ACE OVERVIEW FOR NEW AND EMERGING HEALTH TECHNOLOGIES

Artificial Intelligence and Its Clinical Applications

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This overview presents independent research by the ACE. It is not a systematic review, but rather a rapid overview of the technology and the available evidence based on a limited literature search. It is not intended to provide recommendations for or against the particular technology. The views expressed are those of the author and not necessarily those of the ACE, or the Ministry of Health.

Summary of Key Points

- Artificial intelligence (AI) refers to a set of technologies that allow computers to perform tasks that simulate human traits. Recent techniques of AI involve computers learning from examples rather than explicit programming and some common methods include machine learning (ML), deep learning (DL), and natural language processing (NLP).
- Clinical applications of AI may be dichotomised into physical and virtual: physical applications include AI robots that assist in surgeries, intelligent prostheses, and robots as companions for the elderly. Broad virtual applications include disease diagnosis, treatment selection, patient monitoring, patient risk stratification for primary prevention, interpretation of patient genomes and automated surgery.
- Most overseas regulatory agencies regulate AI as a software as medical device (SaMD). A few countries, including Singapore, regulate SaMD adopting a total product life cycle approach, with additional requirements for AI incorporated medical devices (AI-MD). Regulating AI-MD presents challenges in ensuring the continuous safety and efficacy of the AI systems since they have the ability to continuously learn and change their output.
- AI is leveraged in various clinical areas to improve prioritisation of care through triaging patients, automating detection of disease, enhancing productivity and planning for delivering care through risk stratification for chronic diseases, assistance with earlier diagnosis, and improving quality of care. Clinical areas which have garnered special interest in adopting AI algorithms are radiology, dermatology, pathology, ophthalmology, oncology and neurology.
- Currently there is some evidence supporting the purported benefits of AI, especially in its accuracy in assisting disease detection and prediction, which is generally shown to be comparable to, or sometimes better than, that of the performance of clinical experts. However, most evidence has not demonstrated consistent machine accuracy or clinical utility in real-world clinical environments.
- Cost considerations of implementation of AI software include hard and software costs, installation fees, technical and clinical support, as well as costs related to maintenance and training of staff. The cost impact of AI is currently unknown due to a lack of economic evidence, and it will depend on the accuracy of the AI which varies between technologies.
- Major implementation considerations include
    - Legal considerations are ownership of data and the need for laws to protect patient’s data uses outside of healthcare contexts; liabilities in cases of AI misdiagnosis and infringement of privacy in cases of data sharing across institutions may also present legal issue;
    - Major challenges to the successful implementation of AI in healthcare systems are initial high resource investments, requirement on adequate, large and high-quality data for training of the algorithms, risk of embedding bias and unfairness in datasets used for AI training, and a lack of decision transparency in AI outputs;
    - Ethical concerns are equity of benefit for AI in minority populations, potentials for infringement of patient's freedom to make informed decision due to lack of decision transparency of AI algorithms.

I. Background

Artificial intelligence (AI) is an umbrella term referring to a set of techniques that allow computers to perform tasks that simulate human traits such as knowledge, reasoning, problem solving, perception, learning and planning.[1] The field of AI was founded in the 1956 with interests in AI surging in the 1980s and 1990s with the use of logistic data mining and medical diagnosis.[2,3] Today, the advent of AI in current healthcare application is from the large quantities of data generated from sources such as high-resolution medical imaging, biosensors with continuous output of physiologic metrics, genomic sequencing, and electronic medical records.[4] Limits on analysis of these data by humans have given AI the role of acquiring, analysing and applying both structured (e.g. lab values, patient demographic data) and unstructured (e.g. photos, videos, physician notes) data to treat or manage diseases.[4,5] AI technologies are able to automate data mining and pattern recognition which helps with prediction, diagnosis, treatment or management of diseases.[5] In contrast, non-AI medical software applications uses pure statistical analysis and probabilistic approaches.[5] The problem solving ability of AI has generated great interest in its potentials in addressing longstanding deficiencies in healthcare including diagnostic errors, mistakes in treatment, waste of resources, inefficiencies in workflow and inadequate time between patients and clinicians.[4] In 2016, AI applications in healthcare made up the biggest investments compared to its use in other industries.[3]

During the MTAC meeting in July 2019, AI was nominated as a potential topic of interest for horizon scanning and was subsequently shortlisted for further review due to its potential impact on the healthcare system. Due to the wide range of applications of AI in various clinical fields and a lack of a defined scope during the nomination phase, an overview was developed to provide a broad understanding of AI. This overview focuses on the clinical applications, potential impact and challenges of implementing AI in the Singapore healthcare system with the aim of informing the committee for further scoping of potential AI topics for subsequent review. The use of AI in health education, research or drug discovery and development is outside the scope of this report.

