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Hallmarks of artificial intelligence contributions to precision oncology

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The integration of artificial intelligence (AI) into oncology promises to revolutionize cancer care. In this Review, we discuss ten AI hallmarks in precision oncology, organized into three groups: (1) cancer prevention and diagnosis, encompassing cancer screening, detection and profiling; (2) optimizing current treatments, including patient outcome prediction, treatment planning and monitoring, clinical trial design and matching, and developing response biomarkers; and (3) advancing new treatments by identifying treatment combinations, discovering cancer vulnerabilities and designing drugs. We also survey AI applications in interventional clinical trials and address key challenges to broader clinical adoption of AI: data quality and quantity, model accuracy, clinical relevance and patient benefit, proposing actionable solutions for each.

Cancer remains a leading cause of death globally[1]. By 2040, the global cancer burden is projected to reach 28.4 million, a 47% increase from 2020 (ref. 1). This alarming rise underscores the urgency of advancing cancer research and treatment strategies. A key challenge in addressing cancer lies in its inherent heterogeneity[2]: no single therapy is universally effective. In response, precision oncology, which tailors treatment on the basis of individual molecular tumor profiles, has emerged as a pivotal strategy in the fight against cancer[3,4].

The need to better characterize cancer initiation and progression has driven the generation of large datasets through diverse high-throughput techniques[5,6]. These datasets offer unprecedented insights into cancer biology but also present challenges: their analysis is time consuming, labor intensive and difficult for humans due to the high complexity and subtle patterns within the data. This explosion of big data has positioned AI as an essential tool in cancer research[7,8], owing to its ability to process large datasets without fatigue and with greater accuracy and efficiency than human researchers and conventional statistical models. AI's ability to uncover patterns and correlations that might otherwise remain undetected further underscores its transformative role in advancing cancer research[9–11].

This Review documents AI-driven accomplishments in precision oncology and evaluates the clinical relevance of approaches currently in use and near implementation. We begin by outlining the major AI model types and input data modalities. Next, we synthesize the latest AI achievements into three broad categories, encompassing ten hallmarks, followed by a survey of interventional clinical trials that have incorporated AI. Finally, we address the major challenges hindering the broader clinical adoption of AI and propose actionable strategies to accelerate future innovations.

AI models and data modalities

AI, originally conceptualized as 'thinking machines' in the 1950s, has evolved dramatically (Fig. 1a). From the 1980s to the 2010s, classical machine learning (ML) models, such as Bayesian networks[12], support vector machines[13] and decision trees[14], became mainstream (Fig. 1a). The early 2010s marked a turning point with the rise of deep learning (DL), which demonstrated superiority to classical ML in tasks, such as image and speech recognition[15]. DL, a subset of ML, involves neural networks with many layers between input and output, hence its characterization as deep. Various DL architectures have been developed, including convolutional neural networks (CNNs), recurrent neural networks (RNNs), autoencoders, generative adversarial networks and graph neural networks (GNNs)[16] (Fig. 1a). The 2020s saw the introduction of the transformer[17], a DL architecture featuring an attention mechanism that effectively captures long-range dependencies in sequential input, such as text or video. Transformers have further advanced AI's capabilities, particularly in the development of large language models (LLMs). Trained on massive internet data by

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supercomputers, LLMs such as ChatGPT, Gemini, Claude and LLaMA exhibit remarkable abilities to interpret human input and generate human-like responses[18] (Fig. 1a).

A critical component of AI applications in precision oncology is the diverse range of input data types and modalities[5,7,19] (Fig. 1b). These can be broadly categorized as (1) imaging data, essential throughout cancer screening, treatment and follow-up[20], including radiological imaging[21,22] (for example, computed tomography (CT), magnetic resonance imaging, positron emission tomography, X-ray), pathological imaging[23] (for example, hematoxylin and eosin (H&E) staining, immunohistochemistry staining) and other image types (for example, mammography[24], colonoscopy[25], ultrasound[26], dermoscopy[27]); (2) clinical data, including paper-based or electronic health records (EHRs), blood test results, family history and social determinants of health, often represented as complex, unstructured textual data containing patient-specific real-time observations valuable for precision oncology[28]; and (3) omics data, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, immunomics and microbiomics[29–31], that are collected with molecular biology reagents in various contexts, such as in vitro, in animal models or from the human body and are studied in basic and preclinical research[32]. Human-derived data further comprise non-biopsy data collected without sampling, liquid biopsy data from blood or other body fluids and tumor tissue biopsy data requiring invasive solid tissue sampling (Fig. 1b).

The choice of AI model depends on the data type and research question (Fig. 1c). While AI models span from traditional ML to advanced DL architectures, they are not always interchangeable. For instance, classical ML models, optimized for structured data, are often effective for predicting phenotypes (for example, therapy response or survival time) from tabular features such as genomic or transcriptomic profiles and clinical metrics (Fig. 1c). However, deep multilayer models such as CNNs add indispensable value in analyzing image data by reducing data dimensionality and detecting complex spatial patterns. GNNs and transformers further extend image analysis capabilities, with GNNs capturing spatial relationships across regions of interest and transformers providing a broader context over entire images (Fig. 1c). Finally, RNNs and transformers are particularly well suited for sequential data and unstructured text, such as genomic or amino acid sequences and clinical text records, due to their ability to handle long-range dependencies and contextual relationships, which is also the basis for LLMs (Fig. 1c).

A key distinction between highly parameterized models, such as transformers, versus classical and much simpler ML models, such as linear or logistic regression, lies in their learning paradigms. Transformers leverage self-supervised pretraining on large, unlabeled datasets to learn generalized representations, which can be fine-tuned on smaller, task-specific datasets for various downstream tasks. By contrast, classical ML models rely on supervised training directly tailored to specific, often smaller, target datasets. While complex models can excel in certain tasks, they are not always superior to simple models, especially when interpretability, speed or limited data availability are important[33]. Consequently, aligning model architecture with data type and research objectives is essential for optimizing analyses and outcomes in precision oncology.

AI applications for cancer prevention and diagnosis

Here, we discuss AI applications in cancer screening in asymptomatic populations (Hallmark 1), cancer detection following symptoms or suspicious findings in screening (Hallmark 2) and cancer profiling of confirmed cancers (Hallmark 3) (Fig. 2a). The use of AI in these settings is widespread and has marked commercial success in computer-aided screening and mobile applications, along with many prospective studies and US Food and Drug Administration (FDA)-approved clinical applications across multiple cancers.

Hallmark 1: cancer screening

Cancer screening aims to identify individuals at higher-than-average risk of developing cancer before symptoms emerge. The process typically involves (1) evaluating cancer risk to determine screening frequency, ensuring early detection if cancer develops; (2) identifying precancerous lesions in solid tumors or abnormal blood states in blood cancers for preventive intervention; and (3) referring patients with suspicious findings directly to means of cancer detection (reviewed in Hallmark 2) for further confirmation. Screening has already proven effective in reducing mortality for lung, breast, colorectal and cervical cancers[34,35].

