitoring.” AI systems are being developed and manufactured by AI actors. AI actor plays a vital role in the AI system lifecycle. The AI actors include the public and private sector organisations or individuals that acquire AI systems for deployment and operations. The term comprises technology developers, system integrators and service and data providers.¹ Developers and product managers are being asked to design and implement algorithmic systems in publicly accountable ways. They have an obligation to report, explain or justify algorithmic decision-making as well as mitigate any negative social impacts or potential harms. The principles of Accountable Algorithms document helps in the understanding how decisions can have a significant societal impact. The five guiding principles are: Responsibility, Explainability, Accuracy, Auditability and Fairness.²

Policies are intended to ensure that emerging AI technology can be used in commercial settings as well. The development of AI innovations has been given a higher priority than AI deployment. Agriculture, healthcare, education and finance are just a few of the sectors identified as having the potential to make the most significant advantage from the application of AI. The distribution of policy tasks frequently covers multiple levels of governance and policy domains. Prior to the analysis the national policy on use of AI in India, it is relevant to discuss the development of international policies related to AI and in particular those relevant to healthcare. The following section has been organised into two parts. The first section includes the analysis of the fundamental principles considered for development of policies and their elaboration from an international standpoint. The discussion is grouped into policies that are general in nature and those which are specific to healthcare. In the later part of this chapter the development of AI policy in India in healthcare is discussed.

¹ Artificial Intelligence—OECD (2022).

² Principles for Accountable Algorithms and a Social Impact Statement for Algorithms: FAT ML (2022).

4.3 Ethics and Policy Framework Relating to AI

In every business sector, there are a set of ethics and principles that govern conduct. Healthcare ethics and principles are pivotal for making well-informed judgements and decisions for the welfare of patients and humankind. Awareness, cautiousness and due diligence are important requisites of decision-making that impact healthcare. There are general guidelines and ethical frameworks that have been announced to avoid inadequacy and ambiguity in the use of AI technologies in healthcare.

While developers and designers develop the technology, users utilise the technology for various purposes. For emerging technologies user feedback is considered essential for effective implementation. The discussion on ethical aspects of AI has been ongoing in the major international bodies like World Health Organisation (WHO), Organisation for Economic Cooperation and Development (OECD) etc., such organisations are attempting to bridge the gap between the advantageous and disadvantageous aspects of AI applications by formalising the ethical recommendations for effectiveness, trustworthiness, and responsible AI systems. One of the main pillars of AI is the ethical principle; the legal and ethical constraints are categorised into bias or discrimination, planning, inclusion, transparency, accountability, and security.

4.4 The Organisation for Economic Cooperation and Development (OECD) Artificial Intelligence Principles

The OECD undertook a policy debate first in a *Technology Foresight Forum* in 2016 and then in an *International Conference on AI: Intelligent Machines Smart Policies* in 2017. In due course, the AI Group of Experts at the OECD (AIGO) was constituted, comprising participants from different sectors like academia, industry, civil society, trade unions, government and intergovernmental organisations. Four meetings occurred between September 2018 and February 2019 at various locations. After a series of discussions and deliberations from the experts, OECD Committee on Digital Economic Policy (CDEP) agreed to develop a draft of Council Recommendations to promote a human-centric approach to trustworthy AI that will incentivise stakeholders to innovate and foster research. The recommendation document was drafted in consultation with other relevant OECD bodies and was approved in March 2019. In May 2019, the OECD Council at the ministerial level, on the proposal of the Committee on Digital Policy (CDEP), adopted the Recommendations on AI-the first intergovernmental standard on AI. The objective of the recommendations is to foster trustworthy and responsible AI.

The OECD Guidelines are specific to AI and other existing data protection and privacy and security risk management guidelines. Which are standardised flexibly to be implemented in the future. The OECD AI principles identify five complimentary

value-based principles for responsible and trustworthy AI for actors of AI to promote and enforce them. A brief discussion of these principles is provided below.

- **Inclusive Growth, Sustainable Development and Well-Being**—It envisages a stewardship role to address disparities in technology access and also need to identify existing biases. AI can enhance social good and can contribute significantly to multiple SDGs. Stakeholders involved would need to engage in responsible stewardship of trustworthy AI to secure benefits for people and the planet. This emphasises that AI can be used to empower all members of the society and to define beneficial outcomes with appropriate safeguards.
- **Human-Centred Values and Frames**—This principle deals with the design of AI systems to respect the rule of law, human rights and democratic values throughout the lifetime of the AI system, which includes dignity, privacy, data protection, equity, freedom, autonomy, non-discrimination, fairness, social justice and other related rights. This principle takes into consideration human rights implications. It suggests measures such as due diligence, human rights impact assessments, code of ethical conduct, labels and certification to promote human rights.
- **Transparency and Explainability**—There must be complete transparency and responsibility for the AI actors' disclosure of an AI system. The information provided must be meaningful, consistent, complete and appropriate to the context. It envisages the initialisation, interactions, enablement and outcomes prediction of the AI systems for decision-making. Improving general awareness, conducting multi-stakeholder discourse are expected to increase the acceptability of AI systems. Explainability is a key determinant that enables people to know outcome of an AI system and the process of arriving at it.
- **Robust, Security and Safety**—AI systems should be robust, secure and safe in their lifespan so that no misuse, unforeseeable use or any other adverse condition does not pose any safety risk. There must be traceability regarding the process, datasets and decisions made by the AI systems to enable an analysis of its outcomes and responses. AI actors are suggested to employ a risk management approach for this purpose. Traceability and subsequent analysis and enquiry and applying a risk management approach are the two ways in which AI systems could be secured. Traceability would promote accountability. The OECD guidelines for Multinational Enterprises (mneguidelines.oecd.org) and the OECD Due diligence Guidance for Responsible Business Conduct have been referred for guidance.
- **Accountability**—As per this principle, AI actors maintaining the above principles based on their roles, context and consistency should be held accountable for the functioning AI systems. Based on the cultural as well as organisational context there could be codes of conduct or specific management practices which need to be considered along with the ethical and moral aspects.

In addition to these five value-based principles, it also provides five recommendations to policymakers on national policies and international cooperation:

- **Investing in AI Research and Development**—This recommendation deals with the need for governments to encourage long-term investments in public projects and private investments for research and development in interdisciplinary areas, i.e. to promote trustworthy AI innovations that focus on challenging technical issues, socio-legal, ethical implications and policy issues. Investments in open datasets representing and respecting privacy and data protection to support AI research is an important aspect for consideration. It supports bias free, interoperability and use of standards.
- **Fostering a Digital Ecosystem for AI**—Encouraging a trustworthy AI digital ecosystem for sharing AI knowledge, digital technologies and infrastructure. To propagate this government must promote mechanisms such as data trust and support the safe, fair, legal and ethical sharing of data. Digital technologies access in terms of high-speed broadband networks and services, data generating technologies (including IoT) are suggested. Policymakers have been suggested to specifically consider the SME policies to facilitate such access.
- **Shaping an Enabling Policy Environment for AI**—Government should provide a platform for the AI actors to perform research and development to the deployment and operational stage for a trustworthy AI system. This platform environment will enable the policy and regulatory framers to access the AI system accordingly. Government can review and adapt appropriate policies to encourage innovation and competition for trustworthy AI. In this case also, special attention to SMEs has been suggested. Policy experiments are an important way to test AI systems and the recommendation highlights its inclusion.
- **Building Human Capacity and Preparing for Labour Market Transformation**—This recommendation indicates that need for governments to work closely with stakeholders to empower the society to adopt and empower effective use of AI systems across the breadth of applications, equipping them with the necessary skills. The transition should be made smoothly by conducting workshops and training programs. In collaboration with stakeholders, the government should use AI systems to enhance the safety and quality of jobs, fostering entrepreneurship, productivity and large-scale benefit. The transformation of the labour market is expected. While AI would complement human capability in general, it may replace them in other cases. It is important to assess how the work place organisation is impacted by the use of AI systems. The adoption of labour standards and agreements between management and workers would lead to several challenges that need to be addressed.
- **International Cooperation for Trustworthy AI**—Developing countries, along with their government and stakeholders, should cooperate in adopting and progressing the responsible stewardship of trustworthy AI. Government should encourage internationally comparable metrics to measure AI research and development and deploy and gather evidence. It should also promote the development of multi-stakeholder, consensus-driven global technical standards for AI interoperability and trustworthiness.

