Review Paper

The Role of Artificial Intelligence in Early Cancer Diagnosis

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Simple Summary: Diagnosing cancer at an early stage increases the chance of performing effective treatment in many tumour groups. Key approaches include screening patients who are at risk but have no symptoms, and rapidly and appropriately investigating those who do. Machine learning, whereby computers learn complex data patterns to make predictions, has the potential to revolutionise early cancer diagnosis. Here, we provide an overview of how such algorithms can assist doctors through analyses of routine health records, medical images, biopsy samples and blood tests to improve risk stratification and early diagnosis. Such tools will be increasingly utilised in the coming years.

Abstract:

Improving the proportion of patients diagnosed with early-stage cancer is a key priority of the World Health Organisation. In many tumour groups, screening programmes have led to improvements in survival, but patient selection and risk stratification are key challenges. In addition, there are concerns about limited diagnostic workforces, particularly in light of the COVID-19 pandemic, placing a strain on pathology and radiology services. In this review, we discuss how artificial intelligence algorithms could assist clinicians in (1) screening asymptomatic patients at risk of cancer, (2) investigating and triaging symptomatic patients, and (3) more effectively diagnosing cancer recurrence. We provide an overview of the main artificial intelligence approaches, including historical models such as logistic regression, as well as deep learning and neural networks, and highlight their early diagnosis applications. Many data types are suitable for computational analysis, including electronic healthcare records, diagnostic images, pathology slides and peripheral blood, and we provide examples of how these data can be utilised to diagnose cancer. We also discuss the potential clinical implications for artificial intelligence algorithms, including an overview of models currently used in clinical practice. Finally, we discuss the potential limitations and pitfalls, including ethical concerns, resource demands, data security and reporting standards. Artificial intelligence (AI) is rapidly reshaping cancer research and personalized clinical care. Availability of high dimensionality datasets coupled with advances in high performance computing as well as innovative deep learning architectures, has led to an explosion of AI use in various aspects of oncology research. These applications range from detection and classification of cancer, to molecular characterization of tumors and its microenvironment, to drug discovery and repurposing, to predicting treatment outcomes for patients. As these advances start penetrating the clinic, we foresee a shifting paradigm in cancer care becoming strongly driven by AI.

Keywords: early diagnosis; artificial intelligence; machine learning; deep learning; screening

Introduction

Early cancer diagnosis and artificial intelligence (AI) are rapidly evolving fields with important areas of convergence. In the United Kingdom, national registry data suggest that cancer stage is closely correlated with 1-year cancer mortality, with incremental declines in outcome per stage increase for some subtypes [1]. Using lung cancer as an example, 5-year survival rates following resection of stage I disease are in the range of 70–90%; however, rates overall are currently 19% for women and 13.8% for men [2]. In 2018, the proportion of patients diagnosed with early-stage (I or II) cancer in England was 44.3%, with proportions lower than 30% for lung, gastric, pancreatic, oesophageal and oropharyngeal cancers [3]. A national priority to improve early diagnosis rates to 75% by 2028 was outlined in the National Health Service (NHS) long-term plan [4]. Internationally, early diagnosis is recognised as a key priority by a number of organisations, including the World Health Organisation (WHO) and the International Alliance for Cancer Early Detection (ACED). Many studies indicate that screening can improve early cancer detection and mortality, but even in disease groups with established screening programmes such as breast cancer, there are ongoing debates surrounding patient selection and risk–benefit trade-offs, and concerns have been raised about a perceived ‘one size fits all’ approach incongruous with the aims of personalised medicine [5–7]. Patient selection and risk stratification are key challenges for screening programmes. AI algorithms, which can process vast amounts of multi-modal data to identify otherwise difficult-to-detect signals, may have a role in improving this process in the near future [8–10]. Moreover, AI has the potential to directly facilitate cancer diagnosis by triggering investigation or referral in screened individuals according to clinical parameters, and automating clinical workflows where capacity is limited [11]. In this review, we discuss the potential applications of AI for early cancer diagnosis in symptomatic and asymptomatic patients, focussing on the types of f data that can be used and the clinical areas most likely to see impacts in the near future of data that can be used and the clinical areas most likely to see impacts in the near future