Because cancer screening applies to large noncancerous populations, the data collected are typically non-invasive and high throughput, including medical history, lifestyle factors, biomarkers from serum and non-invasive imaging. AI has improved the efficiency and, in some cases, also the accuracy of screening compared to traditional methods. Notable examples of AI-facilitated cancer screening include detecting suspicious lesions and predicting risk for cancers of the skin (using a smartphone camera photo input to a CNN model[36]), breast (using mammogram data with three DL models[24]), colorectal (using colonoscopy data with DL[25]), prostate (using pathogenic genetic variants and age data with regression models[37]) and lung (using chest CT data with a CNN model[22]). Importantly, regulatory approval is required before these AI applications can be implemented clinically.

Hallmark 2: cancer detection

Cancer detection involves confirming the presence of cancer, typically after a patient exhibits symptoms or a suspicious finding from Hallmark 1. Early detection profoundly influences subsequent treatment choices and patient outcomes, with early-stage cancers generally offering better curative potential and survival rates[38]. The reduction in cancer mortality since the 1990s has been attributed partly to early detection[39] and remains a cornerstone of initiatives such as the Cancer Moonshot, which aims to reduce cancer mortality by 50% by 2047 (ref. 40).

Hallmark 2 typically involves two steps: locating suspicious lesions (for example, through non-invasive imaging) and a pathologist confirming the presence of cancer (for example, by evaluating biopsy images). AI has been deployed in both steps to reduce clinician workload and provide more-accurate detection than human experts[11,41,42].

Fig. 1 | Evolution of AI and key models and major data types in precision oncology. a, Historical evolution of AI and its important models. The *x* axis marks milestone years, while the *y* axis represents the scale of model parameters. AI, initially envisioned as 'thinking machines' in the 1950s, has advanced enormously over the decades. Classical ML models dominated from the 1980s to the 2010s. The early 2010s marked the rise of DL, culminating in the development of transformers and LLMs in the 2020s. **b**, Major data categories and specific data types with measurement contexts in precision oncology. Input data types are broadly classified into three categories: imaging data, clinical data and omics data. **c**, Alignment of major model architectures with major data types in precision oncology. Tabular data are effectively analyzed using classical ML models. Image data are typically processed with deep multilayer architectures such as CNNs. Sequential data and unstructured text are best suited for RNNs and transformer-based models. GAN, generative adversarial network; BERT, bidirectional encoder representations from transformers; GPT, generative pretrained transformer; T5, text-to-text transfer transformer; ViT, vision transformer; MRI, magnetic resonance imaging; PET, positron emission tomography; IHC, immunohistochemistry; SDOH, social determinants of health. [a]X-ray includes mammography and three-dimensional (3D) X-ray techniques. [b]Health record includes both handwritten and electronic (EHR) formats, containing information such as patient demographics, medical history, diagnosis and treatment records.

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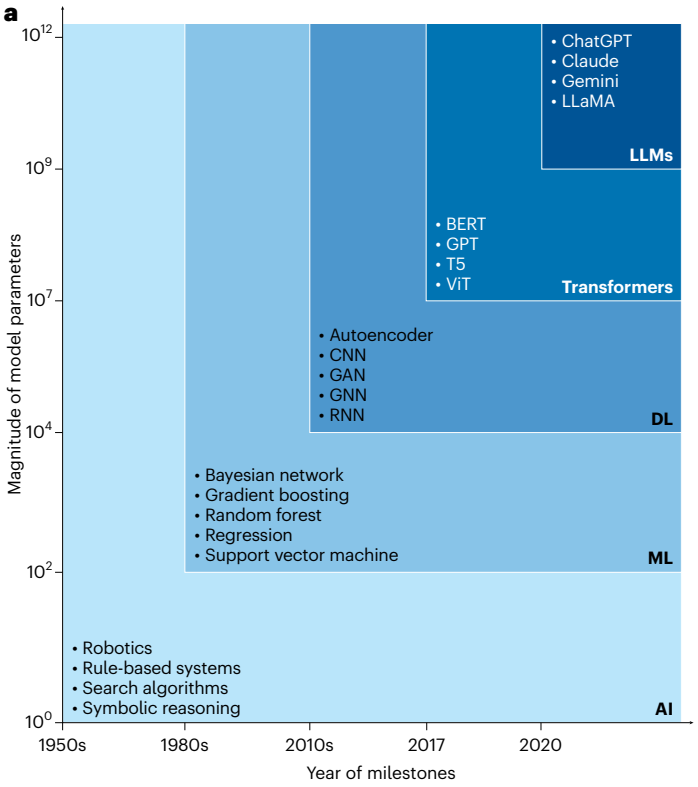
For instance, DL has been widely applied in detecting breast cancer through mammography[41] or ultrasound[26], identifying metastatic breast cancer in H&E- or immunohistochemistry-stained pathology images[42] and detecting lung cancer using CT scans[43].

Liquid biopsy has transformed cancer detection by analyzing plasma proteins, circulating tumor DNA or cell-free DNA (cfDNA) for tumor mutations or methylation. A prospective study demonstrated that ML-based targeted methylation analysis of cfDNA could detect

