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Advancing equitable and personalized cancer care: Novel applications and priorities of artificial intelligence for fairness and inclusivity in the patient care workflow

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ABSTRACT

Patient care workflows are highly multimodal and intertwined: the intersection of data outputs provided from different disciplines and in different formats remains one of the main challenges of modern oncology. Artificial Intelligence (AI) has the potential to revolutionize the current clinical practice of oncology owing to advancements in digitalization, database expansion, computational technologies, and algorithmic innovations that facilitate discernment of complex relationships in multimodal data. Within oncology, radiation therapy (RT) represents an increasingly complex working procedure, involving many labor-intensive and operator-dependent tasks. In this context, AI has gained momentum as a powerful tool to standardize treatment performance and reduce inter-observer variability in a time-efficient manner.

This review explores the hurdles associated with the development, implementation, and maintenance of AI platforms and highlights current measures in place to address them. In examining AI's role in oncology workflows, we underscore that a thorough and critical consideration of these challenges is the only way to ensure equitable and unbiased care delivery, ultimately serving patients' survival and quality of life.

1. Introduction

Although advances in cancer prevention, screening, and treatment have improved cancer survival rates – especially for high-income countries [1] –, nearly 10 million cancer-related deaths occurred in 2020 [2]. The last two decades have been marked by significant efforts in the development of patient-centered approaches, implementing multimodal treatment strategies, inclusive of surgery, systemic treatments, and radiation therapy (RT) [3–5]. Specifically, recent technological improvements in precisely delivering patient-specific radiation treatments impacted on the complexity of the RT workflow, increasingly time-consuming, and reliant on human-machine interactions

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responsible for added variability in care quality. Hence, artificial intelligence (AI) has gained growing attention as a tool to provide faster, higher quality, and safer RT delivery by optimization and automation in the clinical workflow [6,7].

In this narrative review, the progress of AI in oncology is outlined from a workflow perspective, taking RT as a practical example. Key concepts of AI methods are introduced. For each stage, opportunities, applicability, and efficiency of novel AI solutions are considered. Special emphasis is placed on discussing the challenges, recommendations, and future implications of AI-powered cancer care.

2. AI methods in cancer care

AI refers to computers' capability to perform tasks mimicking human intelligence, such as visual perception and pattern recognition for decision-making and problem-solving purposes [8]. Machine learning (ML) is a sub-field of AI and deep learning (DL), in turn, a sub-field of ML (Fig. 1).

ML algorithms are operated by computer programs to learn from data, especially unstructured data. By extracting patterns from a set of provided data objects, the class of future data can be revealed, thus data-driven predictions or decisions can be performed [9,10]. In this context, artificial neural network (ANN) models consist of a group of related input/output nodes, representative of neuron-like units, organized in input, hidden and output layers. Their connection is expressed by a weighted edge, adjusted in the learning stage based on the agreement between predicted output and labeled data. ANN models with multiple self-learning hidden layers herald the modern era of DL. The hierarchical structure of deep networks, with information flowing through successive hidden layers, simulate the hierarchical processing of information in the human brain [9,10].

The inventive learning approach of DL differs from that of "non-deep" ML, which is more dependent on human intervention. In general, a feature hierarchy process is necessary to differentiate categories of data and create structured inputs, required by the learning process. In supervised ML, human intervention is required to determine the hierarchy of features ("hand-crafted" features [11]) and label input data. The hidden layers of DL architectures can instead automate much of the feature extraction process and accept unstructured raw data. Moreover, DL models can effectively leverage partially labeled data [12,13] (Fig. 2). While traditional ML methods encounter limitations in generalizing across diverse input data and achieve variable degrees of clinical utility [14], DL techniques, by learning features over multiple modalities and perceiving complex and non-linear relationships [15], offer better algorithm generalizability [6,7]. Besides, natural language processing (NLP) is an adjacent field within AI, involved in converting unstructured free data (e.g., electronic health records, EHRs) into discrete data elements [16,17]. In this field, further development is represented by large language models (LLMs), a type of DL trained on NL input data to generate text that closely resembles human responses [18] (e.g., ChatGPT, generative pre-training transformer (GPT) model [19]).

The digitalization of health care data and the enhanced parallel computing and cloud storage allow for the advent of AI-based applications in oncology (Fig. 2) [20].