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Moreover, AI has the potential to directly facilitate cancer diagnosis by triggering investigation or referral in screened individuals according to clinical parameters, and automating clinical workflows where capacity is limited [11]. In this review, we discuss the potential applications of AI for early cancer diagnosis in symptomatic and asymptomatic patients, focusing on the types of data that can be used and the clinical areas most likely to see impacts in the near future.
Convolutional Neural Networks: Workhorse for Image Classification Convolutional Neural Networks (CNNs) have been the most popular deep learning architectures used for image classification in cancer (Figure 1). CNNs apply a series of nonlinear transformations to structured data (such as raw pixels of an image) to learn relevant features automatically, unlike conventional machine learning models that frequently require manual feature curation. On the flip side, it is difficult to tell what features are learnt by the CNNs, making them what many have referred to as a "black box." One consequence is that images used for CNNs should be carefully pre-processed to reduce the risk that the model learns from image artifacts. There are two major approaches for CNN models, one is transfer learning that uses images from large collection of natural objects (such as in ImageNet) to train the initial layers of a model (where the model learns to identify general features such as shapes, edges) and then uses the disease specific data to fine tune the training parameters in the last layers; second variation of CNNs is based on an autoencoder where the model learns background features from a subset of representative images and encodes a compressed representation of the basic features later used to initialize the CNN. In the CAMELYON16 Challenge - a crowdsourced competition to identify and classify lymph node metastasis in breast cancer patients from whole slide images (WSI) of Hematoxylin and Eosin (H&E)-stained tumors - 25 out of the 32 submitted algorithms were CNNs and the top five classification models were exclusively based on transfer learning, that were GoogLeNet, ResNet, VGG-16 [2]. Khosravi et al. trained and tested several state-of-the-art deep learning models to classify WSI from H&E-stained tumor tissues of The Cancer Genome Atlas (TCGA) cohort and reported on the relative performance of these methods, noting that transfer learning-based Inception architectures (GoogLeNet V1 and V3) had an overall best performance for tumor-normal tissue and cancer subtype classification tasks [3].

Generating Predictive Models from Other Large Datasets: In the past decade, several national and international initiatives have resulted in the generation of large cancer datasets. These datasets are obtained from profiling tumor samples using diverse high throughput platforms and technologies. They are frequently used to build predictive models that inform research and may eventually inform clinical decisions (Figure 2A). The Cancer Genome Atlas (TCGA) is by far the most comprehensive publicly available compilation of tumor profiles and includes a large number of data types spanning genomics, epigenomics, proteomics, histopathology and radiology images [4]. Other efforts such as The Pan-Cancer Analysis of Whole Genomes (PCAWG), METABRIC, and GENIE have also compiled large numbers of cancer genomic profiles and made these data publicly available. Profiling technologies have evolved over time. For example genomic DNA profiling has expanded

from targeted panels to whole exomes to whole genomes. Gene expression profiling has evolved from genome wide microarrays to RNA sequencing (RNAseq) then to more granular single cell RNA-seq (scRNA-seq). Other mature technologies have led to the production of a wide ranging array of datasets, including DNA methylation profiles, large scale proteomics studies, perturbation studies including cell viability or cytotoxicity assays using small molecules, RNA interference (RNAi) or CRISPR screens, protein-protein interaction networks and more. The sheer breadth and diversity of datasets that are availably publicly or can be generated in minimal time presents a unique opportunity to integrate various data types. Many groups have shown the benefits of such integration. For example training predictive models on multiple integrated rather than singular data sources has been shown, for example by Cheerla et al. to improve prediction of overall survival in patients across cancers [5]. Madhukar et al used such integrative approach to predict the targets and mechanisms of action of small anti-cancer molecules and demonstrated clearly that integrating multiple data types improves prediction accuracy [6].

Data Quality and Model Selection Are Key: The basic strategy for machine learning workflows is fairly standard (Figure 2B). Data collection and cleaning are the first and key components of any workflow, as a model is as good as the data it is trained on. To ensure high quality of the collected data, it needs to be inspected and corrected for possible noise in both non-image (such as inaccurate data entries, missing values) and image (such as high intensity pixels from artifacts, uneven illumination) data types. The data also needs to be reviewed for possible biases that can lead to underfitting the model, or high variance that can lead to overfitting the model. A model overfits the data when it learns from artifacts or noise in the data rather than the true signal. The consequence of overfitting is that a model may generalize poorly to unseen data with different biases. Strategies such as cross validation, increasing the training set size, manually curating predictive features and using ensemble approaches have been recommended to diminish risks of overfitting. Another key step of machine learning workflows is to select and fine tune an optimal model based on its performance. The performance of a machine learning model is commonly measured using the Area Under the Receiver Operator Curve (AUROC or simply AUC), which quantifies the tradeoff between sensitivity and specificity. A good classifier should achieve both high sensitivity and high specificity but emphasis on either of them may be important for some applications. In general, an AUC of > 0.80 is considered good, but whether this threshold is also clinically acceptable may vary depending on the clinical use. Even if widely used, there are pitfalls in relying blindly on AUC as performance metric. For example, the AUC assesses model performance in a population but does not provide confidence in individual calls. For datasets that have a class imbalance such that the positive class (class of interest) examples are much less than the negative class examples and the focus of the model is to accurately detect the positive class, then Area Under the PrecisionRecall Curve (AUPRC) is a preferred alternative to AUC. After training and testing a model on a given cohort (usually split into