II. Technology

Huge technological advancements in AI has pushed computers to learn from examples rather than explicit programming.[6] In the early stages, AI techniques consisted of rule based systems to explicitly define the steps that take from one set of inputs to outputs to help with medical reasoning.[5] Using IF-THEN type rules, this technique is able to interpret electrocardiograms (ECGs), diagnose diseases, choose appropriate treatments, provide interpretations of clinical reasoning and assist physicians in generating diagnostic hypotheses in complex patient cases in a clinical decision support purpose.[7,8] More recently, AI has moved towards data-based systems such as machine learning (ML) methods which can account for complex interactions to identify patterns from data without explicit programming.[5,9] ML is the most common AI technique which involves application of sets of algorithms to analyse a given situation with the ability to learn from feedback about the outcome of analysis in order to self-adjust and improve accuracy.[10] There are three types of ML algorithms: (i) unsupervised is the ability to find patterns in a stack of data, (ii) supervised is the classification and prediction algorithms based on labelled training data, and (iii) reinforcement learning is the use of sequences of rewards and punishments to form a strategy for operation in a specific problem space.[2,5]

Deep learning (DL) is a subset of ML in which an algorithm can analyse structured multiple data sets (e.g. excel charts, genetic or electrophysiological data) and then examine the data according to a predetermined pathway.[11,12] It makes use of mathematical models, artificial neural networks (ANN) and convolutional neural networks (CNN) to perform multiple evaluations until reaching an output. Once AI software that was developed through ML is in use, the model can continue to learn or be fine-tuned with feedback. Real world input data may be used to update the model in real time through a process called "continuous learning".[9] This allows AI to use sophisticated algorithms to first "learn" from a large volume of data and use its self-correcting abilities to improve accuracy based on feedback.[12] Through this feature, AI is also able to extract information from large databases to assist in making real-time inferences for health risk alert and health outcome prediction.[12] Alternatively, AI may use a discrete set of training data to develop a model which can be "locked" and used without automatic updates.[9] The cycle of the training process, clinical trial evaluation, and its implementation in clinical settings for machine learning algorithms in health-care delivery are summarised in Figure 1.[13]