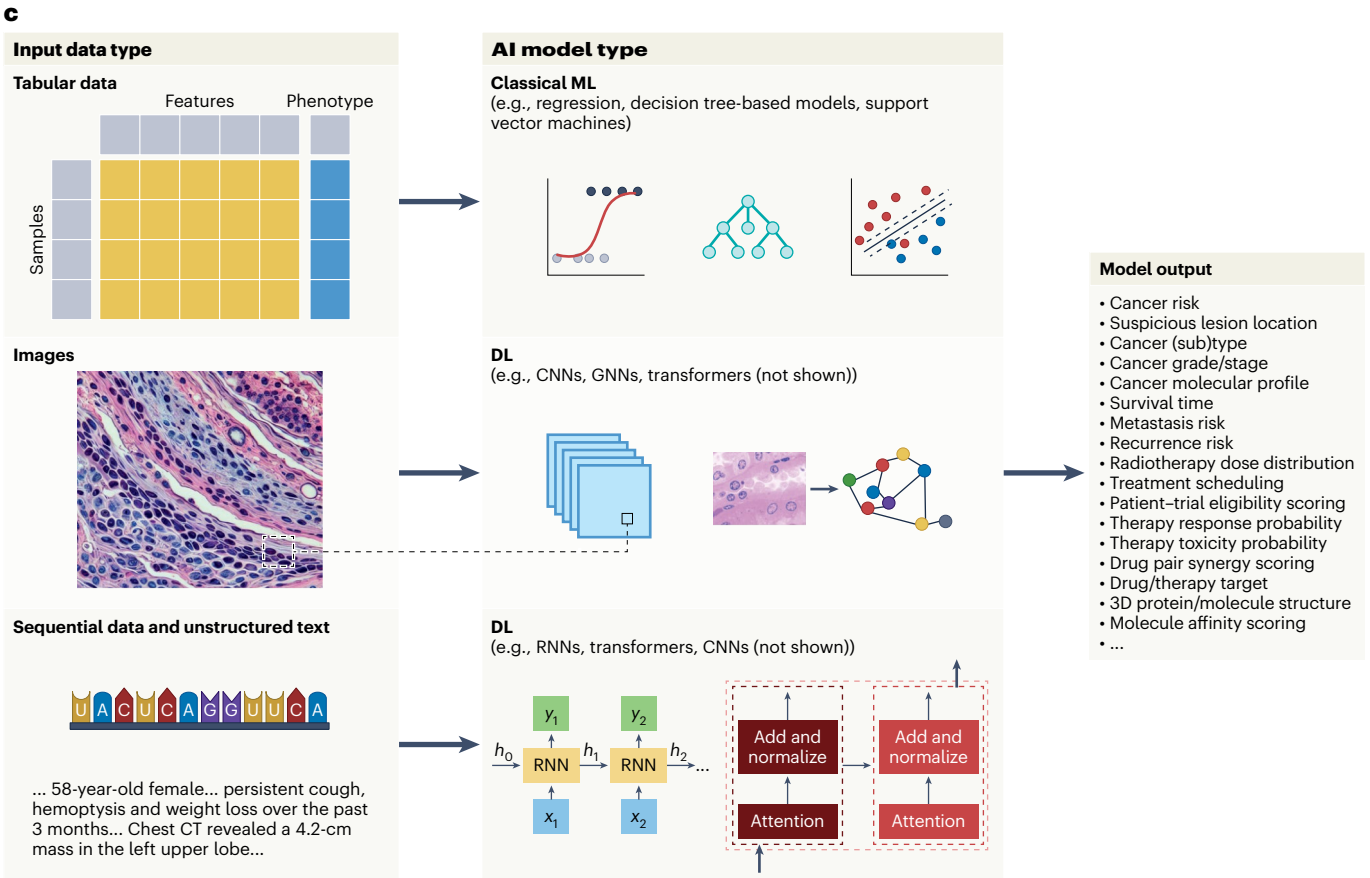
a



b

Data category	Data type	In vitro or in animal models	Human body (non-biopsy)	Human body (liquid biopsy)	Human body (tissue biopsy)
Images	CT		√		
	MRI		√		
	PET		√		
	X-ray[a]		√		
	H&E staining				√
	IHC staining				√
	Endoscopy		√		
	Ultrasound		√		
	Dermoscopy		√		
Clinical	Health records[b]		√		
	Blood test			√	
	Family history		√		
	SDOH		√		
Omics	Genome	√		√	√
	Epigenome	√		√	√
	Transcriptome	√		√	√
	Proteome	√		√	√
	Metabolome	√		√	√
	Immunome	√		√	√
	Microbiome	√	√	√	√

c



and localize multiple cancer types with high specificity[44], receiving CLIA (Clinical Laboratory Improvement Amendments of 1988) certification and FDA Breakthrough Device designation and becoming commercialized as Grail Galleri. Similarly, CancerSEEK, which uses logistic regression based on features obtained by measuring circulating protein biomarkers and tumor-specific gene mutations in cfDNA to detect cancer across eight types, has received FDA Breakthrough Device designation[45].

Hallmark 3: cancer profiling

Cancer profiling, following cancer confirmation, involves the detailed classification and characterization of cancer. This process includes categorizing tumors by type, subtype, grade, stage, molecular features and tumor microenvironment characteristics. Accurate cancer profiling is critical for guiding therapy, directly impacting patient outcomes.

AI-driven cancer classification leverages various data modalities, with some AI models performing on par with or superior to human specialists. For example, a CNN model trained on ~130,000 digital images of skin lesions classified skin cancer with competence comparable to that of dermatologists[27]. A random forest model using DNA methylation profiles to classify central nervous system tumors outperformed standard methods, correcting diagnoses in up to 12% of prospective patients[29]. A multiclass CNN model using multiparametric magnetic resonance digital imaging to detect and grade prostate lesions showed sensitivity comparable to that of experienced radiologists[21]. The Paige Prostate product, based on this technology, became the first AI-based product to receive FDA de novo marketing authorization for diagnostic use.

AI can predict the tissue of origin for cancers of unknown primary origin, aiding therapeutic selection given that modern treatments are tailored to the primary tumor's origin[46]. Similarly, precision oncology is increasingly relying on detailed molecular characterization rather than traditional cancer classifications[47]. AI has made substantial strides in characterizing molecular features of tumors and their microenvironments, particularly from images[48]. For example, AI models using histology images can predict driver gene mutations[23], chromosomal aneuploidy and focal copy-number alterations[49,50], microsatellite instability[51], tumor mutation burden[52], PD-L1 status[53], immune cell infiltration[54], DNA methylation[55] and gene-expression levels[56]. Despite these advances, challenges remain in clinical practice, such as standardizing data and enhancing model generalizability.

Optimizing the use of current cancer treatments

This section reviews progress in predicting patient outcomes (Hallmark 4), planning and monitoring treatment (Hallmark 5), designing clinical trials and matching patients to appropriate trials (Hallmark 6) and developing biomarkers for selecting patients most likely to respond to specific treatments (Hallmark 7). As outlined below, research in these areas is active and expanding but largely retrospective, with commercial products and clinical applications often confined to a few cancer types or specific settings. AI models require optimization and prospective validation to ensure generalizability, interpretability and adherence to regulatory and ethical standards for wide clinical adoption.

Hallmark 4: patient outcome prediction

Patient outcome prediction involves estimating clinical outcomes such as survival, metastasis and recurrence. These predictions are important for designing clinical trials, optimizing resource allocation within healthcare systems and guiding personalized treatment. Outcome predictions help balance treatment efficacy with quality of life, enabling more informed and patient-centered clinical decisions.

Historically, tumor node and metastasis staging was the primary method for cancer outcome stratification. However, AI models have demonstrated the ability to enhance prediction accuracy of prognosis by integrating multiple features. For example, a random forest algorithm generated a 22-gene genomic expression signature for prognostication in patients with prostate cancer undergoing radical prostatectomy, leading to CLIA certification and commercialization of the Decipher product[57]. Similarly, a logistic regression model predicted 180-d mortality across multiple cancers using structured EHR data and was later validated in a large-scale prospective study[58,59].

Integrating multimodal data has further enhanced prediction capabilities. A CNN model integrated genome and transcriptome data from 1,063 patients to predict patient outcomes, representing the largest colorectal cancer study of its kind[60]. Another two-step DL model, trained and validated in 2,072 patients on H&E whole-slide images and tumor stage information, predicted distant recurrence risk of endometrial cancer, outperforming the current gold standard[61]. For breast cancer, a deep neural network integrating multidimensional data, including gene expression profiles, copy number alteration profiles and clinical information, outperformed single-dimensional and existing methods in predicting prognosis[62]. Separately, a multimodal DL algorithm integrated H&E whole-slide images with molecular features to predict pan-cancer prognosis, using multimodal interpretability to identify morphologic and molecular prognostic correlates[63].

However, using high-dimensional omics or multimodal data greatly increases the number of input features, raising the risk of 'overfitting', namely, models losing their ability to generalize to unseen data. Potential solutions are discussed later in this Review.

Hallmark 5: treatment planning and monitoring

Treatment planning and monitoring in cancer care involves selecting appropriate treatments, scheduling, monitoring patient responses, managing drug toxicity and dynamically adjusting therapy as needed. Adaptive treatment strategies, which adjust timing and dosing on the basis of tumor response, hold promise for better controlling resistant tumor cell populations.