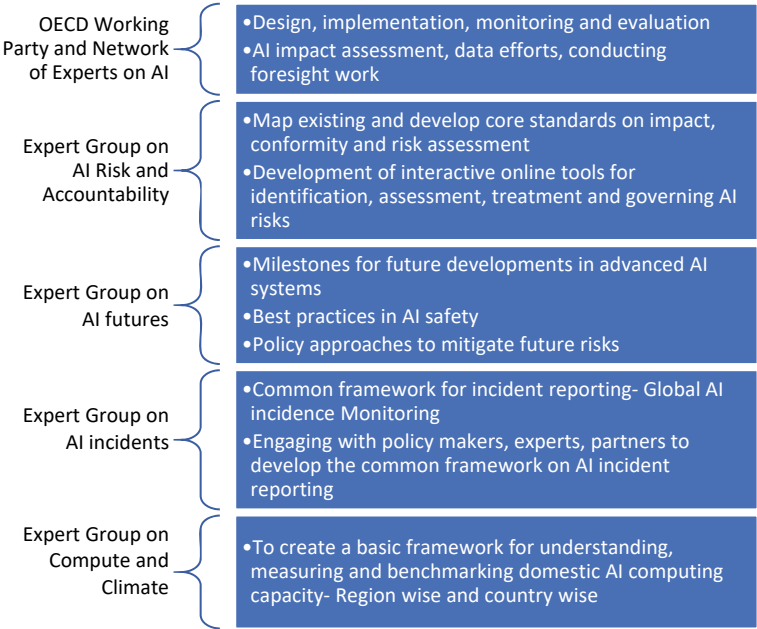


Fig. 4.1 The OECD expert groups on AI. *Source* Composed by the authors

The CDEP has been instructed to monitor the implementation of the recommendations and report to the Council after five years of its adoption and implementation. The CDEP works closely with other international bodies like the United Nations Educational, Scientific and Cultural Organisation, the European Union and the Council of Europe to frame AI Ethics.³ ONE AI (OECD Network on AI) has been created that provides AI specific expertise and advice about policy, technical and business areas. This is a multi-disciplinary and multi-stakeholder group that advises the CDEP (Fig. 4.1). Though the OECD policy document was not the first one to deal with AI ethics and principles, it however has made significant contributions and groundwork for future reference.

4.5 World Health Organisation (WHO)

As an organisation that promotes global health, the policy and regulation announced by WHO provides guidance to other countries in setting up the healthcare practices. It also acts as a platform for expert information healthcare to address the issues and challenges in the global healthcare scenario. WHO has been involved in setting best ethical practices in healthcare across globe by strengthening the process through risk

³ The OECD Artificial Intelligence (AI) Principles—OECD.AI (2022).

management, assessment and standardisation in healthcare. WHO has also discussed the use of AI in healthcare extensively.

4.5.1 Ethics and Governance of Artificial Intelligence for Health

The World Health Organisation created its Science Division in 2019 to support member states in achieving Sustainable Development Goals (SDGs) regarding health and emergency preparedness and response. The Ethics and Governance document was led by two departments in the Science Division—Digital Health and Innovation and Research for Health. The leading group of experts in ethics, law, human rights and digital technology worked with WHO to identify core principles to promote the ethical use of AI for health. In June 2021, the WHO came up with Ethics and Governance of AI for Health Guidelines after numerous discussions and deliberations with expert stakeholders. Modern technology like AI holds lots of potential in the healthcare world to improve the healthcare delivery system and research and development in the medical field. Simultaneously there are several ambiguities in the functioning of AI technology. Section five of the guidelines deals with the six ethical principles the Expert Group identified for guiding the development and use of AI for health.

Six ethical principles are the critical factors of the guidelines:

- a. Protecting Human Autonomy—This section highlights the decision-making autonomy of a human being over an AI system for better and more reliable judgement.
- b. Promoting Human Well-Being and Safety and Public Interest—AI technology should not cause harm mentally or physically to users as well as the receivers. Safety, accuracy and efficiency should be well defined or indicated in the use cases for easy regulatory approval.
- c. Ensuring Transparency, Explainability and Intelligibility—AI technology should be user-friendly for better interpretability and understanding of doctors, health services practitioners and workers, developers, designers, patients and regulators.
- d. Fostering Responsibility and Accountability—It is essential to ensure accountability and responsibility in all the functions performed by the AI system with the utmost diligence, which can make diagnostics and prognosis judgements related to a patient's health.
- e. Ensuring Inclusiveness and Equity—AI technology's principle must be all-inclusive of the population, varying from sex, gender, sexual orientation, race and other factors for equitable and easy access to healthcare.
- f. Promoting Responsive and Sustainable AI—Responsive and sustainability come from a continuous assessment of the AI technology during its use by the developers and designers of the system. The evaluation ensures that the technology is responsive and communicates adequately to fulfil the goals in the healthcare sector.

The report presents the challenges and risks of the ethical nature of using AI for health. The Expert Group identified challenges and guiding principles through disputes, accountability and responsibility for decision-making. The report is a practical guide for implementation of by AI technology developers, Ministers of Health and Health Care Providers.

Though the recommendations have tried to provide elaborate solutions and guidelines through ethical frameworks, there are setbacks regarding the application. There are instances where there needs to be more support from the manufacturers and developers. Accessing and regulating data is one of the major obstacles when it comes to AI technology. The inclusion of varied populations is also one of the obstacles due to geographical and demographic dissimilarity.⁴

4.5.2 Recommendations on Digital Interventions for Health System Strengthening

Recommendations on emerging digital health interventions that are contributing to health system improvements, based on an assessment of the benefits, harms, acceptability, feasibility, resource use and equity considerations. This guideline aims to equip health policymakers and other stakeholders with recommendations and implementation considerations for making informed investments in digital health. This guideline recommends mHealth interventions relevant to newborn health, including birth notification by the mobile device and targeted communication to pregnant or new moms, breastfeeding women living with HIV and more. The recommendations in this guideline represent a subset of prioritised digital health interventions accessible via mobile devices.⁵

Both the policy documents mainly focus on the ethical and governance mechanism of AI in health. The purpose of the stakeholders in the process of development to deployment must be to reduce the potential threat of AI and maximise the capabilities provided by AI like research, scans, decision-making etc.

The Focus Group for AI in Health (FG-AI4H) was developed by a partnership of the ITU and the WHO. Its mandate is to establish a standardised assessment framework for the evaluation of AI-based methods for health, diagnosis, triage or treatment decisions (Fig. 4.2.). The four areas of outcomes of this group are ethics, regulations, technology and the clinical evaluation and use cases.

⁴ Ethics and Governance of Artificial Intelligence for Health (2021).

⁵ WHO Guideline Recommendations on Digital Interventions for Health System Strengthening—NCBI Bookshelf (2019).