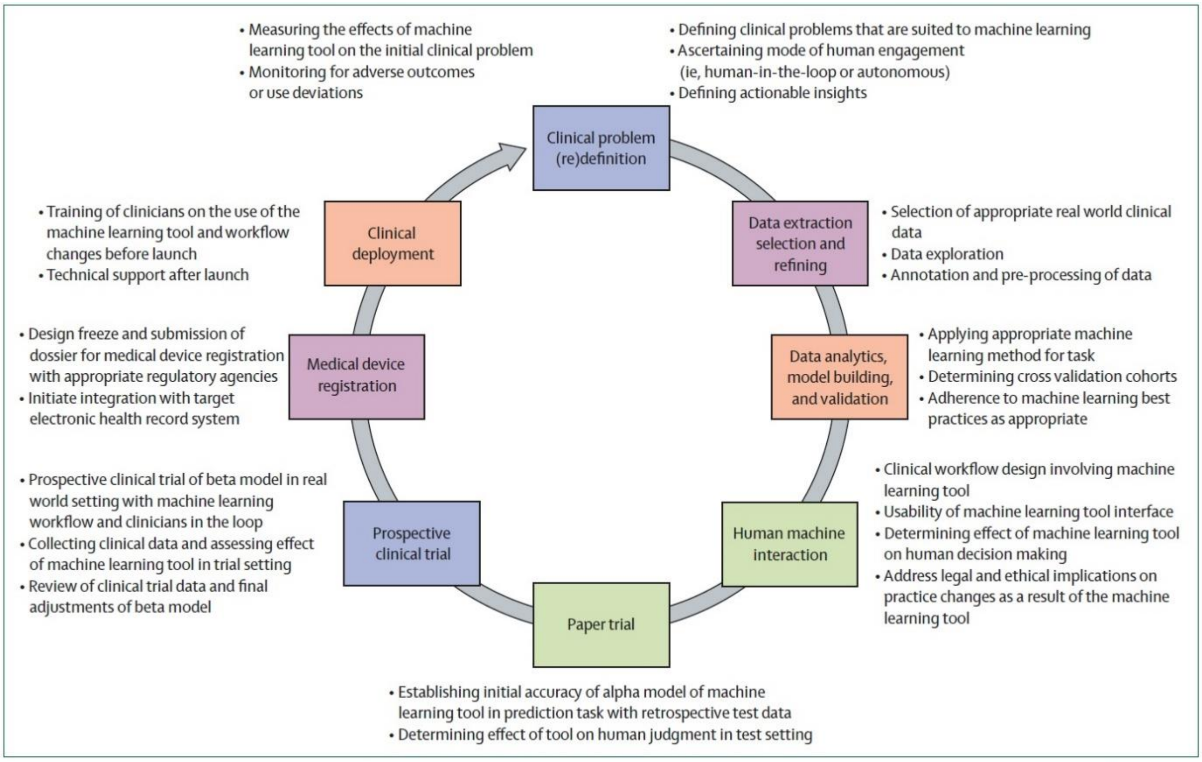

Figure 1: Life cycle of machine learning algorithms for health-care applications from training, clinical trial evaluation to clinical implementation.

Another common AI technique is natural language processing (NLP) which uses software programming to understand and manipulate natural language text or speech for practical purposes.[5] NLP enables machines to read and understand human language which can be used to gather and analyse unstructured data such as clinical notes or medical journals which can supplement and enrich structured medical data.[5] AI systems employing NLP can extract up-to-date medical information from journals, textbooks, and clinical practices to inform clinical decision making.[12]

Applications of AI techniques in medicine may be dichotomised into two subtypes: physical and virtual.[3] Physical applications include AI robots that assisting in performing surgeries, intelligent prostheses and robots as companions for the aging population.[2,3] A further example of the amalgamation of robotics and AI in surgery is the Smart Tissue Autonomous Robot (STAR) developed by Johns Hopkins University which is equipped with algorithms that allowed it to match or outperform human surgeons in autonomous ex-vivo and in-vivo bowel anastomosis in animal models.[14]

Numerous virtual AI clinical applications are in clinical use or research, including disease diagnosis, interpretation of genomic data, treatment selection, patient monitoring and risk stratification for primary prevention, and automated surgery.[8] In terms of publications, robotics surgery has the highest volume[15], followed by ML for large and complex dataset analysis for genetics and prediction of disease.[15] An increasing number of AI research has been seen on non-communicational diseases such as heart disease, stroke, and respiratory diseases.[15]

Most recently, AI has been employed for bio-surveillance to detect outbreaks of COVID-19, including early identifications of COVID-19 cases, especially amongst quarantined patients, and predicting prognosis in COVID-19 patients.[16] Given that AI offers opportunities to make better use of health care's increasingly data-driven environment, it has the potential to change the way future health care is delivered.[17] However, due to the highly data dependence nature, a key limitation of AI would stem from the often heterogeneous, complex and poorly coded health data which could lead to poorly performing systems.

III. Regulatory Considerations

Currently AI is generally regulated under the existing frameworks for medical devices, or software as a medical device (SaMD), in most countries. In Singapore, HSA has published a regulatory guideline for software medical devices using a total product life cycle approach (TPLC).[1] It includes additional regulatory requirements for AI incorporated medical devices (AI-MD) from development of the dataset to post market monitoring. Specific considerations include quality requirements for AI with continuous learning capabilities, level of human intervention (manual to fully autonomous AI systems), training of models and retraining.[1] Similar to other registered medical devices, when there are any modifications to a registered AI-MD, a Change Notification to HSA is required based on a risk-based approach to managing the changes to registered AI-MD. Compared to non-significant changes, significant changes will undergo a more in-depth review to ensure the safety and effectiveness of the software.