3. AI in the cancer care workflow: from screening to diagnosis, staging, prognosis, treatment decision-making, and follow-up

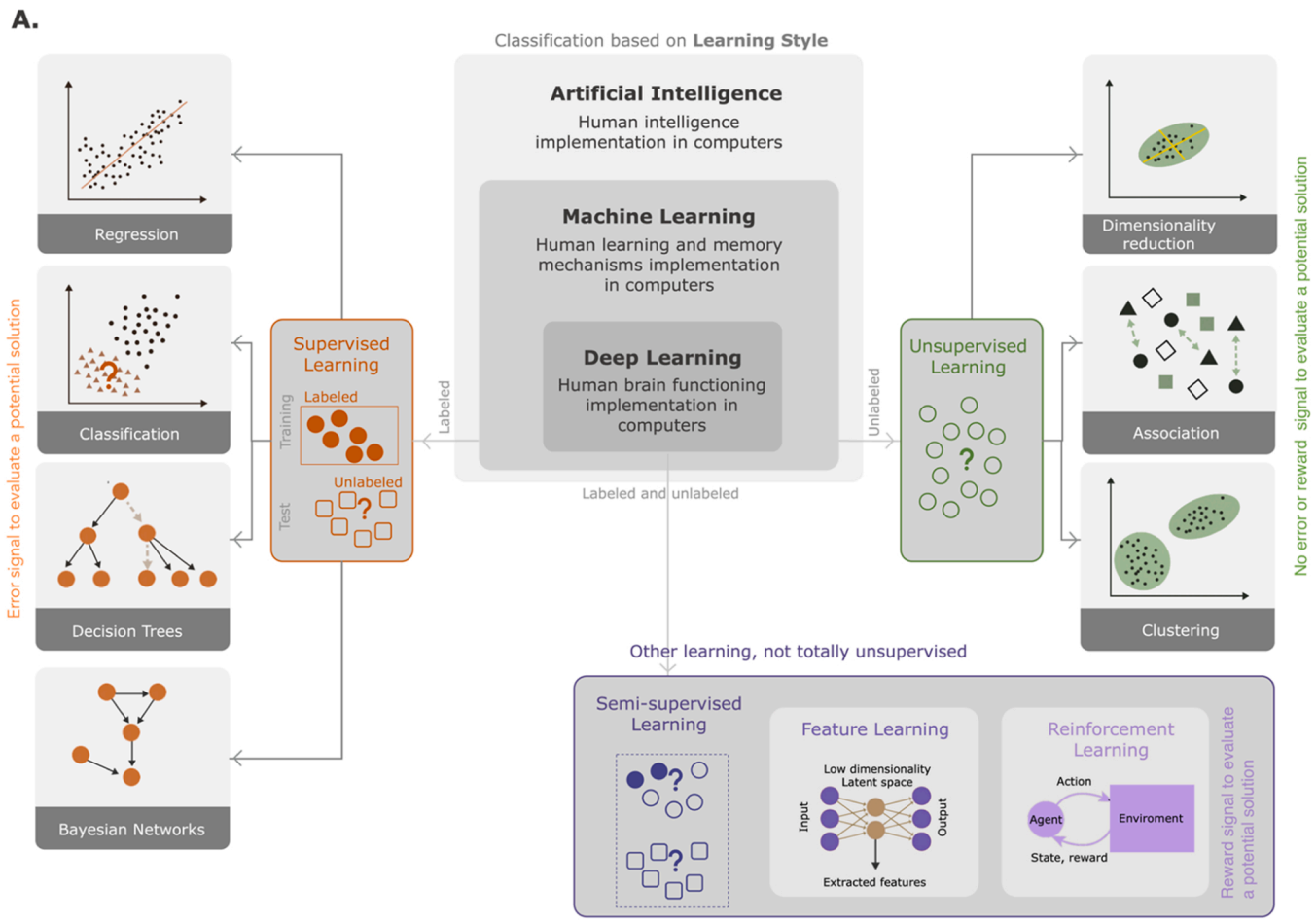
The clinical cancer therapy workflow starts with the oncologist's assessment of the patient's medical history, symptoms and functional status, patient and tumor genomic data, diagnostic and staging imaging, and prior treatment response, to define a tailored treatment decision strategy (Fig. 3).