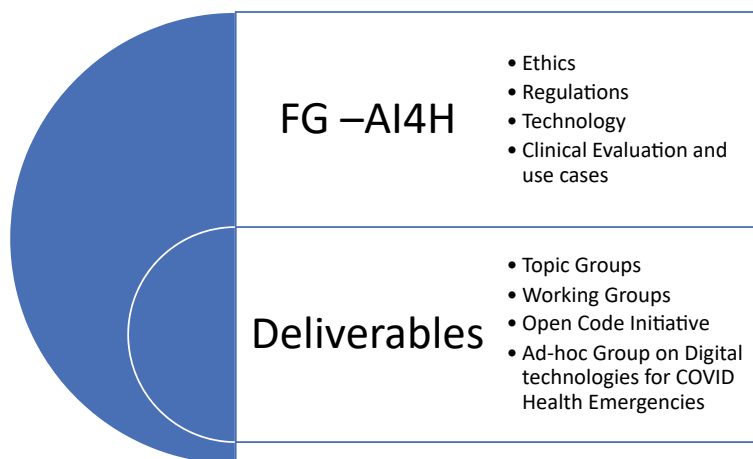


Fig. 4.2 FG-AI4H of the WHO and deliverables. *Source* Composed by the authors

4.6 United Nations Educational, Scientific and Cultural Organisation (UNESCO) Recommendations on the Ethics of Artificial Intelligence

The main idea of UNESCO is to bring AI to society to reduce its risk by ensuring the digital transformation of remote human rights and contribute to sustainable development goals, which can be addressed by maintaining transparency, accountability and privacy with action-oriented policy plans on data governance, education, culture, healthcare and economy.

In November 2019, the General Conference of UNESCO, at its 40th session, adopted 40 C/Resolution 37, by which it was mandated to the Director General “to prepare an international standard-setting instrument on Ethics of AI in the form of Recommendations” which was submitted in 41st Session in 2021. An expert group of Ad-Hoc Expert Group (AHEG) was established and directed to produce the first draft of the proposed recommendations. The expert committee includes various stakeholders from different fields. UNESCO adopted the Recommendations on the Ethics of AI in November 2021 after three years of deliberation, negotiation and inputs from hundreds of experts worldwide. All member states had elaborate discussions and recommendations on the draft and officially adopted the ethical framework. The recommendation report of UNESCO has two parts. The first is about ethical values and principles, and the second is about policy actions.

The values are organised into four subcategories

- **Respect, Protection and Promotion of Human Rights and Fundamental Freedoms and Human Dignity**—Human rights and fundamental freedoms must be respected, protected and promoted during the lifecycle of AI systems. The AI actors, including the government, private sector, international organisations, civil

society, technical communities and academia, must respect human rights instruments and frameworks in the invention process and during the lifecycle of the AI system.

- **Environment and Ecosystem Flourishing**—The idea behind recognising, protecting and promoting AI systems is to protect the environment and ecosystem. The AI system must comply with all the rules, regulations and legislations followed nationally and internationally to reduce the carbon footprint and prevent the unsustainable exploitation and deterioration of the environment.
- **Ensuring Diversity and Inclusiveness**—The diversity and inclusiveness of race, ethnicity, gender, sex and social and economic origin must be promoted by the AI systems.
- **Living in Peaceful, Just and Interconnected Societies**—The value ensures maintaining peace, justice, inclusiveness and interconnectedness of different societies must be promoted throughout the AI system lifecycle.

The principles are divided into several subcategories.

- **Proportionality and Do Not Harm**—The AI system and method should be proportional to achieve a legitimate aim. In the pretext of fulfilling any goal, human rights and fundamental freedom, communities, societies at large or the environment and ecosystem should not be harmed; risk assessment and proper measures should be implemented.
- **Safety and Security**—The AI system should avoid and address unwanted risks and harms in its lifetime. A safe, secure AI has the potential to achieve goals like sustainability.
- **Fairness and Non-Discrimination**—Digital knowledge divide between countries needs to be addressed throughout the lifecycle of AI systems. AI actors must avoid reinforcing or perpetuating discriminatory or biased applications and outcomes during the lifecycle of AI systems. The idea of fairness, social justice, non-discrimination and compliance with international law should be promoted by AI actors.
- **Sustainability**—Sustainability relies on achieving complex objectives on a continuous assessment of human, social, cultural, economic and environmental dimensions.
- **Right to Privacy and Data Protection**—Privacy, adequate data protection frameworks and governance should be respected and promoted throughout the life cycle of the AI system. There must be enough privacy impact assessments that look into the AI systems and the societal and ethical considerations arising from them.
- **Human Oversight and Determination**—In some cases of decision-making and opinion, the control of humans or physical entities will prevail over an AI system.
- **Transparency and Explainability**—Transparency and explainability are essential for protecting other dimensions, such as human rights, fundamental freedoms and ethical principles. For liability regimes to work properly internationally and nationally, transparency is a prerequisite. The government and private sector institutions should provide relevant explainable information about AI systems. The

individuals should be able to access the logical reason behind any decision-making to review and correct the decision made by an AI system.

- **Responsibility and Accountability**—The ethical responsibility and accountability for the decisions and actions of any nature made by an AI system should always be attributable to AI actors corresponding to their role in the lifecycle of the AI system. Due diligence, audit, risk assessment and appropriate oversights are mechanisms for AI systems to ensure accountability.
- **Awareness and Literacy**—Disseminating proper knowledge and literacy among the stakeholders and general public through workshops, civic engagement, digital skills and training. It should also help in learning about the impact of AI systems on human rights and fundamental freedom.
- **Multi-Stakeholder and Adaptive Governance and Collaboration**—International law and national sovereignty must be respected in the use of data. Each state that generates data has access and the right to make effective regulations to protect data based on the privacy laws prevailing in that territory. The adoption of open standards and interoperability to facilitate collaboration should be in place.

The policy areas operationalise the values and principles set out in the recommendation. There are 11 policy areas elaborated on in the recommendation document. The one related to healthcare is policy area 11- Health and social well-being. One of the use cases is data protection in health and health crisis management. For instance, it is mentioned that “in the health sector, we should go for the principle of equity and justice rather than equality” and “certain areas like healthcare, security, education which needs higher transparency and explainability of the AI systems”.⁶

Even though the recommendation committee has tried to take a holistic approach, the drafting committee has overlooked various rights and dimensions in the law and practice. The utmost priority has been given to human rights and the right to privacy by the drafting committee. Regardless of the UNESCO AI policy and its drawbacks, the policy was not directly associated with healthcare, but the principles mentioned in the policy are relevant to healthcare. It is relevant to mention here that the UNESCO has developed a global guidance generative AI in education and research in 2023. This aims to support countries to implement immediate actions, policies in the long term and develop capacity building in a human centred approach. This guidance also presents an assessment of potential risks of generative AI to core humanistic value.⁷ As this guidance deals with research also it would be relevant for research developments related to health.

⁶ Recommendation on the Ethics of Artificial Intelligence (2021).

⁷ <https://unesdoc.unesco.org/ark:/48223/pf0000386693>.



Fig. 4.3 Thematic areas of work of the Partnership on AI. *Source* Composed by the authors

4.7 Partnership on AI

The Partnership on AI (PAI) was created to bring together experts and stakeholders to advance responsible governance and best practices in AI.⁸ Among the several programs that it undertakes, the Safety Critical AI Program is relevant for the area of health. Best practices that can help in averting accidents, misuses and unintended consequences of AI technologies were developed as a part of this program. Through its SafeLife, a novel reinforcement learning environment, the safety of reinforcement learning agents and the algorithms that train them are tested. PAI publicly launched the AI Incident Database (AIID), composed of more than 1,200 reports of AI failures that caused harm or injury. This crowdsourced database can be useful for AI practitioners to lessen or avoid repetitive negative outcomes.⁹ The overall six thematic areas of work of PAI on the risks and opportunities for AI are shown in Fig. 4.3.