In the US, the FDA has recognised the issues with existing SaMD framework on regulating continuous learning AI models which may change the output initially cleared for a given set of input. Together with considerations on the risk categorisation and type of modifications of the AI, the FDA has developed a discussion paper on its proposed TPLC approach framework for modifications of AI-based SaMD to provide reasonable assurance of safety and effectiveness throughout the lifecycle of the developer and products.[18] The paper lays out when a new submission would be required for the modifications of AI-based SaMD. Feedback from industry have largely supportive of the TPLC approach, with some comments for FDA to add defined categories based on level of human intervention which will provide clarify on the submissions required, enforce additional monitoring that an ML algorithm is behaving correctly when deployed, and provide guidance on best software practices.[19,20]

The Australian TGA has also proposed and sought public consultation for its scope of regulating software-based products.[21] The general feedback includes the need for simple decision rules and clear rationale for the kinds of software based products that should be excluded from TGA regulation.[22] Also, the need for an intermediary category for products that warrant exemption but not full exclusion was raised, so the TGA would have some oversight for this group of products. Of notable difference between the three countries is the lack of cybersecurity controls in the FDA and TGA's discussion papers, whereas the HSA regulatory guideline requires manufacturers to submit a post-market plan detailing active surveying, detecting of possible threats, monitoring and their response to evolving and newly identified threats.

In Europe, AI is currently regulated under medical device directives[23] and a guideline is in development by the EMA. In February 2020, the European Commission released a report on the liability implications and safety of AI, the Internet of Things and robotics, emphasising the need for a high quality digital infrastructure and regulatory framework.[23] Similarly, there are currently no specific regulatory frameworks for AI-MD in Canada, but Health Canada is establishing a new division for pre-market review of digital health technologies through the Regulatory Review of Drugs and Devices initiative. Some AI devices in Canada have received Class 1 medical device licence.[24]

Table 1: Regulatory status landscape of AI locally and in reference agencies

	HSA	FDA	Health Canada	EMA	TGA
Regulatory guideline	Yes	No – currently a discussion paper	No	No – guideline in development	No – currently a consultation paper
Approved products	Yes	Yes	Yes	Yes	Yes
HSA: Health Science Authority; Singapore, FDA: Food and Drug Administration, United States, Health Canada; Canada, EMA: European Medicines Agency; UK, TGA: Therapeutic Goods Administration; Australia					

The regulatory framework by HSA and discussion paper by FDA both take a TPLC approach to encompass the regulatory requirements for software medical devices. Unlike other medical devices, AI-MD will likely present more variation between performance in the testing environment and in actual practice settings, presenting potentially less certainty on their benefits.[25] Regulators may request for in-depth human factor analysis of how healthcare professionals react to outputs of particular AI and require training for users to help minimise variance.[25] The regulators could also require information related to the culture of quality and organisational excellence of the manufacturers including ongoing system monitoring, periodic retraining, software and usage inspections, review of aggregate usage statistics to identify possible drifts in treatment frequencies and decision styles of users.[25] However, these additional requirements would likely demand more time and efforts from the regulators.

IV. Current Development in Singapore

Stage of diffusion	Clinical applications
Investigational	Disease prediction, screening, treatment recommendation, lifestyle coaching, clinical decision support systems, personalised medicine
Newly entered	Neurological disease prediction, classification, risk prediction
Nearly established	Eye disease screening
Established	-

In 2018, a national AI programme, AI.SG, was set up and comprises a government wide partnership to support initiatives to invent AI algorithms, conduct research and encourage inter-institutional collaboration.[26,27] Subsequently in 2019, a National Artificial Intelligence Strategy was announced which highlights five national AI projects, one of which is chronic disease prediction and management.[28] The first program is the Singapore Eye LEsioN Analyser (SELENA+), which analyses retinal photographs using a DLS to detect three major eye conditions: diabetic eye disease, glaucoma and age-related macular degeneration. It may be used at primary healthcare settings.

Various local research activities on AI are happening. As part of the national effort, the AI in Health Grand Challenge, which aims to encourage innovative approaches to enhance primary care in health promotion and disease management, has awarded three research projects :

- An AI platform that gathers local healthcare data to enable predictive stratification for preventative actions and treatment recommendations in diabetes, hypertension and hyperlipidaemia [29] (https://www.aisingapore.org/grand-challenges/awardees-jarvis-dhl/);
- An AI prototype device to be deployed in the community for patients with chronic diseases which allows automatic lifestyle coaching (https://www.aisingapore.org/grand-challenges/explainable-ai-as-a-service/);
- An AI system that assesses the status of patients and identifies pre-diabetic, hypertensive and high cholesterol patients based on early behavioural patterns, health systems and other non-medical factors (https://www.aisingapore.org/grand-challenges/awardees-ai-a3c-2/).