Radiation therapy is a prime example of AI-driven treatment planning, as determining the timing and precise physical placement

Fig. 2 | Ten AI hallmarks characterizing its contributions to precision oncology. a, The ten hallmarks (H1–H10) are organized in three groups: (1) the first three focus on cancer prevention and diagnosis, encompassing cancer screening, detection and profiling; (2) the next four focus on optimizing current treatments, including patient outcome prediction, treatment planning and monitoring, clinical trial design and matching, and developing new response biomarkers; and (3) the remaining three aim at advancing new treatments by identifying effective treatment combinations, discovering new cancer vulnerabilities and designing new drugs. **b**, The ten AI-powered hallmarks form a cohesive network of defenses that collectively combat cancer. Directed interconnections between hallmarks: regular cancer screening facilitates early detection (Hallmark 1 → Hallmark 2). Samples and data from cancer detection further contribute to cancer profiling (Hallmark 2 → Hallmark 3). Comprehensive cancer profiling enhances patient outcome prediction (Hallmark 3 → Hallmark 4), informs treatment planning (Hallmark 3 → Hallmark 5) and improves patient–trial matching (Hallmark 3 → Hallmark 6). Accurate outcome predictions are crucial for effective treatment planning and patient–trial matching (Hallmark 4 → Hallmarks 5 and 6). The discovery of novel response biomarkers and cancer vulnerabilities is essential for identifying effective treatment combinations (Hallmarks 7 and 8 → Hallmark 9) and for designing new drugs (Hallmark 8 → Hallmark 10). In turn, validated response biomarkers are integral to treatment planning and monitoring (Hallmark 7 → Hallmark 5) and, together with validated cancer vulnerabilities, can also enhance cancer profiling (Hallmarks 7 and 8 → Hallmark 3). Ultimately, all AI-driven clinical solutions from Hallmarks 7–10 must undergo rigorous testing in clinical trials before implementation in clinical practice (Hallmarks 7–10 → Hallmark 6). Hallmarks 3 and 6 serve as hubs, exhibiting extensive connections with multiple other hallmarks.

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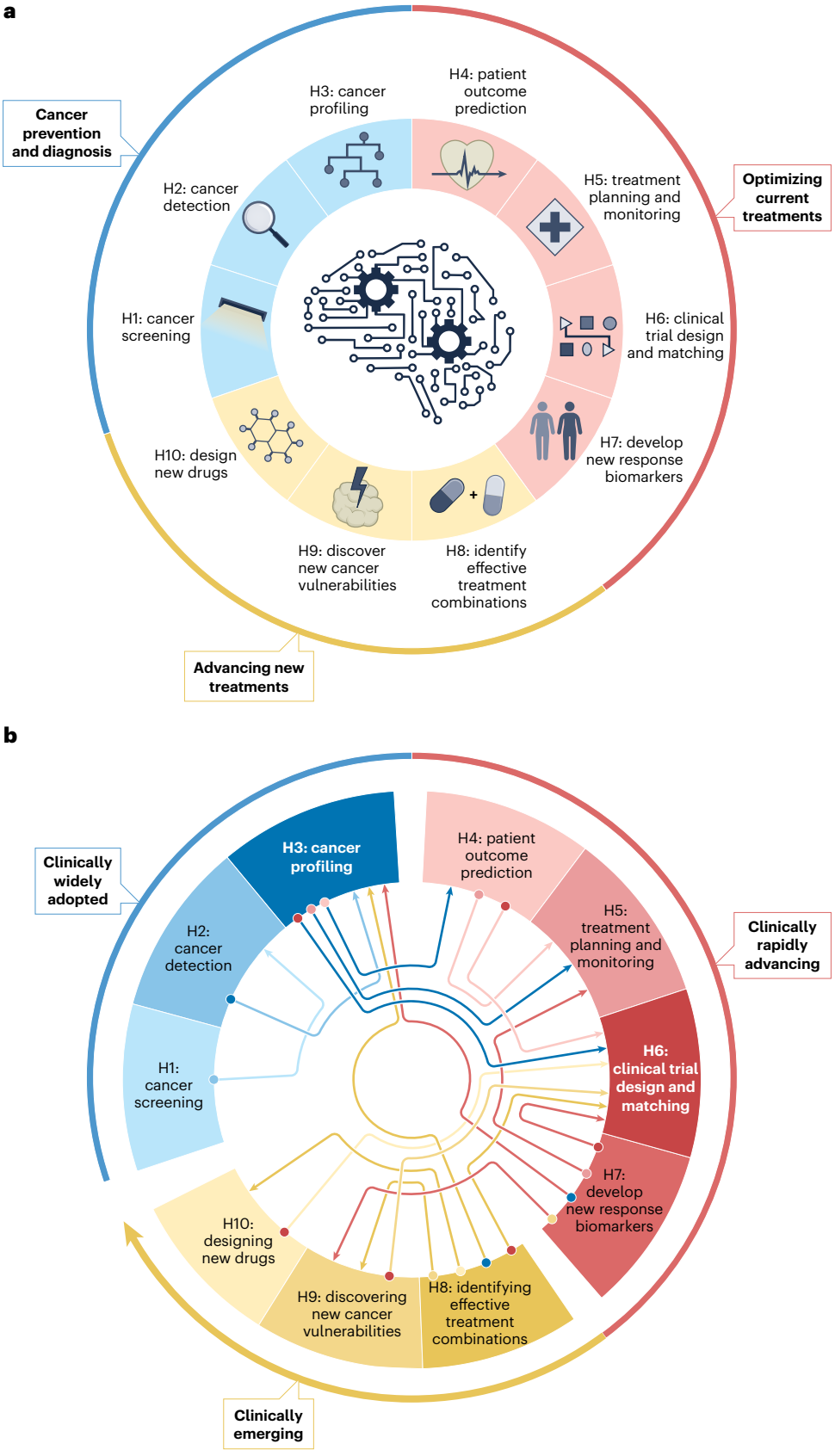
of ion beams relative to the patient's body and delineating the target volume and organs at risk are labor-intensive tasks. A random forest model predicted dose distribution and generated radiation therapy plans for prostate cancer, with 89% of AI-generated plans deemed clinically acceptable and 72% preferred over human plans. The model reduced median planning time by 60%, from 118 hours to 47 hours[64].

AI is also employed in monitoring treatment, including dynamic adjustments in drug timing, dosing and sequencing for combination



therapies[65–67]. Additionally, AI has been deployed to predict the onset and severity of side effects[68] and acquired drug resistance[69], both critical for adapting treatment strategies. However, these applications remain largely exploratory, requiring further prospective studies to validate their clinical utility.

Hallmark 6: clinical trial design and matching

For patients unresponsive to or not treatable with standard-of-care options, clinical trials offer a vital alternative. Clinical trial design and matching involve carefully crafting inclusion and exclusion criteria and identifying the most suitable trial for each patient, both essential in advancing new therapies from bench to bedside. However, Hallmark 6 is often suboptimal due to the complexity of eligibility criteria and the labor-intensive nature of the matching process. This inefficiency contributes to major challenges, including the enrollment of only 7% of patients with cancer in clinical trials[70], the premature termination of approximately 20% of trials due to insufficient accrual[71] and persistent disparities in trial participation by race, sex and age[72–74].