4.8 Foundation for Responsible Robotics (FRR)

The Foundation of Responsible Robotics is a not-for-profit organisation which envisions to shape a future of ethical robotics, design, development, use, regulation and implementation. It engages with policymakers at the local, national and international levels for the creation of ethical regulations on robotics and AI technologies. The FRR Quality Mark for (AI-Based) Robotics is a label on robotics products. It indicates that this product has received a positive assessment/evaluation from an independent external expert group. Values considered are security, safety, privacy, fairness, sustainability, accountability and transparency. Robotics and artificial intelligence (AI) have great potential benefits for humanity, from monitoring and repairing climate change destruction to assisting in the early diagnosis of diseases. The best practices developed are by way of public–private collaborations and this allows discussion in the interface of ethics, technology, regulation, law and policy.¹⁰

⁸ Home—Partnership on AI (2022).

⁹ <https://incidentdatabase.ai/>.

¹⁰ FRR Quality Mark for (AI Based) Robotics—Responsible Robotics (2022).

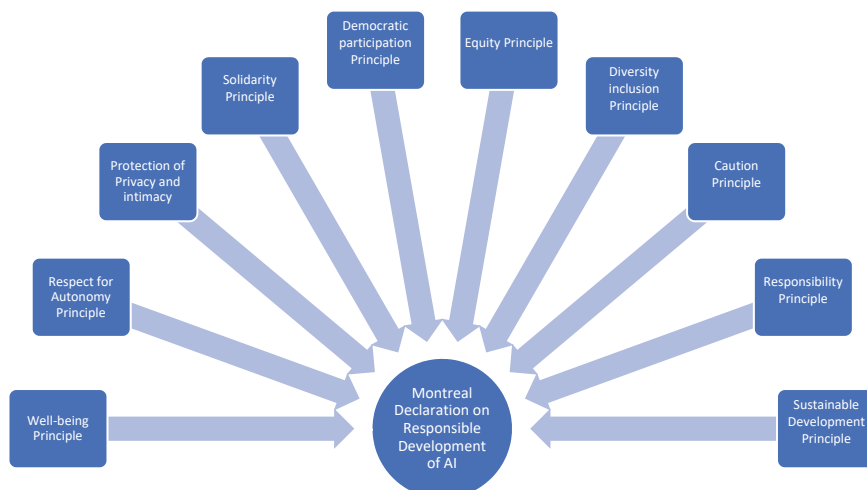


Fig. 4.4 Principles of the Montreal declaration on responsible development of AI. *Source* Composed by the authors

4.9 Montreal Declaration for Responsible Development of Artificial Intelligence

The Forum on the Socially Responsible Development of AI, held at the Palais des congrès de Montréal, concluded on 3 November 2017, with the announcement of the Montreal Declaration for a Responsible Development of Artificial Intelligence. The Declaration aims to encourage discussion among the general public and a progressive and inclusive approach to the advancement of AI.¹¹ The three main objectives of the declaration are the development of an ethical framework for the development and deployment of AI, guiding the transition for benefit of everyone and open a national and international forum for discussion for the collective achievement of equitable, inclusive and ecologically sustainable AI development.¹² There are ten different principles outlined in the 2018 Montreal Declaration take into consideration aspects such as equity, autonomy, privacy, diversity and sustainability (Fig. 4.4.).

¹¹ Declaration of Montréal for a Responsible Development of AI (*respaideclaration*) (2022).

¹² https://monoskop.org/images/d/d2/Montreal_Declaration_for_a_Responsible_Development_of_Artificial_Intelligence_2018.pdf.

4.10 International Labour Organisation (ILO) and AI

The International Labour Organisation (ILO) has recognised the potential advantages and disadvantages of employing artificial intelligence (AI) in the field of occupational health. They have called for the responsible use of artificial intelligence in this field, including the protection of workers' rights and the elimination of discrimination. To prevent AI and automation from displacing workers, the ILO has also emphasised the need for training and skill enhancement. In addition, the ILO has suggested that the use of AI in labour health should be governed by the principles of the Decent Work Agenda, which include workers' rights, social protections and social dialogue. ILO has also carried out various AI initiatives out of which one is related to AI and Health of labours called "Algorithmic management in the logistics and healthcare sectors". Algorithmic management practices that are often associated with platform work are being increasingly utilised by traditional companies in the logistics and healthcare sectors. Project looked at impact of such practices on work organisation, efficiency and working conditions in European (France, Italy) and non-European (India, South Africa) countries. The report examined the enforcement of existing social and human rights standards where key employer functions are performed by algorithms and are thus opaque.¹³

The aforementioned developments represent efforts of not-for-profit organisations, international organisations in development several standard principles of AI in general as well as in specific areas that impact health.

4.11 European Union—AI Act and Policy

The European Commission (EC) in the year 2017, adopted a set of legislative and non-legislative initiatives which were related to robotics and AI.¹⁴ It published the "Artificial Intelligence for Europe" document in 2018, which outlines the advantages of AI and the risks. Later in 2018, a High-Level Expert Group on AI (AI HLEG) appointed by the Commission had fifty-two experts from academia, civil society and industry. After the deliberations a draft of AI ethics guidelines was released.¹⁵ This guideline came up with an updated definition of AI. As per the guideline, a trustworthy AI must "respect fundamental rights, core principles and values, applicable regulation, ensuring an ethical purpose, and technically robust and reliable since even with good intention, a lack of technical mastery can cause unintentional harm." The EC has been considering the development of a conducive regulatory framework based on the multi-dimensional perspectives of AI and has announced various official reports and guidelines to regulate AI. The basic and main focus is principles of ethics, lawfulness and robustness from a technical and societal perspective.

¹³ Building Partnerships on the Future of Work (EMPLOYMENT) (2022).

¹⁴ Civil Law Rules on Robotics, 2017—Google Search (2022).

¹⁵ High-Level Expert Group on Artificial Intelligence (*Shaping Europe's digital future*) (2022).

Prior to 2021, EU conducted several discussions and developed guidelines for AI and ethics. In the month of April 2021, it came up with a draft legislation on regulating AI. The Act was its first to make a holistic regulation of AI.¹⁶ It considers the definitional aspect, implementation at every level, inclusivity of the technology and a redressal mechanism. The proposed Act complies with the new legislative framework (NLF), i.e. ensuring that the new range of products (medical products) comply the existing regulation before they are placed in the EU market. The Act is proposed for public interest, for safeguarding their fundamental rights, safety and security of the people. The proposed regulation focusses on the utilisation of AI systems and the risk associated with it. Various recommendations were received on the draft regulation like.

1. Technology—neutral definition of AI systems (*Article 3*).
2. Classification of AI systems with different requirements.
3. Obligations to be set on the basis of risk involved like high to low.
4. Transparency of the AI systems will be based on the based to risk factor. (*Article 52*).

The Act has been extensive about the categories of AI systems, its enforcement and the redressal mechanism.

Under the proposed Act, the high risk AI systems have been categorised in two parts. Only the first part deals with the medical devices which comes under high-risk AI systems (*Title 3, Article 6*) as its affects the people's life or their fundamental rights. The Act has detailed enforcement and redressal system for high risk AI such as the ones available earlier for compliance with respect to the CE marking (*Article 49*). The surveillance authorities have been proposed in the regulation who will have access to all the confidential information and assess the compliance with the obligations and requirement of the high risk AI systems. (Chap. 3).