AI methods in cancer-related image analysis and omic data analysis proved efficient applications for tumor screening [21–33], diagnosis [34–46], classification and grading [47–56] (Fig. 2). In image analysis, AI applications for radiology [21–26,31–36,43–48], endoscopy [37–39,49], and pathology [30,41,42,50–54] outperformed conventional computer-aided detection systems in many cases [16], simplifying the pipelines and reducing false positives [57]. In radiology, Mirai is one of the most promising DL-based tools for cancer screening [31]. Mirai obtained 5-year areas under the curve (AUCs) of 0.76, 0.81, and 0.79 across multi-institutional validation sets of 128,793 mammograms from Massachusetts General Hospital, Karolinska, and Chang Gung Memorial Hospital, respectively [32]. Similarly, Sybil, a three-dimensional convolutional neural network (3D CNN)-based model, predicts lung cancer risk from a single low-dose computed tomography (LDCT). Sybil achieved 1-year AUCs of 0.92, 0.86, and 0.80 on a held-out dataset of 27,383 LDCTs from National Lung Screening Trial (NLST), MGH, and CGMH, respectively, further lateralizing future cancers' location and likelihood of high-risk score [33]. Besides, DL-based tools for cancer diagnosis such as QuantX [43], Koios DS [44,45], ProFound [45], and Transpara [46], some of the most advanced in development, are already adopted by some United States-based institutions for breast and thyroid cancer. As for pathology, a successful GoogLeNet-based algorithm for breast cancer diagnosis, developed in the Cancer Metastases in Lymph Nodes Challenge 2016 (CAMELYON16), detects lymph nodes in whole slide imaging (WSI) stained with hematoxylin-eosin (HE). The model outperformed pathologists' interpretation with an AUC of 0.99 vs 0.88 [41]. Furthermore, DeepPATH, an Inception-v3 architecture-based model, distinguishes lung cancer types in WSIs of HE-stained lung tissue. DeepPATH classified images from The Cancer Genome Atlas (TCGA) into lung adenocarcinoma, lung squamous cell carcinoma or normal lung tissue with an AUC of 0.97 [50]. In molecular-omic data analysis, AI techniques unlocked new opportunities for genome and transcriptome sequencing [55,56]. Notably, SCOPE, a Supervised Cancer Origin Prediction Using Expression algorithm trained on TCGA, identifies the closest match for a tumor from among 40 cancer types and 26 adjacent-normal tissues from whole-transcriptome RNA sequencing data. The classifier achieved an overall mean accuracy of 99% on primary cancers and 86% for metastatic disease [55].

Subsequently, AI approaches for patient prognosis [58,59] and treatment response [60–67] prediction may offer tools to support individual treatment decision-making (Fig. 2). Specifically, applications in systemic [60–64] and RT [65–67] response assessment have the potential to develop clinical decision support systems (CDSSs) [68–71]. In radiomics, AI-driven advancements in pattern recognition allow for the automated extraction of discriminating quantitative features that capture properties of the tumor phenotype which correlate with clinical outcomes [72]. Typically, a feature selection step reduces a pre-defined set of features to a subset suitable for the intended purpose, ultimately fed into a predictive or prognostic ML model. Novel DL strategies leverage DNNs to create deep features, eventually interpreted by the final layer of the network as likelihood of a therapeutic outcome [73]. AI tools in radiogenomic methods correlate imaging and genomic data to develop predictive biomarkers reflective of tumor's genotype [74]. AI-supported dosiomic analysis employs radiomics approaches to estimate patient-specific spatial dose distributions and allow for toxicities prediction [75–77]. Although findings are encouraging, these approaches are currently restricted to inconsistent implementation and retrospective studies, thus limited to research settings [78–80]. Randomized controlled trials, comparing patient's care workflow assisted and unassisted by CDSSs, are warranted.

Lastly, AI methods in 'shape radiomics' analysis, which refers to any feature characterizing the 3D shape of a tissue, may provide tools for patient surveillance [7,16,73] (Fig. 2). Beyond traditional metrics such as The Response Evaluation Criteria in Solid Tumors (RECIST), which accounts for the tumors' change in size over the course of treatment, shape radiomics enables sophisticated morphological measurements able to better assess whether a tumor is stable, progressing or responding [73,81].