Furthermore, other experimental uses of AI include personalised medicine in oncology. Researchers from NUS have developed an AI platform that use a patient's own clinical data such as drug doses and corresponding changes to tumour sizes of cancer biomarkers to create an individualised drug dose for the best possible treatment outcome.[30] Applying advanced ML techniques on medical imaging to identify a range of conditions from neurological disorders to cardiac and lung disease has been researched on, resulting in the international market approval of an AI platform applying on large volume of MRI scans to assist diagnosis of a range of brain tumours.[31] Currently a number of other AI products have also been approved by HSA for use in stroke prediction[32] and classification of neurological diseases such as acute brain infarction, white matter hyperintensity and cerebral microbleeds.[31]

As mentioned previously, COVID-19 has also seen the development and deployment of AI solutions, such as temperature screening using smartphone fitted with thermal and 3D laser cameras to screen for febrile people in a crowd,[33] clinician decision support using clinical chat assistant smartphone app to extract clinical information from large amounts of information relating to COVID-19 from different data sources,[33] and screening device for lung infections and pneumonia employing DL to analyse X-ray images to highlight abnormal areas.[34]

V. Expected Impact on Healthcare

Many benefits have been proposed in AI applications in health care, such as triaging patients as AI is able to conduct preliminary analysis to suggest likely diagnosis, automating detection of disease through pattern recognition in imaging results, enhancing productivity and planning for delivery of care through detection high risks population for chronic diseases, predictive modelling to aid early diagnosis, and improving quality of care through AI applications that routinely collect healthcare data.[28,35] Due to the width of AI algorithms use in medicine, only several clinical areas in which AI has generated special interest are discussed here, particularly radiology, dermatology, pathology, and ophthalmology. A brief summary of the potential benefits for healthcare system as a whole was also presented.

Radiology

Radiology is one of the specialties which has seen the most application of AI. It is often used to automate disease detection enabling clinicians to quickly characterise diseases. Recent studies suggest that, when interpreting images, DL can make predictions at a level of competence comparable to that of a clinician in some areas such as echocardiograms and chest and wrist X-rays.[4,17] A randomized control trial using real cases from the dataset showed that the DL algorithm could interpret scans 150 times faster than radiologists (1.2 versus 177 seconds), but the algorithm's diagnostic accuracy in screening acute neurologic scans was poorer than human performance.[4] With the reported area under the curve (AUC) scores ranging from 0.99 for hip fracture to 0.84 intracranial bleeding and liver masses to 0.56 for acute neurologic case screening, current evidence does not appear to show AI applications in this field have high and reproducible machine accuracy nor clinical utility in the real-world clinical environment.[4] When AI tools become more sensitive, it may have the potential to enable earlier disease diagnosis and track treatment progress due to their ability to identify small image variances not visually discernible by the human eyes, informing treatment decisions.[17]

Dermatology

Most AI applications in dermatology are aimed at supporting dermatologist's clinical decision making for general skin conditions and specific cancers. It is expected that AI may help in decreasing unnecessary biopsies and increasing the number of life-saving early detection events as ML classification algorithms may be used in identification of cancerous lesions such as border demarcation features which are often subtle and difficult to determine through visual diagnosis.[17] There is some evidence showing that, for algorithms classifying skin cancer by image analysis, the accuracy of diagnosis of deep-learning networks has been comparable to, or sometimes better than, that of dermatologists, with AUC scores varied between 0.86 to 0.96.[4] However, none of the studies thus far were conducted in a clinical setting.[4,17] Despite these concerns, most skin lesions are diagnosed by primary care physicians, who generally perform worse than experienced dermatologists, so AI may represent a significant advance. Given its ability to assist in the diagnosis of skin diseases, AI may also help clinicians in the management of workloads and competing priorities.[4,17]

Pathology

AI innovations in pathology are emerging albeit at a slower rate than radiology. AI is leveraged to automate complex and time consuming tasks such as object quantification, tissue classification and rare target identification to help address the shortage of pathologists, potentially contributing to workflow efficiencies and reducing inconsistency in interpretation of pathology slides.[17] In particular, application of DL in interpretation of digitised pathology slides was shown to improve accuracy and speed of interpretation in a few retrospective studies in breast, lung and brain tumours.[4] In a prospective study in a real clinical setting to identify presence of breast cancer micro-metastases, the combination of an algorithm and pathologists led to the best accuracy, and the algorithm markedly sped up the review of the digitised slides.[4]