The Act has been proposed to foster the use of AI in different domains and boost the innovation (*Article 53, 54 & 55*) but at the same time it is important to regulate the risk and threats arising out of these emerging technologies.¹⁷ But at the same time the definition of AI, regulatory body and redressals mechanism is limited in the draft proposal, since the Act will be applicable in all the domains like healthcare, education, finance, etc., it might to lead to under or over regulation in some domains.

The EU has several policy initiatives related to AI and healthcare. One key initiative is the EU's Digital Single Market strategy, which aims to create a single market for digital goods and services, including in the area of eHealth. The EU is also investing in research and innovation in AI through its Horizon 2020 program, with a focus on applications in healthcare such as precision medicine and telemedicine. Additionally, the EU has issued guidelines on the ethical use of AI, including in healthcare, and is working to establish a legal framework for AI. The European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) is another policy initiative,

¹⁶ https://eur-lex.europa.eu/resource.html?uri=cellar:e0649735-a372-11eb-9585-01aa75ed71a1.0001.02/DOC_1&format=PDF.

¹⁷ EUR-Lex—52021PC0206—EN—EUR-Lex (2022).

which aims to harness innovation to support independent living and active aging for Europe's aging population. The Joint Programming Initiative on More Active and Healthier Ageing (JPI on AHA) is a collaboration between several European countries to support research and innovation in the field of active and healthy aging. Additionally, EU has also issued guidelines on data protection and data governance related to AI in healthcare to ensure patient data security, privacy and to promote trust in the technology. EU also encourages member states to establish national strategies for AI in healthcare and to establish partnerships between healthcare providers, research institutions and industry to develop and implement AI solutions.

The AI Act is still under negotiations. In the recent negotiations, the Members of European Parliament have included many other aspects under the unacceptable level of risk category. They are real time remote biometric identification systems in public places, utilising post remote biometric identification systems, use of sensitive characteristics, such as gender, race, in biometric systems, predictive policing systems, emotion recognition systems, untargeted scraping of facial images from the digital medium.

4.12 United States of America—AI Act and Policy

In 2016, the White House for the first time released a report called 'Preparing for the Future of Artificial Intelligence' on future directions and considerations for AI. Another report laying out strategic plans for research and development in AI was also published following the updated version of the report.¹⁸ Under Section 1051 of the John McCain National Defence Authorization Act for the Fiscal year 2019, the National Security Commission on Artificial Intelligence was initiated with the aims to review advances in AI,¹⁹ related machine learning developments and associated technologies. In the year 2020, ten principles for regulatory and non-regulatory approaches to narrow AI applications were listed in a document called 'Guidance for Regulation of Artificial Intelligence Applications.' This serve to set policy considerations that are permitted by law and regulation for AI applications developed and deployed in the non-governmental use of AI.²⁰

This guidance is with respect to narrow or the weak AI context only.

Legislation to regulate artificial intelligence (AI) could be coming from the Federal Trade Commission. The FTC has developed AI expertise in enforcing a variety of statutes, such as the Fair Credit Reporting Act and Equal Credit Opportunity Act. The Federal Trade Commission (FTC) and National Institute for Standards and Technology (NIST) are leading efforts to standardise AI risks. NIST released an initial

¹⁸ The National Artificial Intelligence Research and Development Strategic Plan: 2019 Update—Catalog (2019).

¹⁹ Home—NSCAI (2022).

²⁰ <https://www.whitehouse.gov/wp-content/uploads/2020/01/Draft-OMB-Memo-on-Regulation-of-AI-1-7-19.pdf>.

Fig. 4.5 Characteristics of trustworthy AI systems.
Source <https://nvlpubs.nist.gov/nistpubs/ai/NIST.AI.100-1.pdf>S



draft of an AI Risk Management Framework (AI RMF) on July 29, 2021. By 18 August 2022, it had already been revised twice.²¹ The AI RMF is intended for voluntary use and to improve the inclusion of trustworthiness into the design, development, use and evaluation of AI products, services and systems. The characteristics of trustworthy AI systems are provided in Fig. 4.5.

The US government published a blueprint of the AI Bill of Rights, a set of guidelines for the responsible design and use of AI. This is a collaboration between the Office of the Science and Technology Policy, academicians, human rights groups, companies and the general public. There are no potential enforcement actions in this blueprint. It, however, offers five fundamental principles that would regulate the use of artificial intelligence, that include the development of safe and effective systems, protections against discrimination, data privacy, notification and explanation, human alternatives, consideration and fall-back. One of the primary goals of the “Bill of Rights” framework is to reduce the discriminatory effects of training sets on existing bias.²²

The Food and Drug Administration (FDA) has issued guidance on the use of artificial intelligence (AI) in healthcare, including the development and regulation of AI-based medical devices as discussed in the earlier chapter. In addition, the National Institutes of Health (NIH) have a number of programs that support the research and development of AI in healthcare. The Precision Medicine Initiative in the United States aims to develop more personalised treatments for patients by employing genetic and other data. The Nutrition for Precision Health is involved in advancing nutrition research by the use of AI-based approaches.

In contrast, the United States has a regulatory framework that ensures AI-based medical devices meet the same safety and efficacy standards as conventional medical devices.

There are numerous other healthcare-related policy initiatives in the United States. The 2010 Affordable Care Act (ACA) aims to expand healthcare access and reduce

²¹ “AI Risk Management Framework (NIST) (2021).
²² Blueprint for an AI Bill of Rights | OSTP | The White House (2022).

costs. The ACA includes provisions to encourage the use of health IT, such as electronic health records (EHRs), to enhance the quality and efficiency of healthcare. The Centre for Medicare and Medicaid Services (CMS) also has several programs to promote the use of health IT and to encourage the use of alternative payment models, such as value-based care, which is designed to incentivize providers to deliver high-quality, cost-effective care.

The Medicaid and Children's Health Insurance Program (CHIP) Payment and Access Commission (MACPAC) is another initiative that provides policy and data analysis and makes recommendations to Congress, the Secretary of the Department of Health and Human Services (HHS) and the states on a variety of Medicaid and CHIP-related issues.

The Centre for Medicare and Medicaid Innovation (CMS Innovation Centre) has several programs to test and scale new payment and service delivery models, such as Accountable Care Organisations (ACOs), which aim to coordinate care for Medicare recipients and reduce costs. Predictive algorithms in AI tools have been used in some programs for assistance in payments. However, there have been concerns that agencies are utilising unregulated AI-based prediction to cut off payments.

AI policies developed by international agencies, intergovernmental institutions and countries establish guidelines and frameworks for the development and application of AI in a way that promotes its benefits and minimises its risks. The ethical use of artificial intelligence and the development of transparency and accountability mechanisms to ensure that AI is used in a manner that respects human rights and dignity is paramount. Several countries such as the European Union, United States of America, Canada, Singapore, Japan, China and Australia have discussed state policies regarding the importance of ethics of artificial intelligence while deploying it in different sectors. In the healthcare sector, technology development and deployment based on AI should promote well-being of the population and minimise the risks and challenges associated with it.

4.13 Indian Policies on Artificial Intelligence

As a growing economy and also implementing several technological advancements, India has been developing policies time to time. The implementation of AI is happening in several sectors. In the healthcare sector, new technologies based on AI are being developed and products are already being deployment as part of the healthcare requirements. Several policies have been developed in India to utilise its potential for economic growth, social development and national security. The policy intends to establish India as a global leader in AI and to utilise the technology to address national challenges such as healthcare, agriculture and education.