AI can streamline the matching process, reduce screening times, increase enrollment rates and optimize trial protocols by efficiently identifying eligible patients and refining trial eligibility criteria. For example, Trial Pathfinder, an AI tool, was developed using retrospective real-world data from 61,094 patients with advanced non-small cell lung cancer[75] and not only predicted patient–trial matches but also used simulations to perform a standard ML ablation procedure. This procedure identified exclusion criteria that could be removed, one by one, without significantly altering the hazard ratios between trial arms, thereby potentially enabling the design of more inclusive trials without compromising safety. Commercial products also exist in this domain. For instance, IBM Watson for Clinical Trial Matching uses AI to help healthcare providers match oncology patients with suitable clinical trials. By leveraging ML, the platform enhances the efficiency and accuracy of trial matching across multiple cancer types and populations[76,77].

Finally, the recent advances in LLMs offer unprecedented opportunities for efficiently interpreting complex eligibility criteria within unstructured medical records[78]. Numerous studies have highlighted the transformative potential of LLMs in enhancing patient–trial matching[79,80].

Hallmark 7: developing new response biomarkers

Developing new response biomarkers involves generating models and signatures to predict each patient's response to a specific cancer treatment, including current standard therapies, off-label uses or experimental interventions. Accurate response prediction enables clinicians to make informed treatment choices, reducing healthcare costs, minimizing unnecessary toxicities and delaying or halting disease progression. Identifying biomarkers predictive of response to off-label or experimental treatments can expand therapeutic options, particularly for patients with advanced or refractory cancers. It is important to distinguish this hallmark from Hallmark 4: while both employ predictive techniques, Hallmark 4 focuses on 'prognosis': predicting the likely course of the disease regardless of treatment, such as survival or recurrence. By contrast, Hallmark 7 focuses on 'treatment response prediction', specifically identifying biomarkers that predict an individual's response to a particular therapy.

Many AI models can predict therapy response by incorporating multiple features, including genomic mutations[81], transcriptomics data[82], pathology images[83], liquid biopsy data[84,85] and emerging gut microbiome data[30]. Recent models also integrate multimodal data[31,86] and leveraged advanced high-resolution omics, such as single-cell RNA sequencing (scRNA-seq)[87–89]. However, many of these models lack interpretability, limiting their clinical translation.

To address this issue, recent efforts have focused on developing interpretable AI-derived biomarkers[90–92]. A common strategy involves integrating biological domain knowledge into AI models. As an example, an experimentally derived hierarchical map of multiprotein assemblies (NeST) was used to create an interpretable DL model for predicting tumor response to CDK4 and CDK6 inhibition[91] but also offering structural insights and highlighting key protein assemblies where cancer mutations converge to influence drug resistance or sensitivity.

Another approach for interpreting image-based models involves identifying key regions using gradient-based localization or attention mechanisms[93]. This has been applied to H&E slides to pinpoint clinically relevant regions for survival and therapy response predictions[94,95]. However, these visual explanations are not always sufficient or accurate[96].

AI applications for the development of new treatments

This section highlights three emerging applications of AI in the development of new treatments: identifying effective drug and therapy combinations (Hallmark 8), discovering new cancer vulnerabilities (Hallmark 9) and designing new drugs (Hallmark 10) (Fig. 2a). While these emerging hallmarks are less clinically mature, they hold great promise for future precision oncology.

Hallmark 8: identifying effective treatment combinations

Identifying effective treatment combinations involves discovering and validating combinations of existing drugs and therapies tailored to specific cohorts or individual patients. Combinatorial therapeutic strategies are gaining attention in precision oncology, as response rates to single therapies are often low and tumors frequently develop resistance. Combinatorial strategies are increasingly recognized as the future of cancer treatment[97,98].

Treatment combinations can be beneficial in cohort trials when different treatments enhance each other's effects within individual tumor cells via genetic or biochemical mechanisms, resulting in a synergistic effect greater than the sum of individual effects[99,100]. Alternatively, they are advantageous when different treatments are more effective for different patients within a cohort[101]. This scenario is closely related to Hallmark 7 because, if one could predict which patients benefit from each treatment more precisely, then individual patients would receive fewer treatments, reducing toxicity and costs. Although synergistic combination therapies offer great potential, the sheer number of possible combinations makes clinical testing impractical financially and in terms of patient availability.

AI has shown promise in predicting drug synergy from large-scale cancer cell line data. For example, DrugCell, an interpretable DL visible neural network trained on the responses of 1,235 tumor cell lines to 684 drugs, can predict drug synergy in patient-derived xenograft models and drug response in patients with ER^+ breast cancer[102]. Other recent DL models for predicting drug combination synergy include RECOVER[103], ForSyn[104] and DeepTraSynergy[105].

Also emerging is the use of LLMs to identify drug and therapy combinations by extracting prior knowledge from text. For instance, CancerGPT, an LLM initially trained on general text corpora and common cancer data, was fine-tuned on small drug synergy datasets from rare tissues[106]. Engineering considerations included selecting the appropriate LLM, converting existing tabular data on cell line experiments into free text and designing prompts to yield synergy predictions. CancerGPT successfully predicted drug pair synergies for treating rare cancer cell lines, including from soft tissue and stomach cancers[106].

Hallmark 9: discovering new cancer vulnerabilities

Discovering new cancer vulnerabilities focuses on identifying new genes, proteins, pathways and metabolites that are essential for the survival of specific cancers but non-essential for normal cells. This process can lead to the design of new drugs (Hallmark 10), the repurposing

of existing non-cancer drugs or expanded use of current cancer drugs to new indications.

To uncover cancer cell vulnerabilities, large-scale CRISPR-based screening[107] platforms, such as the cancer dependency map (DepMap, a global collaboration aimed at identifying genetic and pharmacological dependencies across hundreds of cancer cell lines)[6], have been developed. Additional key data resources for discovering cancer vulnerabilities are reviewed elsewhere[5]. Numerous AI models have leveraged these resources to identify vulnerabilities at the gene, pathway, protein and metabolite levels, highlighting the great value of building and sharing multiomic functional screens for downstream analysis.

One promising application of AI is the identification of cancer-specific synthetic lethality[108], which occurs when the simultaneous mutation or inhibition of two genes leads to cell death, whereas inhibition of either gene alone does not. A well-known clinical example involves using PARP inhibitors to treat patients with *BRCA1* or *BRCA2* mutations[109] or mutations in other homologous recombination genes, such as *BARD1* (ref. 110). AI algorithms have been developed to identify cancer type-specific synthetic lethality pairs in which one gene is mutated in cancer cells, making the second gene a drug target that, when inhibited, would kill the tumor cells while sparing normal cells. Representative AI models for synthetic lethality prediction include SELECT[111], ENLIGHT[112] and $TCGA_{DEPMAP}$ (ref. 113).