training and test sets), it is equally important to also validate the model on external independent datasets to ensure that the model is stable and generalizes well. AI model development is not a static process; the model needs to be tested from time-to-time as newer updated datasets become available. Routine maintenance is frequently required to ensure that model performance does not degrade due to concept drift, that is, when the relationship between the input and output variables change over time in unforeseen ways. In this Review, we sought to survey a broad spectrum of publications and studies that together capture the breadth and versatility of AI applied to oncology. We sought to describe models that range from those with prospective utilization in the clinic to models that drive research and discovery (Figure 3). This Review places special emphasis on deep learning as a technique for making machine learning models, but also covers use cases where traditional machine learning techniques have been used very effectively. Finally, we highlight the limitations and challenges that pave the path towards integrating AI models in clinic.

EARLY DETECTION, DIAGNOSIS, AND STAGING OF CANCER

Timing of cancer detection, accuracy of cancer diagnosis and staging are key determinants of tumor aggressiveness and impact clinical decision-making and outcomes. In just a few years, AI has made significant contributions to this critical area of oncology, sometimes with performance comparable to that of human experts and with an added advantage of scalability and automation.

Making Cancer Diagnoses More Accurate: Deep learning-based models that accurately diagnose cancer and identify cancer subtypes directly from histopathological and other medical images have been reported extensively. Deep neural networks (DNN) are powerful algorithms that can, with appropriate computing power, be applied to large images such as H&E-stained whole slide images (WSI) of tissue derived from biopsies or surgical resections. These model architectures have indeed exceled at classification of images such as determining whether a digitized stained slide contains cancer cells or not [2,3,7–13]. While attaining highest prediction accuracies for distinguishing tumor from healthy cells (AUCs > 0.99), DNNs are used for more challenging classification tasks as well, such as distinguishing between closely related cancer subtypes (such as adenocarcinoma vs. adenoma in gastric and colon cancers, adenocarcinoma vs. squamous cell carcinoma in lung tumors) and detecting benign vs. malignant tissue. As an example, Coudray et al. developed and applied DeepPATH, Inception-v3 architecture-based model, to concurrently classify WSI for the TCGA lung cancer cohort into any of the three classes - normal, lung adenocarcinoma and lung squamous cell carcinoma - with a reported AUC of 0.97 [11]. The success of DNNs is not confined to histopathology images but extends to other medical images acquired through non-invasive techniques such as Computed Tomography (CT) scans, Magnetic Resonance Imaging (MRI) and mammograms, and even to photographs of suspicious lesions. For example, Esteva et al. trained a DNN (Inception-V3 architecture) on skin lesion images labelled for 757 granular skin disease classes [14]. Their model, when tested for carcinoma and melanoma classification of photographic and dermoscopic images of skin lesions, outperformed (AUC 0.91–0.94) the average accuracy attained by 21 board certified dermatologists. Importantly, their model was robust to variabilities inherent to digital photographs (due to different camera angles, uneven exposures, and so on), hence making the applicability of this model highly generic [14]. In radiology, Anthimopoulos et al. showed that CT scans of patients with lung disease can be used to build DNNs that classify textural patterns in lung (such as ground glass opacity, micronodules) with an average accuracy of 0.85 [15]. Similarly, Jian et al used CT scans to develop DNN that predict occult peritoneal metastasis in gastric cancers with an improved AUC (0.92–0.94) compared to that achieved from clinical and pathological features (AUC = 0.51–0.63) [16]. In another work, Wang et al. used MRI images from 172 prostate patients to train and test a DNN (developed using Caffe deep learning framework by Berkeley