4.13.1 Artificial Intelligence Task Force Report, 2018

The Ministry of Commerce and Industry launched the Artificial Intelligence Task Force in 2018.²³ The task force's objective was to create a legal and policy framework for deploying AI technologies in various fields like education, fintech, transport, healthcare and agriculture and provide recommendations to the government, industry and research programs. It addressed three policy aspects; areas of governmental role, ways in which AI can improve quality of life and sectors in which the use of AI can generate employment and national growth. Health is one of the ten specific domains that have been identified. Section 4.2c of the report deals with healthcare sector. AI has been suggested to transform rural healthcare services. It can be utilised to create electronic health data repositories and clinical decision support systems.²⁴ The growth of AI in genomics is expected to be under three categories: predictive, prescriptive and in the workflow improvements.

4.13.2 NITI Aayog Report on AI, 2018

The Planning Commission was replaced in 2015 by the National Institution for Transforming India (NITI Aayog), a policy think tank established by the Indian government. One of its main functions is to provide strategic and technical advice to the government on various policy issues, such as the development and deployment of artificial intelligence (AI) in India. In accordance with its mandate, NITI Aayog has actively participated in the formulation of India's AI policy in collaboration with the World Economic Forum. In 2018 it published the National Strategy for Artificial Intelligence. This report indicated the potential of AI in all sectors. The government aims to leverage AI at a large scale, i.e. Responsible AI-AI for All.²⁵ The report has advised setting up a consortium of Ethics Counsel and frameworks for privacy and security. The report's key five focus areas are Healthcare, Agriculture, Education, Smart Cities and Infrastructure and Smart Mobility and Transportation. The Part 1 of the NITI Aayog report 2021 titled "Approach Document for India Part 1- Principles for Responsible AI" indicates the need to establish the broad ethical principles for designing, developing and deploying AI in India. National Strategy for Artificial Intelligence (NSAI) has focussed on various sectors, out of which healthcare is also one of them, and the ethical background for using high-risk AI in healthcare. The Part 2 of the Report published later in 2021 is called 'Approach Document for India: Part 2—Operationalizing Principles for Responsible AI'. A risk-based approach for AI in India is recommended based on the low or high risk. The document also suggested a framework for governing the responsible use of conversational AI in healthcare by

²³ Artificial Intelligence Task Force (2018).

²⁴ <https://dpiit.gov.in/whats-new/report-task-force-artificial-intelligence>.

²⁵ National Strategy for Artificial Intelligence (2018).

bringing chatbot developers, chatbot platforms, the medical community, civil society, academia and healthcare regulators.

There are several initiatives by which the government is facilitating the large-scale adoption of AI. They are the Make in India, Atal Innovation Mission, Start-up India, etc. Under this, various Indian healthcare start-ups and companies leverage AI in healthcare. For instance, the Empowered Group 6 (EG6) engaged with several international organisations, industries to build synergies based on AI and several healthcare applications have been developed. Some of these have been deployed in large-scale time during the COVID-19 times. Several AI Excellence centres have been set up across India. The use of Facial Recognition Technology has been identified in several areas. It has been deployed in the Digi Yatra Platform in India. This document also provides a comparative view of recent judgements in other jurisdictions, the laws relating to privacy and the regulations in countries like the US and the EU.²⁶

4.13.3 National Artificial Intelligence Strategy

In 2018, NITI Aayog published the National Artificial Intelligence Strategy (NAIS), which outlines the government's vision for making India a global leader in AI by maximising on the country's strengths in data and analytics, engineering and computer science. The National Centre for AI (NCAI) provides a platform for cross-disciplinary collaboration and partnership between industry, academia and government on AI initiatives, as well as contribute to the development of a robust ecosystem for the development and deployment of AI across the nation. The National Artificial Intelligence Strategy (NAIS), released by the Indian government lays out a vision for making India a global leader in AI by leveraging the country's strengths in areas such as data and analytics, engineering and computer science. The portal called www.ai.gov.in was launched in 2020 as a one-stop digital platform for AI related developments in India. The portal shares articles, start-ups, investment funds in AI, resources, companies and educational institutions related to AI. It has also launched a national program for youth named 'Responsible AI for Youth'.

4.13.4 Ministry of Electronics and Information Technology (MeitY) and Promotion of AI

The MeitY has further elaborated the NITI Aayog discussions from the perspective of technology standardisation in different domains. The department constituted four committees under the policy framework of AI in 2018. The first Committee A was on data and artificial intelligence, and the second Committee B was on leveraging

²⁶ Adopting the Framework: A Use Case Approach on Facial Recognition Technology (2022).

AI to identify national missions in the key sectors. The third Committee C was on mapping technology capabilities, key policy enablers required across sectors, skilling and reskill, and the fourth Committee D was on cyber security, safety, legal and ethical issues. MeitY has developed a National Health Stack, digital infrastructure and services to support health information management and sharing. It has also set up a number of initiatives to promote the use of artificial intelligence (AI) in the healthcare sector which include establishing AI-based diagnostic centres, developing AI-led solutions for healthcare delivery and encouraging research and development in AI and healthcare, through initiatives such as the Digital India program.

The MeitY has published successful stories by Government, Indian start-ups, enterprises and academia leveraging AI in various sectors. Like Telangana, the government has used drone-based delivery for healthcare supplies during COVID-19. Param SIDDHI AI, ranked in the top 100 supercomputers globally, will be capable of large-scale advancements in healthcare, agritech, cybersecurity, robotics and more.²⁷

Department of Telecommunication and its technical arm, Telecommunication Engineering Centre (TEC), work closely on standardisation work on AI, including the Focus Group on AI for Health (FG-AI4H). BIS is also working to carry out the standardisation of AI. The MeitY has also been rolling out the National Artificial Intelligence Mission, a five-year program; healthcare is also one of the critical areas.²⁸

4.13.5 Pradhan Mantri Digital Health Mission (PM-DHM) 2020

The National Health Authority is the government body in charge of implementing the blueprints of the National Digital Health Mission, 2020 (now known as Ayushman Bharat Digital Mission). In the five-year Action Plan of the government, AI also holds a unique role in the decision-making, analytical functions, security and privacy, and this policy adds to the digital systems of the ecosystem such as digital health ID, electronic health records, health facility registry. The mission also envisages to “keep a check on the reliability of AI systems by laying down guidelines and standards” and has created a sandbox to allow products to be tested in a contained environment and evaluate consumer and market reactions to it. The policy will soon mark its second anniversary, and till now, we have seen personalised digital healthcare during the surge of COVID. AI will be used as a tool to use health data analytics. The use of AI to increase equitable access to health services, improve health outcomes and reduce costs have been indicated. Further, the use of AI to extract the relevant health records and the creation of a Unified Health Interface (UHI) has been envisaged. Though the National Digital Health Mission has created an environment to foster healthcare

²⁷ India's AI Journey: 75@75 (2022).

²⁸ Artificial Intelligence Committees Reports | Ministry of Electronics and Information Technology, Government of India (2022).

companies and start-ups. It is important to interlink several policies as healthcare sector is diverse.²⁹

4.13.6 State-Based AI Policies

Some Indian states have also drafted their individual guidelines document regarding AI policies. With AI being used on a global and national scale in every industry, several Indian states have already begun to use AI in a variety of sectors such as agriculture, healthcare, education, safety and security. State governments are integral towards putting AI into practice and realising its full potential, together with governmental and intergovernmental organisations. Additionally, they are assisting AI start-ups with cash and a policy framework.

Most Indian pharmaceutical companies are employing AI for radiography, diagnosis and drug discovery, such as targeted molecule discovery. Indian pharmaceutical companies are actively operating and collaborating in the field of AI. To tackle COVID-19, the Health Ministry has also collaborated with AI-based start-ups. Through various policies and initiatives, the state's aid these start-ups in flourishing in that particular sector using AI. Tamil Nadu and Telangana, two Indian states, have created comprehensive AI standards.