AI is also anticipated to reduce diagnostic variability especially in prognostication of prostate cancer. In prostate cancer diagnosis, which is one of the most active fields in adopting DL because of its large dependence on tissue morphology, there is some evidence demonstrating an accuracy varying between 0.99 to 0.70, and DL algorithms outperformed pathologists in grading accuracy in some cases.[36]

Ophthalmology

Applications of AI in ophthalmology are mostly in automation of screening for retinal diseases and triage for urgent referral. In both cases, there is evidence that DL algorithms performed was as good or better than clinical experts with AUCs reported varying between for accuracy 0.999 and 0.992. Combined with an imaging device, a DL algorithm use in primary care to screen for diabetic retinopathy in patients with diabetes but no known retinopathy was assessed in a prospective trial. Although the accuracy (sensitivity 87%, specificity 91%) was reported as not as good as the in silico studies, it led to FDA approval of the device and algorithm for autonomous detection of more than mild diabetic retinopathy.[4]

Screening for diseases such as diabetic retinopathy using AI was also assessed in Singapore. An automated AI system for diabetic retinopathy screening is suggested to reduce the current wait time for results from a day to a few minutes, and reduce resource use and clinician workloads.[37,38] A local validation study comparing the accuracy of a deep learning system (DLS) against professional grader showed the DLS was as sensitive as professional graders but not as specific in detecting DR (details in Table A1 in the Appendix).[39]

Others

Beyond innovation in AI for clinical areas mentioned previously, an increasing application of AI in cancer-oriented cognitive computing systems is seen due to its ability to synthesis vast amounts of information and integrating it into decision making more quickly than humans. This can be useful to enhance personalised patient treatment plans.[17] One such application is clinician decision support system (CDSS), which was reported to make recommendations that were in agreement with those made by physician 81% to 93% of the time for colon and rectal cancer respectively. Further, AI algorithms in detecting brain abnormalities in stroke has been considered promising as it is thought to improve the speed of diagnosis and service for people who need urgent diagnosis and treatment.[40] However, a review showed that AI was as effective as neuroradiologists at detecting only intracranial haemorrhages, but not in other conditions such as large vessel occlusion, neurological abnormalities in trauma, dementia and stroke.[40]

Healthcare system benefits

Besides the productivity and workflow gains which can be derived from AI-assisted image interpretation and clinician support, there is potential to reduce the workforce for many types of back-office, administrative jobs. Some examples have showed potential resources savings for healthcare system, such as genetic counselling provided by AI chatbot instead of highly trained personnel.[4] In addition, with the regulatory approval of wearable sensors that can continuously monitor all vital signs, there is the potential to prevent a large number of hospitalisation, which accounts for a large proportion of healthcare expenditure. Further, some potential benefits have been modelled for AI due to its ability to predict key outcomes which could theoretically help to plan for hospital resources more efficiently, especially in critical and palliative care. Despite some preliminary evidence, currently it is unknown how well AI can perform this task without robust validation of the results in real world clinical environments.[4]

VI. Expected impact on healthcare costs

Current information on the costs of AI and its implementation is limited. Cost considerations of AI software include initial installation fees, technical and clinical support and maintenance costs.[41] Based on the potential benefits of AI, it may play a role in the sustainability of a public healthcare system by detecting disease earlier, providing a more accurate diagnosis, and reducing the cost of and increase the speed in analysing imaging. This may help to reduce health care and legal costs due to improving diagnostic accuracy and reducing therapeutic errors that occur in the human practice of medicine. However, AI could contribute to misdiagnosis if the performance of the algorithms is not sufficiently accurate. Further, AI may also lead to improvements in patient outcomes as it supports clinical decision-making and ensures that interventions and treatments are personalised to each patient which may reduce costs associated with treatment-related complications.[17]

Examples for resource implications of risk prediction and screening programs for colorectal cancer showed an increased need for human resources such as primary care physicians, specialists and administrators to attend and cope with increased patient load. Information technology (IT) integration and training as well as clinical training to help with interpreting the results may also be required in adoption of AI technologies.[41] In a study of a local diabetic retinopathy screening program using AI, despite additional costs related to a tele-ophthalmology platform to enable AI analysis of retinal images, models using DL system leads to net savings of up to 20%, compared to current human assessment model, per appropriate case referral.[42,43] With a projected population with diabetes of 1 million by 2050 in Singapore, the estimated annual savings would be $15 million.[43]

In a NICE report on AI for analysing CT brain scans, the costs for automated AI analysis of radiology images, include the technology's licence costs, ranged from £8,250 to £60,000 in subscription models or £45 a pay per patient model.[40] Resource impact of such technologies is expected to be greater than standard care, however, costs may be offset by faster diagnosis of time-sensitive cases and reducing complications related to delayed treatment.[40] Experts comments on the use of this AI technology argue that currently there may not be reduced diagnosis time as radiologists would need to carefully review results generated by the AI to ensure accuracy.[40] Others suggested downstream savings may only be realised if the diagnostic accuracy is better than current model of care.[40]

A conclusion on the impact on healthcare cost of implementing AI cannot be made at this time given the paucity of economic evidence and the dependence on the accuracy of the AI which may vary between different technologies.