AI Research) that could distinguish prostate cancer from benign prostate conditions (such as the prostate gland enlargement) with a reported AUC of 0.84 [17]. In a retrospective study with biopsy confirmed diagnosis and longitudinal follow-ups, McKinney et al. published an ensemble approach with three independent deep learning models that predict cancer risk score directly from the mammograms of approximately 29,000 women (AUC = 0.75–0.88) [18]. The group also reported an improvement in absolute specificity (1.2%−5.7%) and sensitivity (2.7%−9.4%) of cancer detection from mammograms compared to an average radiologist. All in all, such models if their performance is confirmed in prospective studies, may play an important role in early detection and classification of cancers, especially since their performance is comparable, if not better, to experts in the field. Outside the hospital settings, AI aided smartphone apps have also started to be adopted, potentially bringing early detection of cancerous lesions directly to a user's handheld device [19,20]. However convenient and promising, the diagnostic accuracy of such smart phone applications still remains to be clinically validated. Of particular concern are cases predicted as false negatives, as they may delay patient from procuring timely medical attention [19].

Cancer Staging and Grading: Cancer staging and grading, that is, determining how aggressive and advanced the cancer is, is another important component of the diagnostic process. Staging can indeed impact treatment choices, such as deciding between watchful waiting vs aggressive treatment involving radiation, surgery and chemotherapy. In prostate cancer, staging is achieved using the Gleason Score, a combination of two scores measuring prevalence of tumor cells in two distinct locations on a slide. Deep neural networks have shown promising initial results in predicting Gleason scores from histopathology images of prostate tumors [21,22]. Nagpal et al. used WSI for H&E-stained prostatectomy specimens to train and test a DNN (InceptionV3) and k-nearest-neighbor classifier-based model to predict Gleason Scores [21]. The group reported an improved prediction accuracy of Gleason Scores estimated from their model (0.70) compared to those determined by a panel of 29 independent pathologists (0.61). Cancer staging can also be done from radiology images: Zhou et al. developed a deep learning approach (based on SENet and DenseNet) to predict grade (low versus high) from the MRI images of patients with liver cancer and reported an AUC of 0.83 [22]. Overall, these studies indicate promising application of AI to cancer staging, with reported performance on par with trained experts despite modest AUC. Increasingly, non-imaging data such as genomic profiles are also being used for diagnosis and staging. Data obtained from next generation sequencing (NGS) – such as whole exome, whole genomes, and targeted panels, transcription profiles from microarray, RNA-seq, and microRNAs, methylation profiles – can be used to diagnose cancer and classify tumors into subtypes. Because

the data provided by these platforms is highly multidimensional (tens of thousands of genes can be assessed simultaneously), their use for cancer classification requires statistical methods or machine learning [23–25]. The use of machine learning for cancer diagnosis and staging from molecular data has in fact been around since the early 2000's, where machine learning approaches such as clustering, support vector machine and artificial neural networks were applied to microarray-based expression profiles for cancer
classification and subtype detection [26]. Over the years omics technologies have advanced and so have the innovations in the machine learning algorithms. Capper et al. demonstrated that a random forest classifier trained exclusively on tumor DNA methylation profiles can significantly improve the prediction accuracies for the hard to diagnose subclasses of the central nervous system (CNS) cancers (AUC=0.99) [27]. Their subclass predictions for 139 cases did not match pathologists' diagnosis, but follow-up of those select cases revealed that ~93% of those mismatched cases were in fact accurately predicted by the model [27]. Moving into deep learning methods, Sun et al. built and applied DNN to genomic point mutations to classify tissues into either of the 12 TCGA cancer types or healthy tissues obtained from the 1000 Genomes Projects [28]. The classifier, trained on the most frequent cancer specific point mutations obtained from whole exome sequencing profiles, was able to distinguish between healthy and tumor tissue with high accuracy (AUC=0.94), but did not perform as well in a multi-class classification task to distinguish all of 12-cancer types at the same time (AUC= 0.70). This work highlighted that accurate cancer classification using mutation data is challenging, possibly because of intra-tumor heterogeneity and low tumor purity (making mutation detection challenging), together with the presence of shared mutations across different cancer types. Nonetheless, the work also shows that similar models that use genomic information to assess cancer can be applied to genomic profiles obtained from other sources such as cell free DNA (cfDNA).