Emerging data modalities, including single-cell and spatial multiomics[114], which reveal tumor heterogeneity and detailed information about the tumor microenvironment, offer further promise for AI-driven discovery of drug targets and therapeutic mechanisms. For example, a random forest predictor and CNN models used to analyze single-cell expression data from 412 tumors across 17 cancer types and 12 normal organs predicted logic-gated (AND, OR, NOT) gene pairs that best discriminate between malignant cells and normal cells, identifying tumor vulnerabilities potentially targetable by dual-target chimeric antigen receptor T cell engineering and new chimeric antigen receptor targets, such as FOLR1 for ovarian cancer and CEACAM5 for colorectal cancer[115]. Additionally, AI models leveraging spatial transcriptomics data that integrate gene expression with spatial information, mapping transcriptomic activity to regions of the tumor microenvironment, can identify cell types, states and metabolic activity across tissue regions, aiding biomarker and therapeutic target discovery[116,117].

Hallmark 10: designing new drugs

Designing new drugs includes the discovery of natural compounds, de novo drug design and the development of novel treatments, such as cancer vaccines. Drug design is costly, time intensive and prone to high failure rates[118], and AI is expected to revolutionize it by enabling virtual screening of millions of compounds, identifying or designing drug candidates and predicting their interactions with target proteins or metabolites. AI could also accelerate lead optimization by predicting properties such as solubility and toxicity. These advances would result in faster, more cost effective and precise drug development, with the potential to expand the cancer drug repository.

This field is among the most active areas of AI-related industry involvement. For example, the deep generative GENTRL model, part of Insilico Medicine's AI-driven drug discovery platform, combines reinforcement learning and variational inference for de novo small-molecule design. Its application in targeting DDR1, a kinase implicated in fibrosis and certain cancers, successfully identified inhibitors in just 21 days[119].

Deep generative models assist in designing new molecules with desirable properties, such as solubility, half-life, binding affinity and molecular size and shape[120–122]. Meanwhile, the recent development of DL-based AI models has revolutionized the prediction of protein three-dimensional structures (AlphaFold[123]), molecule interactions (AlphaFold 3 (ref. 124)) and dynamic processes, including protein folding and unfolding (AI^2BMD (ref. 125)). By combining these approaches, it is now possible to efficiently develop a wide range of potential drug candidates, as exemplified by the de novo design of a series of high-affinity antibodies specific to HER2, which were functionally equivalent or superior to current drugs[126].

Table 1 provides a representative example for each hallmark, detailing the cancer type, input data, AI model, model output and validation method, together with a curated list of relevant reviews for further reading.

AI-involving interventional clinical trials

To assess the application of AI in oncology clinical trials, we used Trialtrove, a curated database of all interventional clinical trials[127], following the approach described in the Supplementary Methods to identify 353 candidate trials. Among those, we identified 125 trials mentioning AI and focused on 31 that explicitly applied AI in their design or analysis and were reported in peer-reviewed publications. These 31 trials most commonly addressed Hallmark 7 (20 trials), Hallmark 5 (7n trials), Hallmark 3 (6 trials) and Hallmark 4 (6 trials), with some trials involving multiple hallmarks. Our search considered all ten hallmarks, whereas previous attempts concentrated on Hallmark 10 (refs. 128,129).

Our main interpretation from this survey is that only a small fraction of completed clinical trials have used AI in a manner that meaningfully influenced study design or data analysis. However, many AI-using meeting abstracts presented in 2023–2024 give hope that AI usage in peer-reviewed, published clinical trials will increase in studies completed in 2025 and beyond. A secondary but much more cautious interpretation is that valuable clinical information presented in short biomedical meeting abstracts might not always reach peer-reviewed journals, where it could be detailed and rigorously vetted by referees and editors. This issue may partly stem from the fact that many scientists conducting AI-based analyses of clinical trial data are trained in computer science fields, where publication of extended abstracts in competitive peer-reviewed conferences is more common than in journals.

Challenges and future perspectives

The advancements in cancer prevention, diagnosis, treatment optimization and therapy development discussed in previous sections (Table 1) highlight AI's potential to improve cancer care by enabling more personalized, effective and efficient treatment strategies. The ten AI-powered hallmarks in precision oncology operate synergistically rather than in isolation, each reinforcing and complementing the others to form a cohesive network that collectively combats cancer (Fig. 2b).

For example, precise cancer profiling (Hallmark 3) serves as a hub, facilitating treatment planning and monitoring, optimizing clinical trial design and matching, and improving patient outcome predictions while also benefiting from the discovery of new response biomarkers and cancer vulnerabilities. Clinical trial design and matching (Hallmark 6), serves as another hub benefiting from accurate cancer profiling, patient outcome predictions and treatment response predictions and plays a crucial role in evaluating new treatment combinations or drugs (Fig. 2b). As AI-based clinical solutions require validation through clinical trials, future AI efforts to enhance clinical trial design and matching will further expand AI's impact across other hallmarks.

Despite the impressive achievements, several challenges must be addressed to fully realize the potential of the 'AI revolution' in precision oncology and ensure its effective and ethical application.

Quantity and quality of data

The quantity of cancer data remains relatively small compared to that in fields such as computer vision[5]. For large-scale pan-cancer studies, data availability for individual cancer types, especially rare ones, is often 'absolutely' small[33]. Furthermore, as the feature space expands, data can become 'relatively' small; for example, 500 samples might suffice for regression models using a handful of clinical features but

Table 1 | Summary of the ten hallmarks of AI in precision oncology: target populations, key examples and suggested further reading

Hallmark	Target population	Representative example						Further reading
		Cancer type	Input data	AI model	Output	Validation	Ref.	
H1: cancer screening	Asymptomatic populations	Breast	Mammography image	CNN+transformer	Cancer risk across 5 years	Large-scale globally diverse retrospective	166,167	168–170
H2: cancer detection	Patients with symptom or suspicious signal	Pan-cancer	cfDNA	Classical ML	Cancer detection and cancer tissue of origin	Case–control prospective	44	171–174
H3: cancer profiling	Patients with confirmed cancer	Brain	H&E slide	CNN+autoencoder+multilayer perceptron+classical ML	Tumor cell DNA methylation and cancer subtypes	Retrospective	56	175–178
H4: patient outcome prediction	Patients with confirmed cancer	Endometrial	Multimodal data	DL (hybrid architecture)	Distant recurrence risk	Retrospective	61	9,179–181
H5: treatment planning and monitoring	Patients with confirmed cancer	Prostate	CT image, organ regions of interest	Classical ML (random forest)	Per-voxel radiation dose distribution to radiotherapy treatment plan	Prospective	65	68,182–184
H6: clinical trial design and matching	Subset of patients with cancer	Lung	EHR	Classical ML	Hazard ratio upon changing eligibility criteria	Retrospective	76	185–187
H7: developing new response biomarkers	Cell lines, animal models or patients	Melanoma	Transcriptomics	Classical ML (Cox–proportional hazards regression)	T cell dysfunction score (correlates with immunotherapy response)	Retrospective	82	188–190
H8: identifying effective treatment combinations	Cell lines, animal models or patients	Seven rare cancer types	Two-drug pair	LLM	Drug pair synergy prediction ('yes' or 'no')	In vitro	106	191–193
H9: discovering new cancer vulnerabilities	Cell lines, animal models or patients	Ovarian cancer, colorectal cancer	Single-cell transcriptomics	Classical ML+CNN	Optimal logic-gated (AND, OR and NOT) gene pairs	In vitro	116	194–196
H10: designing new drugs	Cell lines, animal models or patients	Multiple	Structural antibody database	Generative DL	High-affinity antibodies	In vitro	126	197–200

are inadequate for DL models using images. AI models trained on small sample sizes or limited data sources often suffer from overfitting and poor generalization.