4.13.6.1 Tamil Nadu AI Policy, 2020

Tamil Nadu announced its first Safe and Ethical AI Policy in 2020. Tamil Nadu has strategically launched three policies, i.e. the ABC policy. The artificial Intelligence Policy, Blockchain Policy and Cybersecurity Policy. The policy document aims to provide a framework for inclusive, safe and ethical use of AI in the government domain. It aims at fairness, equity, transparency and truthfulness in AI-assisted decision-making systems. The policy also aims to build a self-sustaining AI community to aid the growth of AI in the state and among the people skilled in AI. It proposes a sandbox system for individuals starting start-ups to experiment with their innovative ideas. The policy recommends the six-dimensional TAM-DEF frameworks for evaluating AI-based systems.

1. Transparency and Audit (T).
2. Accountability and Legal Issues (A).
3. Misuse Protection (M).
4. Digital Divide and Data Deficit (D).
5. Ethics (E).
6. Fairness and Equity (F).³⁰

²⁹ NHA | Official Website Ayushman and Ethical Artificial Intelligence Bharat Digital Mission (2022).

³⁰ Safe Policy 2020 | Tamil Nadu Information Technology Department (2020).

The government has encouraged all governmental departments to use AI. The e-governance of Tamil Nadu's AI policy is expected to give many opportunities for inventors in education, healthcare, agriculture, etc. The AI policy of Tamil Nadu is unique as it has launched two other approaches that are moderately interconnected with each other. The TN AI Policy mentions the transparency of decisions made by AI. In many cases, it has faults as it might need to recognise the geographical and other differences in the data. Researchers from IIT Madras are working the use of AI to keep track of the number of pregnant women who drop out of health care programs, which can lead to more deaths and other health problems for mothers and babies.

4.13.6.2 Telangana State Policy on AI, 2020

In 2020, Telangana announced its AI Framework. The state has taken a scientific and structured approach to understand the scope of AI in various domains like education, healthcare, agriculture, mobility and law enforcement. The policy document is in consultation with academia, start-ups, industry and civil society. The six pillars of the policy are

- Data Exchange Platform and HPAIC.
- Skilling and Education.
- Research and Innovation.
- Enabling Adoption and Community Collaboration.
- Governance, Ethics and Privacy.
- AI Investment Fund.

The policy also discusses the incentives (financial as well as non-financial) to the skilled talent through start-ups, fellowships or scholarships. The AI framework will provide grants through zero duty on software and hardware inputs and access to R&D credit to global and Indian companies to set up AI labs. Along with the use of AI for safe and affordable quality care for all, the policy also suggests establishing, raising and managing a dedicated humanitarian investment fund for AI innovation. Under this policy framework, the Telangana government launched an Applied Research Centre focusing on healthcare. The co-founding partners are Intel, The International Institute of Information Technology—Hyderabad, and the Public Health Foundation of India. Under this policy during the pandemic, the Telangana government initiated a flagship program called the COVID Data Platform. The COVID-19 Data Platform delivers over 100 dashboards using anonymised government and public datasets. The image recognition feature was also used for face mask violations. It has also launched an app called COVID-19 Application, which has telemedicine and remote consultation features.³¹

India through its policy framework has been actively supporting AI healthcare start-ups through investment and funding, partnership and collaboration, data and

³¹ Telangana AI Mission (T-AIM) (2020).

infrastructure support and policy. These efforts are aimed at harnessing the potential of AI to improve healthcare service delivery and address the healthcare challenges faced by the country. For example, the government-funded Biotechnology Industry Research Assistance Council (BIRAC) has been providing funding and support to AI healthcare start-ups through its various initiatives. The Indian government-funded start-up accelerator, start-up India, has been providing mentorship and support to AI healthcare start-ups through its various initiatives. The Indian Government's National Health Stack initiative is promoting collaboration between AI healthcare start-up, healthcare providers and research institutions to develop solutions that can be integrated into the national health stack. The government has been providing access to large healthcare datasets through its various initiatives, such as the National Health Stack initiative, for instance the Digi Yatra Project.

Promoting AI in any sector will need a better governance and support system for delivering the resources. It is important that India ensure that the development and use of artificial intelligence (AI) are guided by ethical and societal values and is inclusive and equitable. The government can create a framework for the ethical use of AI and establish institutions to monitor and regulate its use in the country. It is important to interlink industry policies on use of AI. With the greater number of collaborations with multinational companies in development and deployment of technologies, it is important to develop common practice guidance that would remove hurdles in incubating research and development.

By comparing and contrasting the policy documents of various international, national, and intergovernmental bodies, it is concluded that AI has been a subject of governance due to its wide adaptability in multiple sectors. International organisations and intergovernmental organisations are more actively working towards framing ethical guidelines. The intergovernmental organisations are also collaborating with national and international bodies to develop regulatory frameworks and guidance on the ethical implementation of AI.

Each AI policy is different in some way, but national policies need to talk more in-depth about healthcare. There is a need to enhance its application of those principles. Indian central and state policies support healthcare start-ups and companies through various initiatives under different ministries. While the general frameworks may be relevant, sector specific guidance and practice is also necessary. The analysis reveals that healthcare is one of the core areas of a great number of AI policies at international as well as national levels. The state-based policies help in fostering healthcare start-ups and companies that want to use AI-based healthcare innovations in individual state setting. Various ministries have come up with different AI documents and programmes.

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Chapter 5

Way Forward for AI in Healthcare



Improving quality of life has been a constant objective of research and development in healthcare. Achieving global solutions is the target of healthcare innovations of today. Healthcare industry has been significantly impacted by digital revolution. Information technology tools have not only helped in the development of digital approaches to patient care and management, but also in dealing with vast amounts of health data for specific diseases/disorders to improve prescription/use of medical devices. Such has been the incredible growth of healthcare due to the application of information technologies that today individuals can monitor health status and connect more easily to various parts of the healthcare system.

The use of artificial intelligence applications in various sectors is a reality now. The magnitude of application of AI and their significant impact on daily life has been realised. From automobiles to wearables, there are plenty of AI applications. AI's role in medicine goes back to the 1950s. Since then several tools and AI expert systems have pervaded the healthcare system. The most prominent of the AI applications in healthcare has been in field of radiology. Different AI expert systems that are deployed are easy to use and implement and do not always require specialised skills. The nature and scope of AI developments in healthcare indicates greater growth post-2000s. It is interesting to note the elaboration of AI expert systems for more comprehensive applications in healthcare. Initially, more AI tools were developed on academic campuses. However, towards 2010, IT-based companies collaborated with pharma to develop AI tools and AI expert systems. It is observed that some collaborations are made for unique applications and others for a suite of applications. The AI innovation landscape in the healthcare indicates the developments and rapid technical advances in innovations involving information technology applications in biology. This has resulted in newer arrangements of collaboration involving doctors, researchers, data scientists and entities in unique ways. Academic institutes, governmental authorities and companies have generated a vast amount of data—big data as a vast healthcare knowledge. The data types are diverse which include clinical trial data as well. Data mining of this knowledge and deriving applications has become

an important aspect of identifying innovation. The analysis of big data provides an ability to draw inferences with respect to individual preferences and decisions related to health. Data sources could be from hospitals, pharmacies, insurance firms, etc., and the use of this is bound to raise challenges from the point of view of ethics and intellectual property. The analysis of this data is expected to lead to improvement in personalised care, assessment of health conditions and management of population health. Such assessment could be valuable for modelling disease progression, predict epidemics and pandemics, lessening hospital admissions, contribute to pharmacovigilance and enhance precision medicine. AI tools are assisting in arriving at correlations leading to creation of novel processes and products. The intersection of such large data and the derived IP is leading to a worrisome situation on concerns of ‘proptertising’ healthcare and rights to restrict access healthcare information due to IPR grants.