On the Road to Early Cancer Detection: AI is gradually paving its path towards early detection of cancer from emerging minimally invasive techniques as well, such as liquid biopsies for circulating tumor DNA (ctDNA) or cfDNA. Liquid biopsies, obtained via minimally invasive techniques such as a simple blood test, in theory allow for early detection of cancer, monitoring risk of relapse over time and guiding treatment options. As an example, MSI status can be predicted from ctDNA in endometrial cancer patients in order to inform immunotherapy-based treatment [29]. Chabon et al. developed a machine learning based approach, Lung-CLiP (cancer likelihood in plasma), that predicts the likelihood of ctDNA in blood drawn from lung cancer patients [30]. The method first estimates the probability that a cfDNA mutation is associated with the tumor (using elastic net model and features that include cfDNA fragment size) and then integrates outputs of this model together with copy number

scores in an ensemble classifier with five distinct algorithms to predict the presence of ctDNA in a blood sample. The method showed modest predicative performance (AUC = 0.69–0.98), with performance depending on cancer stage, and a tradeoff between specificity and sensitivity for the predictions. In another promising work, Mouliere et al. reported a random forest-based classifier trained on features derived from the cfDNA fragment sizes that predicts the presence of ctDNA in blood across multiple cancer types at a high accuracy (AUC= 0.91– 0.99) [31]. As a complete end-to-end blood test for cancer, Cohen et al. developed CancerSEEK - for 8 distinct cancer types - that not only detects early cancer but also predicts any of the eight cancer types directly from the ctDNA [32]. Samples are first classified as cancer-positive by a logistic regression model applied to mutations in 16 genes and expression levels in 8 plasma proteins. The cancer type is then predicted using a random forest classifier (accuracies range from 39–84% depending on cancer type) [32]. This work is particularly important because 5 out of the 8 cancer types covered in this test have no
early screening tests currently available. Taken together, the initial progression of AI in the early cancer detection area is notable but has so far been limited to traditional machine learning algorithms. As data acquisition from liquid biopsies expands, we anticipate that more advanced deep learning architectures will eliminate the need for manual selection and curation of most relevant discriminatory features. We also anticipate further use of multimodal approaches (like CancerSEEK) that combine several data types, e.g. liquid biopsy and imaging to enhance early detection and monitor disease risk over time.

DETECTING CANCER MUTATIONS USING MACHINE LEARNING

The ubiquitous availability of Next Generation Sequencing (NGS) has made it possible for thousands of cancer laboratories to routinely sequence cancer genes, exomes and genomes. Identifying genetic variants and mutations in NGS data can be done using a variety of computational tools, but frequently fails in certain scenarios, such as low coverage or complex, repeat-rich regions of the genome. Several groups have explored the idea to re-cast mutation detection as a machine learning problem [33,34]. As an example, DeepVariant, a DNN (Inception-V2 architecture) based method, was developed to detect variants from aligned NGS reads by first producing read pileup images for candidate variants (thereby making it an image classification task), and then predicting the probabilities of their genotype likelihood states (homozygous reference, heterozygous variant or homozygous variant) [33]. This method won an award at the second PrecisionFDA Truth Challenge (2016) for best performance in SNP detection.