VII. Implementation Issues

Successful implementation of AI in health care depends on several factors which include the public's acceptance of AI in playing a role of their treatment and trained staff who will come in contact with the technology.[17] Additionally, potential challenges such as resource considerations, data reliance, risk of bias, decision transparency, ethical and legal issues present initial barriers for successful adoption.

Resource considerations

A realistic business model is needed when implementing AI, which involves investment resources for hardware, software and technology expertise to ensure compatibility with current hardware and software used in the healthcare institutions.[17,42] Portability of programs across different systems is also a potential issue as usage of different software in different institutions that may also impact on how readily and successfully an AI system can be deployed.[17] The processes to solve these issues may be labour intensive which could be a barrier for initial investment as the financial and resource requirements are high and the benefit is not immediate.[42]

Data requirement

AI systems require large amounts of high quality data to learn, and large datasets are required in order to reach acceptable levels of accuracy and performance.[17] However purely increasing the amount of data will not necessarily enhance the performance of the AI due to the potential to increase the likelihood of spurious connections.[42] In addition, building datasets also requires skilled experts to accurately label images or other information sources which present additional resource consideration.[17] Therefore, a clear guideline for the optimal quality and number of cases for training of particular AI system is required.[42] A particular limitation of training AI in orphan diseases exists which may still require clinicians for accurate identification and diagnosis.[42]

Algorithmic fairness and risk for bias are issues developers should consider when deciding which ML technologies to employ and what datasets, including their quality and diversity, to use for programming.[23] Biases may occur when the datasets used are not representative of particular subpopulations, or the way data scientists and ML systems choose and analyse the data, or the context in which AI is used which may lead to discrimination of some populations. An algorithm would also need testing in the intended setting as it may work well in an academic or limited clinical setting but may not be scalable to a real world setting.[17] This is a potential risk for harm if an AI algorithm contributes to misdiagnosis[17] which has subsequent legal implications.

Decision transparency

There is a challenge for physicians to understand how a neural network like DL reaches a decision or to identify which exact features it utilises for its decision.[44] Deep learning prediction capabilities are often described as a "black box". Hence, AI tools should also be able to provide evidence as to how they arrive at specific conclusions allowing physicians to confirm that the conclusion makes sense.[17] A potential solution is multi-step algorithms that would first detect certain clinically known features through DL that will then predict or classify based on these features to help physicians explain the how the AI system generates an output.[44]

Legal considerations

The generation of large databases of patient data raise the question of ownership of data.[23] Some patients may not be agreeable with companies or governments using patient data for profit.[23] This presents a need for laws to protect patients against data uses outside the context that might negatively affect patients on their health, insurance premiums as well as privacy of data. Some of these will require anti-discrimination laws similar to those for genetic privacy.[23] Other legal issues are liability in the scenario where an AI-based clinical decision software gives an incorrect treatment recommendation resulting in harm to the patient. Similarly, hospitals that purchase and implement AI systems may be liable to negligent credentialing when they do not adequately review the AI system they use.[23]

Acquiring large database poses additional challenge to privacy rules whenever data needs to be shared between different centres. AI developers that work with healthcare institutes and patient data need to meet security, data compliance, and audit requirements.[17] The use of patient data should adhere to the principle that those seeking to use patient data must show that they are adding value to the health of the very same patients whose data is being used.[23] Possible solutions include having usage agreements and permissions in place and commitments to patient data privacy and security.[17]

Ethical issues

Ethical concerns are the potential that not all populations will benefit equally from AI due to lack of data from minorities, the malicious use of AI particularly its use in covert surveillance or screening, as well as the long term safety and reliability of the AI systems.[17] Other issues are potential infringement of the patient's freedom to make informed decision when a physician is unable to explain the logic behind an AI-based treatment recommendation.[17]