Several approaches can mitigate this challenge. (1) Data augmentation techniques[130], slightly altering feature values to generate more samples, can increase data size. (2) Few-shot or zero-shot transfer learning[131], which pretrains models on large, general datasets, requires fewer samples to fine-tune the models when applied to specific tasks. This approach has been successful in creating predictive models based on high-throughput screens using cancer cell lines and then fine-tuning them to predict individual patient treatment responses using a small number of samples[88–90]. (3) Collaborative AI networks across institutions can also facilitate data sharing and model development, leading to more robust and generalizable AI solutions. Federated learning, which enables model training and testing without data sharing, is an approach to overcome interorganizational data-sharing challenges[132]. (4) Foundation models trained on massive, diverse datasets offer a transformative approach by being applicable to numerous downstream tasks with minimal or no task-specific labeled data[133]. These models, which combine the benefits of transfer learning with the scale and versatility of multipurpose architectures, represent a new paradigm for medical AI[134]. By outperforming task-specific models trained from scratch[135,136], foundation models offer a powerful solution to address data scarcity in healthcare AI.

Another challenge is data quality[137]. Clinical data, including health records and treatment response evaluations, can be subjective and noisy, often containing incomplete data fields or inconsistent measurement protocols across institutions. Addressing these issues necessitates data harmonization, especially for multimodal models[138]. Standardizing data collection and recordkeeping, such as using standardized EHRs and establishing guidelines for measurements and response evaluations, is essential. Additionally, developing community-standard datasets will facilitate the creation of new algorithms and enable objective assessment of emerging approaches. Computational methods for retrospective data harmonization are also needed to address existing inconsistencies[139].

Developing more-accurate AI models

Many AI models, despite claims of superior performance, often yield moderate or unstable predictive power when tested independently[140,141]. This is often due to overfitting caused by small sample sizes, poor-quality data or limited data sources. Appropriate model training, cross-validation and careful data division are also essential to enhance generalizability, following established guidelines such as TRIPOD[142].

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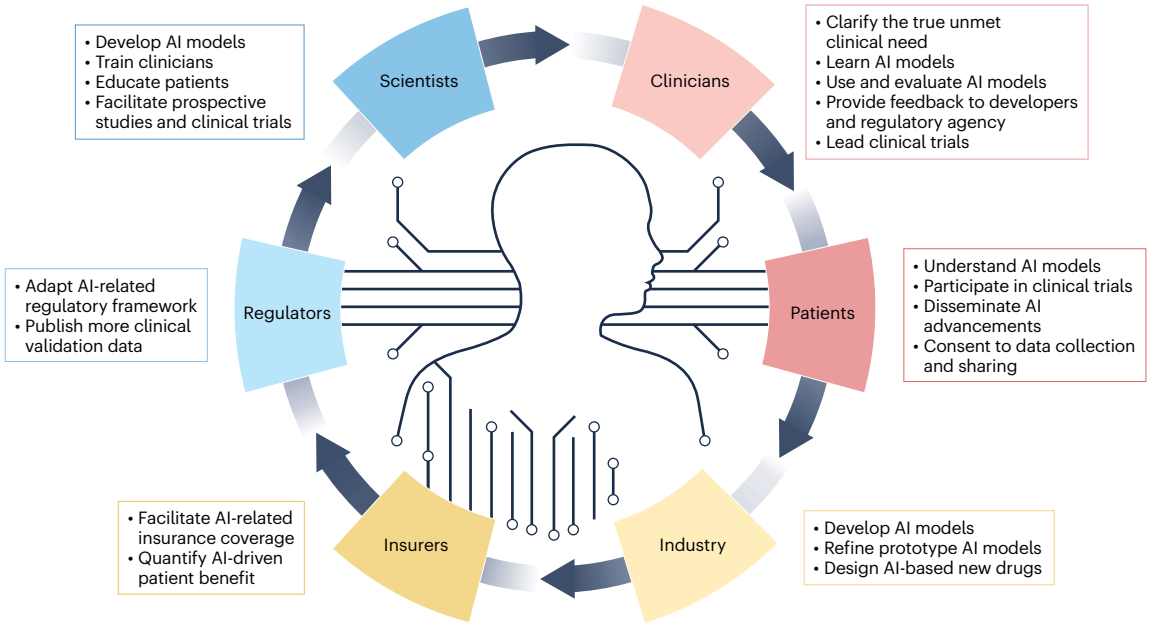

Fig. 3 | Collaboration among key stakeholder groups for AI-driven patient benefit. Six stakeholder groups (scientists, clinicians, patients, industry, insurers and regulatory agencies) each play a crucial role in maximizing AI's impact in healthcare. Their primary roles are outlined alongside their respective groups. Effective collaboration among these stakeholders is crucial for achieving meaningful patient outcomes. Before approval, clinical trials demonstrating AI's utility require coordinated efforts to ensure robust design, inclusivity and standardized reporting. Academia–industry–healthcare partnerships are vital for pooling resources and expertise during AI development and testing. After approval, AI developers must prioritize transparency to build trust, insurers need to clarify reimbursement policies and large-scale real-world data collection is critical for monitoring performance and safety, particularly from a regulatory standpoint.

To improve accuracy, several strategies can be employed. First, multimodal data integration, which combines different data types, has shown potential in improving predictive accuracy[19,137,143]. Second, harnessing new data modalities is crucial. For example, longitudinal data[144] capture the dynamics of cancer progression, allowing AI to provide dynamic, recursive predictions for continuous monitoring and adaptive treatment planning[145]. Additionally, microbiomes have emerged as a hallmark of cancer[146]. Leveraging microbiome data, AI has shown promise in predicting immunotherapy response[30,147] and advancing additional microbiome-based applications[148]. High-resolution data, such as single-cell and spatial multiomics[114], are also becoming increasingly prevalent, with exciting translational potential[115–117,149]. These high-dimensional datasets are challenging for human interpretation, positioning AI as a pivotal tool in advancing precision oncology. Recent advances include large pretrained foundation models for scRNA-seq, which facilitate cell type annotation, multibatch and multiomic integration, response prediction and gene network inference[136,150]. Furthermore, DL models trained with matched spatial transcriptomics and H&E slides can now infer spatial gene expression from H&E slides alone[151,152], offering transformative clinical applications such as tumor molecular characterization, outcome prediction, therapy response assessment and the identification of tumor vulnerabilities and drug targets.

Recent studies have shown that unstructured clinical notes from EHRs can be used to train clinical language models as all-purpose prediction engines, improving area under the curve by 5–15% across various tasks (for example, readmission, mortality, comorbidity, insurance denial) compared with traditional models[28]. However, current LLMs still suffer from drawbacks, such as generating non-existent facts, a phenomenon known as AI hallucination, and making logical errors. Developing new model structures to address these limitations will improve AI's application to precision oncology.