Companies typically concentrate on patents, copyrights and trade secret protection. Some patent offices have developed guidelines for examination of patent applications related to AI. The WIPO Conversation on AI and IP is an open, inclusive and multi-stakeholder forum on setting global norms for the relationship of AI and IP rights. So far eight Conversations have been conducted, and the latest one is in relation to Generative AI and IP. The recent Conversation discussed about the opportunities and challenges that lie ahead in the use of Generative AI. Important distinctions of Generative AI with other AI models, on the limitations and how much human input would be required were discussed. Another discussion was on the need for regulation considering the ethical and social implications that Generative AI technologies could present. A specific panel was identified to discuss a host of IP issues; implications of Generative AI for novelty and originality of works and designs, whether human inventions would become obvious in the light of Generative AI innovations, how the performances of actors, singers, musicians and dancers need to be protected and how current IP law models can apply to Generative AI models. The Conversation dealt with the discussions on the perception of benefits and risks, development of regulation and use cases that include the medical imaging area and IP strategies.¹

Technologies related to AI are globally dispersed. Judicial pronouncements in various jurisdictions have clarified that AI cannot be an inventor. As more is being discussed about the impact of Generative AI, there are also increasing lawsuits being faced by companies that have developed AI platforms. For instance, ChatGPT and OpenAI are being sued for issues related to violation of copyright, author’s rights and personal information. Holding exclusivity to large sets of data has become key to healthcare companies. The outcome of these cases would determine to what extent healthcare companies could rely on claims in future for data-related patents.

Securing patent rights assist not only in obtaining market exclusivity but also fosters innovation. Our analysis of the patenting activity shows increased trends from 2010 in patents for AI in the healthcare domain. The significant domains represented

¹ Eight WIPO Conversation on AI and IP—https://www.wipo.int/edocs/mdocs/en/wipo_ip_conv_ge_2_23/wipo_ip_conv_ge_2_23_1_prov_4.pdf.

by patents are computer technologies, medical technologies and internet technologies for management. The analysis of the patent applications reveals AI-assisted inventions for healthcare management, medical image processing, predictive diagnosis and health monitoring in disease conditions. The earliest priority countries are predominantly USA and China. There is a diversity of patent applicants who file applications in India (individual inventors, start-ups, academic institutes and companies). Analysis of the patent prosecution of Indian applications indicates most often twin challenges of the application of Sec 3i² and Sec 3k³ restrictions. Section 3i deals with restrictions on inventions related to medical treatment methods, and Section 3k relates to ineligible subject matter in case of inventions that are software per se. Section 3m⁴ restrictions have also been applied in a few instances. Section 3m relates to restriction on schemes or rules or performing mental acts.

The interview analysis of the selected companies in India indicates significant developments related to imaging. Some have partnered with other companies and start-ups to develop newer applications. A few companies utilise patenting as a vital strategy to leverage markets abroad. In some cases, unique AI-based health applications are being developed to solve unmet needs in India and on the global front. As the public acceptance of AI technologies increases and industry adopts responsible AI approaches, AI applications are expected to grow further.

With the rising demand on accessible and affordable medical care, meeting the needs and expectations has been a central concern for governments and industry alike. While norms of use of Generative AI are being developed, assistive AI has been used widely to develop several applications. While this is so, companies need to keep this pace with the applicable regulation in order to bring AI products and processes to market. The development of regulations has also grown in parallel. The innovations related to healthcare are extending into different branches, such as diagnosis, radiology, computing vision, robotics and data analysis. The approval requirement has also seen a shift in AI-based medical devices, whether in the form of separate classification, approval process or accommodating it in the existing drug legislation.

The analysis of the statutory perspective indicates that there are several challenges in AI-based medical device regulation. From a cross-country perspective, the USA is the first country to approve software as a medical device, which is regulated as per Section 510k of the Drugs and Cosmetics Act. While the classification of medical devices is being accepted uniformly in many jurisdictions, the norms for implementation and enforcement are still in the development phase.

In the past two years, there has been an emphasis on risk regulation and its elaboration (especially so in the EU). With the greater prevalence of such devices in the

² Sec 3i of Patents Act 1970—any process for the medicinal, surgical, curative, prophylactic diagnostic, therapeutic or other treatment of human beings or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products.

³ Sec 3k of Patents Act 1970—a mathematical or business method or a computer program per se or algorithms.

⁴ Sec 3m of Patents Act 1970—a mere scheme or rule or method of performing mental act or method of playing game.

USA and EU markets, many companies have been trying to introduce products in India. Many products in India have at least one or more certifications (regulatory compliance) from abroad. Interview analysis on the regulatory perspective reveals that Indian companies are already preparing devices as per international standards. Nevertheless, for diseases unique to India, they believe there is uncertainty regarding the extent of submission of information required for marketing approvals. The companies have challenges implementing these devices in the market as Indian regulation is still nascent in this area. Differing regulatory standards and norms in the development phase have compelled some companies to work more for the export market. The way forward for Indian drug regulation can be envisaged in the new Bill (the New Drugs, Medical Devices and Cosmetics Bill 2022) being discussed, including digital interventions associated with medical devices. With respect to AI-based medical devices, there are ample concerns for regulation of device on one hand and the regulation of data. This is where the context of Responsible AI gains importance. The use of data for research, health claims, interpretation for prescription and patient care needs to be done in an ethical way. The ethical appropriateness of utilising identifiable data must be determined. Also, there is a clear need to define exemptions. Ethical concerns in turn reflect privacy, risks and accountability. The ethical norms that exist are expected to help in the development of a uniform set of standards that can be applied. Such standards should clearly help in the protection of privacy, security and confidentiality of data.

Along with IPR laws and regulation, policy support through governmental initiatives is vital when new technology-based products are introduced into market. Policies and relevant institutions play an important role in the appropriate utilisation and management of technologies. Public policies provide a platform for promoting socially inclusiveness and sustainable development. That is true of healthcare as well. The analysis of international and national policies related to AI and their relevance to the healthcare area reveals development of principles that govern ethical use, governance of AI and accountability. International and national institutions identify pathways for implementation of the policies to beneficiaries. Healthcare needs, problems and issues in implementation of AI help in the assessment of public policies. Further, the response of the beneficiaries helps bring in changes to policy and initiatives taken by governments. The policy framework analysis indicates a need to coordinate different ministerial agencies to deploy the technologies effectively. This can be effective only when a practical risk regulatory framework considers multi-stakeholder views, as AI could be single-application only or multiple-application based. During the COVID-19 times, AI tools were used widely due to the enabling policy support.

The development of Responsible AI principles heralds a path for inclusion into AI development processes and outcomes. 'Trustworthy AI' and 'AI for All' reflect how public policy and good governance can play a critical role in the implementation of AI tools. While there is no denial that accessibility and affordability are core to healthcare, equally important is the identification of potential bias and risks associated with use of AI applications. From a definitional perspective, the nature and scope of what AI should do or not do continues to evolve. The WHO's work on AI related

to assessment framework for AI-based methods for health, diagnosis and treatment serves as an important guidance. India has implemented policies related to AI and healthcare at the national level. Some states in India have announced a general AI policy which also includes healthcare. Other states are engaging consultations with industry and stakeholders to foster an enabling ecosystem for the growth of start-ups and companies working in AI and healthcare. As our society transitions into use of AI-based technologies in healthcare, governments and private entities have an important role in ensuring safety standards and effective AI applications. A bottom-up approach based on the response of the beneficiaries and cross-sectoral inclusion is the way forward for AI in healthcare.