VIII. Expected Future Developments

Currently the narrative of bringing AI to medicine is just beginning, with lots of research ongoing. It has been highlighted that there has been remarkably little prospective validation for tasks that machines could perform to help clinicians or predict clinical outcomes that would be useful for health systems, and even less for patient-centred algorithms, resulting in potentially higher risk of faulty algorithms than that of a single doctor–patient interaction.[4] The work for developing deep-learning algorithms to enable the public to take their healthcare into their own hands also lags behind that for clinicians and health systems. To this end, promising research are ongoing in areas such as smartphone apps using AI to monitor medical adherence, and the use of AI with multimodal data to guide an individualised diet which sets a precedent for virtual medical coaching in the future.[4]

There is interest in development interpretable DL models to enable physicians in interpreting the outputs of the AI technology to address the issue of lack of transparency and complexity in how AI reaches a decision. For clinical use, it would be important for any decision support system to justify its analysis particularly if there were concerns about unreliable predictions.[45,46] There is program being developed on a new machine learning system that will have the ability to explain their rationale and characterise their strengths and weakness.[45]

There has also been interest in enhancing precision of current AI models by combining algorithms from multiple imaging tools and developing deep learning algorithms that could infer disease progression patterns and determine reliable predictors of disease such as diabetic retinopathy.[24] There is also potential for combination of image data with other health data that could inform of risk of systemic disease.[24]

Although machine and deep learning has been used in the analytics of genomic and other -omics biology datasets, they are generally taking a single -omics approach. Currently there are multi-omic algorithms being developed that integrate the various datasets. The use of genome editing has also been facilitated by algorithmic prediction of CRISPR guide RNA activity and off-target activities.[4]

AI may also be used in telehealth screening programs which may increase assess to screening.[24,47] There has also been research in validation of telehealth screening programs to ensure the AI systems is able to identify retinopathy per accepted standards and in a clinical setting.[48] Ongoing efforts to digitise surgery also include using observation of the team and equipment in the operating room and performance of the surgeon, real-time AI-processed imaging of the relevant anatomy of a patient, and integration of all of a patient's preoperative data, including full medical history, labs, and scans.[4]

IX. Additional Information

Social issues associated with the use of AI pertain to the perception of patients and members of the public on the impact of AI on their relationship with physicians and their expectations of its use in healthcare and medical research.[49] A study by Ipsos MORI, a London based market research company, performed 978 interviews with members of public on the perception of ML found the largest concern was the risk of loss of human interaction with the fear that AI technologies could encroach or in some way degrade patient and healthcare professional relationships.[49]

In 2018, a survey was conducted on UK adults on the perspectives for use of AI in health and use of data to develop healthcare algorithms. The survey found less than half of the respondents (45%) felt that AI should be used for diagnosis of a disease and over 60% felt AI should not be used for tasks performed by doctors and nurses such as answering medical questions and suggesting treatments. The results suggest that there are concerns and gaps in knowledge in the potentials and benefits of AI in members of the public.[49]

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Appendix

Table A1: Primary validation dataset showing area under the curve, sensitivity, specificity of the DLS vs trained professional graders in patients with diabetes with reference to a retinal specialist's grading

	DLS		Trained professional graders		
	Value	**95% CI**	**Value**	**95% CI**	**P value**
Referable diabetic retinopathy					
AUC	0.936	0.925 – 0.943	-	-	-
Sensitivity, %	90.5	87.3 – 93.0	91.2	88.0 – 93.6	0.68
Specificity, %	91.6	91.0 – 92.2	99.3	99.2 – 99.4	<0.001
Vision-threatening diabetic retinopathy					
AUC	0.958	0.956 – 0.961	-	-	-
Sensitivity, %	100	94.1 – 100.0	88.5	75.3 – 95.1	<0.001
Specificity, %	91.1	90.7 – 91.4	99.6	99.6 – 99.7	<0.001
Possible glaucoma					
AUC	0.942	0.929 – 0.954	-	-	-
Sensitivity, %	96.4	81.7 – 99.9	-	-	-
Specificity, %	87.2	86.8 – 87.5	-	-	-
Referable AMD					
AUC	0.932	0.928 – 0.935	-	-	-
Sensitivity, %	93.2	91.1 – 99.8	-	-	-
Specificity, %	88.7	88.3 – 89.0	-	-	-
DLS=Deep learning system, AUC=area under the curve, AMD=age-related macular degeneration					