Making clinically relevant AI

Currently, there are still big gaps between AI research and its clinical use[8]. First, most AI models, even well-developed ones, have only been tested retrospectively. Prospective testing, ideally through randomized controlled trials, is essential for demonstrating clinical validity and applicability.

Second, both data and models need to be more clinically relevant. (1) Data: scRNA-seq-based models are currently difficult to implement clinically due to their lack of standardization and high cost. However, emerging models that use histology images to infer gene expression and predict patient outcomes and therapy responses show promise[56,151,152]. If validated prospectively, these models would have substantial translational value. (2) Model interpretability: many AI models suffer from poor interpretability, hindering their clinical adoption. Classical, interpretable ML models, such as regressions and decision trees, still remain important. Over time, more advanced explainable DL models[153] and LLMs capable of reasoning through their outputs may build clinical trust and facilitate broader application. Using complex uninterpretable AI models without efforts to develop interpretable alternatives should be avoided[33,96]. (3) Evaluation metrics: while metrics such as area under the curve are commonly used in academic research, it is essential to use clinically relevant measures that are meaningful to clinicians, such as odds ratios, hazard ratios or precision and recall rates[137]. (4) Interface: most clinicians are not data scientists and prefer intuitive tools, such as interactive dashboards and point-and-click analysis platforms, over raw code[8]. AI-driven clinical decision support systems[154], integrating measurement hardware and pre-installed software, offer an ideal solution by providing real-time, actionable insights that enable informed clinical treatment decisions.

Fairness is another ethical consideration. Poor-quality data or nonrepresentative datasets can lead to biased models that reinforce healthcare disparities. It is crucial to report potential biases, such as sex and ethnicity, in research journals and clinical trials[74,155]. Ensuring that AI models are developed with regulatory and ethical concerns in mind and deployed in ways that respect patient privacy, mitigate bias and promote equity is vital for sustainable and inclusive cancer care improvements.

Finally, ensuring the safety of AI models in clinical practice is essential. It has long been known that adding human-invisible noise to images can dramatically decrease the performance of classical DL models[156]. More recently, similar vulnerabilities were observed in LLMs, where prompt injections into original medical images can greatly affect model outputs[157]. LLMs are also susceptible to generating misleading content that poisons medical knowledge graphs constructed from medical literature[158], often struggle with following instructions accurately and are sensitive to input order and quantity, posing risks to patient safety[159]. Better testing of LLMs in real clinical applications is needed[160].

Collaborative implementation of AI for patient benefit

Interdisciplinary communication and collaboration among key stakeholder groups are necessary for the successful implementation of AI in healthcare (Fig. 3). These groups are as follows:

1. Scientists: as primary developers of AI models, they are responsible for educating clinicians and patients, gaining their trust and ensuring proper understanding of the models' benefits and risks. Implementing AI tools into clinical workflows requires major changes in infrastructure and healthcare professional training, areas in which scientists can provide leadership and guidance.
2. Clinicians: they identify unmet clinical needs and communicate them to AI developers. After AI solutions are developed, they evaluate their effectiveness in practice and provide feedback on the costs and consequences of false positives and false negatives, enabling the AI system to be (continuously) fine-tuned for real-world applications. Clinicians also advise on user interface design, ensuring that it is intuitive and suitable for everyday use.
3. Patients: as the most directly affected stakeholders, patients are motivated to engage in their own care and can be taught to use healthcare apps to manage their data and promote their health. Engaged patients play a crucial role in disseminating advancements to their peers and driving consent for data collection and sharing, which is vital for scientific progress.
4. Industry: companies are at the forefront of advancing AI technology, developing new AI architectures and models, such as Google's transformer[17] and DeepMind's AlphaFold series[123,124]. AI-driven pharmaceutical firms are also actively creating models for drug design. Companies refine prototypes, enhance model accuracy and make AI accessible by developing user-friendly systems and mobile applications.
5. Insurers: they facilitate AI adoption in clinical practice by covering licensing fees for AI software. Insurers also quantify the benefits of AI-driven interventions to ensure that they are cost effective.
6. Regulators: organizations, such as the FDA or the European Medicines Agency, define standards for clinical computational tools, including AI models. The FDA currently classifies AI models as medical devices, requiring premarket review and risk assessment before clinical use[161]. Although nearly 1,000 FDA-approved AI products exist as of 2024 (ref. 162), many have only been retrospectively validated or validated by single institutions, with data remaining unpublished and proprietary. Increased transparency and availability of clinical validation data are needed to support broader AI adoption. Multiple FDA subgroups are working to streamline standards to improve regulation around AI[163]. Adapting regulatory frameworks to approve AI technologies within reasonable time frames and with appropriate standards is key for ensuring their broad deployment[10].

Realizing real patient benefits from AI requires effective collaboration among these stakeholders, despite inherent challenges. AI models must demonstrate clinical utility through prospective clinical trials that expand beyond single institutions and retrospective datasets. This necessitates funding and coordination among scientists, clinicians, patients and regulatory agencies to ensure comprehensive trial design, respect patient privacy and ensure inclusion of underrepresented populations and establishment of standardized reporting guidelines[164]. Academia–industry–healthcare partnerships are essential for pooling resources and expertise during development and testing phases. For approved AI models, developers must prioritize interpretability and transparency to build trust among clinicians and patients, while insurers clarify reimbursement policies. After approval, communication and coordination remain crucial, as large-scale real-world data collection becomes crucial for ongoing performance and safety monitoring[140], particularly from a regulatory standpoint[165].

Conclusion

Driven by the exponential growth of data, AI algorithms and computational power, AI holds transformative potential for precision oncology across the entire cancer care spectrum, from prevention and diagnosis to treatment and drug development, encompassing ten interconnected hallmarks. Realizing this potential hinges on a concerted effort focused on translational research, including expanding access to large, diverse datasets, developing robust and interpretable AI models and rigorously validating these models through unbiased, prospective clinical trials. Moreover, establishing robust regulatory frameworks is essential for safe, equitable and effective implementation. By prioritizing these efforts and fostering interdisciplinary collaboration among key stakeholders, we can accelerate AI's integration into routine clinical practice, maximizing its impact on patient care and ultimately diminishing the burden of cancer.

Data availability

The raw data from Trialtrove are available under restricted access only to license holders of Trialtrove at https://citeline.informa.com/trials/results. The processed data are available at https://github.com/ruppinlab/ProcessTrialtrove/blob/main/SupplementaryTableInterventionalTrialsUsingAI.xlsx.

Code availability

The Python programs used in this study are available at https://github.com/ruppinlab/ProcessTrialtrove. Running the programs requires a Trialtrove license and download of the trial data. Other readers may find the programs useful to read to understand in detail how we processed the Trialtrove data.

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Competing interests

E.R. is a cofounder of MedAware, Metabomed and Pangea Biomed (divested) and is an unpaid member of Pangea Biomed's and GSK Oncology's scientific advisory boards. The other authors declare no competing interests.

Additional information

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