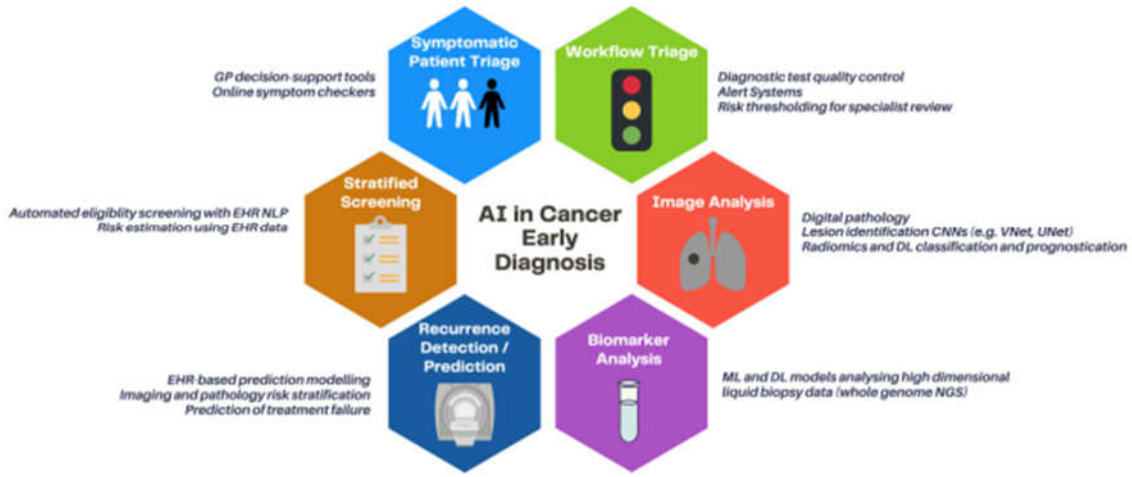

Figure: Clinical applications of AI in early cancer diagnosis. Abbreviations: GP: general practitioner, NLP: natural language processing, EHR: electronic healthcare record, ML: machine learning, DL: deep learning, NGS: next-generation sequencing.

Conclusion and Future Scope

Artificial intelligence (AI) has revolutionised early cancer detection by enhancing diagnostic accuracy, reducing time to diagnosis, and assisting medical professionals in identifying malignancies at an early stage. Machine learning models, image recognition techniques, and predictive analytics have significantly improved screening methods, ultimately contributing to better patient outcomes.

We have seen that the application of AI to healthcare data holds transformative potential for early cancer diagnosis and could help address healthcare capacity challenges through automation. AI enables the effective analysis of complex, multi-modal data, including clinical text, genomic, metabolomic, and radiomic information.

In this review, we identified a range of convolutional neural network (CNN) models capable of detecting early-stage cancers on scan or biopsy images with high accuracy, some of which have demonstrated proven impact on workflow triage. Commercial solutions for automated cancer detection are increasingly available, and their adoption is expected to rise in the coming years.

In the context of decision-support for symptomatic patients, we emphasise the need for caution. Models must be rigorously validated and published in peer-reviewed journals before clinical deployment. Furthermore, several challenges remain regarding AI implementation, including data anonymisation and storage, which can be both time-consuming and costly for healthcare providers.

We also addressed concerns around model bias, particularly the under-reporting of key demographic data such as race and ethnicity. This limitation can impact the generalisability and fairness of AI systems, highlighting the importance of inclusive data practices and continuous model evaluation in diverse populations.

In terms of improving study quality and encouraging broader model uptake, quality assurance frameworks—such as SPIRIT-AI—and methods to standardise radiomic feature values across institutions, as proposed by the Image Biomarker Standardisation Initiative, may provide significant benefits . Additionally, disease-specific 'gold standard' test sets could help clinicians benchmark multiple competing models more effectively and consistently.

Despite the aforementioned challenges, the implications of AI for early cancer diagnosis are highly promising, and this field is expected to grow rapidly in the coming years. In the future, AI is likely to integrate more deeply with personalised medicine, enhancing detection precision through genetic and biomarker analysis. Advances in deep learning and federated learning will further improve AI-driven diagnostics while maintaining patient data privacy. Moreover, AI-powered wearable devices and real-time monitoring tools could enable proactive cancer detection, making early intervention more accessible and effective.

From the clinical perspective, building clinicians' trust in AI assisted decision making is also critical for the entry of AI in clinic. To this end. recommends development and adoption of systematic and pragmatic measures of uncertainty quantification in AI models [. Uncertainty in a model may come from the choice of data, accuracy and completeness of data, inherent biases in the data, artifacts, and model misspecifications. Estimation of uncertainty in data-driven prediction models is an area of active research and in the future will provide a systematic framework for improving models and increasing confidence in AIassisted clinical decision making. Deep learning currently has the reputation of being a "black box" but is in essence capturing complex correlations within data. Hence additional research to increase model interpretability by understanding how deep learning models learn from a given data, and what cellular and molecular mechanistic insights such models can provide, will also make the clinical use of AI models more agreeable to clinicians.

Thinking prospectively, prevention rather than treatment may end up being the most compelling application of AI to cancer care. Seminal research has already led the community to compile a portfolio of risk factors for cancer. Advances in technology has enabled various means of collecting data at an individual patient level. Aside from genetic tests and EHR, sensors from smart phone or other wearable devices also collect vast amount of data points just for a single patient. These data can empower AI to improve precision of diagnosis by sensing physiological and environmental status. They may help facilitate highly personalized disease prevention and treatment plans for each patient. Such AI systems may help monitor cancer patients remotely, and alert clinicians if need be. In the future, AI models that integrate genetic predispositions and EHR, together with lifestyle and environmental factors may be able to accurately assess cancer risk for a person in near realtime and suggest personalized options for early intervention and appropriate management of risk factors.

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