For next-generation precision oncology, the required combination of



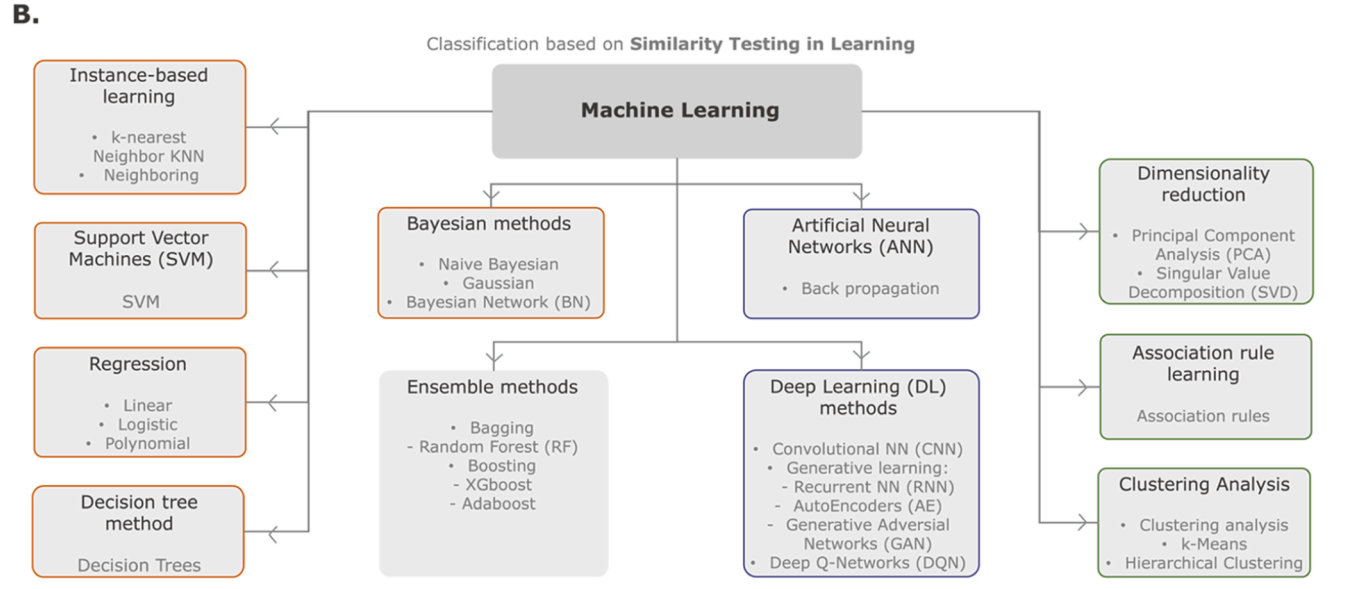


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Fig. 1. Classification of ML algorithms. (A) Classification based on learning style. According to input data in the learning process, machine learning (ML) algorithms can be classified into three categories. (1) Supervised Learning: input data are labeled (training set). The model is constructed through training of the training dataset, improved by receiving feedback predictions (validation set, part of the training set), and tested through incoming data (without known labels, test set) [9,10]. (2) Unsupervised Learning: input data are not labeled (no training set). The model is constructed by exploring the structures in the input data to extract general rules [9, 10]. (3) Other Learning. Semi-supervised Learning: mixture between supervised and unsupervised learning, input data are both labeled and unlabeled (incomplete training set). The model learns the structures to organize the data to make predictions and different assumptions are made to model the unlabeled data [9]. Reinforcement Learning: the correct input/output pairs are never presented. The agent takes proactive actions to strengthen the quality of the input data to promote prediction accuracy (performance reward). The algorithm is rewarded with positive/negative reinforcement for each correct/incorrect action, learning through experience which actions need/do not need to be performed [9]. Representation/Feature Learning: useful features learning through raw input data transformation into a representation (pre-processing) that can finally improve the prediction model. The design of efficient feature learning techniques aims to automate the learning process employing supervised feature learning, based on labeled input data, or unsupervised/self-supervised feature learning, generating features with unlabeled input data [9]. (B) Classification based on similarity testing in learning. According to the similarity testing functions adopted in the learning process, ML algorithms can be classified into twelve categories. Namely, (1) regression relies on statistical learning, (2) instance-based learning (or memory-based learning) methods apply similarity measures stored in the database, (3) tree-based methods employ tree-structured decision models, (4) Bayesian methods are based on statistical decision theory, (5) clustering analysis relies on similarity tests to group data, (6) neural networks are based on cognitive models, inspired by the structure and function of biological neurons to model the complex relationships in between, (7) ensemble methods are composed of multiple weaker independently trained models, whose prediction results are combined, and (8) deep learning methods are based on much deeper and complex neural networks [9,10]. Deep learning (DL) is often applied to semi-supervised learning problems, where large datasets contain very little labeled data. Being the acquisition of labeled data and feature extraction a challenging and resource-intensive process, partially labeled data, along with self-supervised feature extraction, can lead to powerful and cost-effective DL solutions. For each category, model examples are listed.

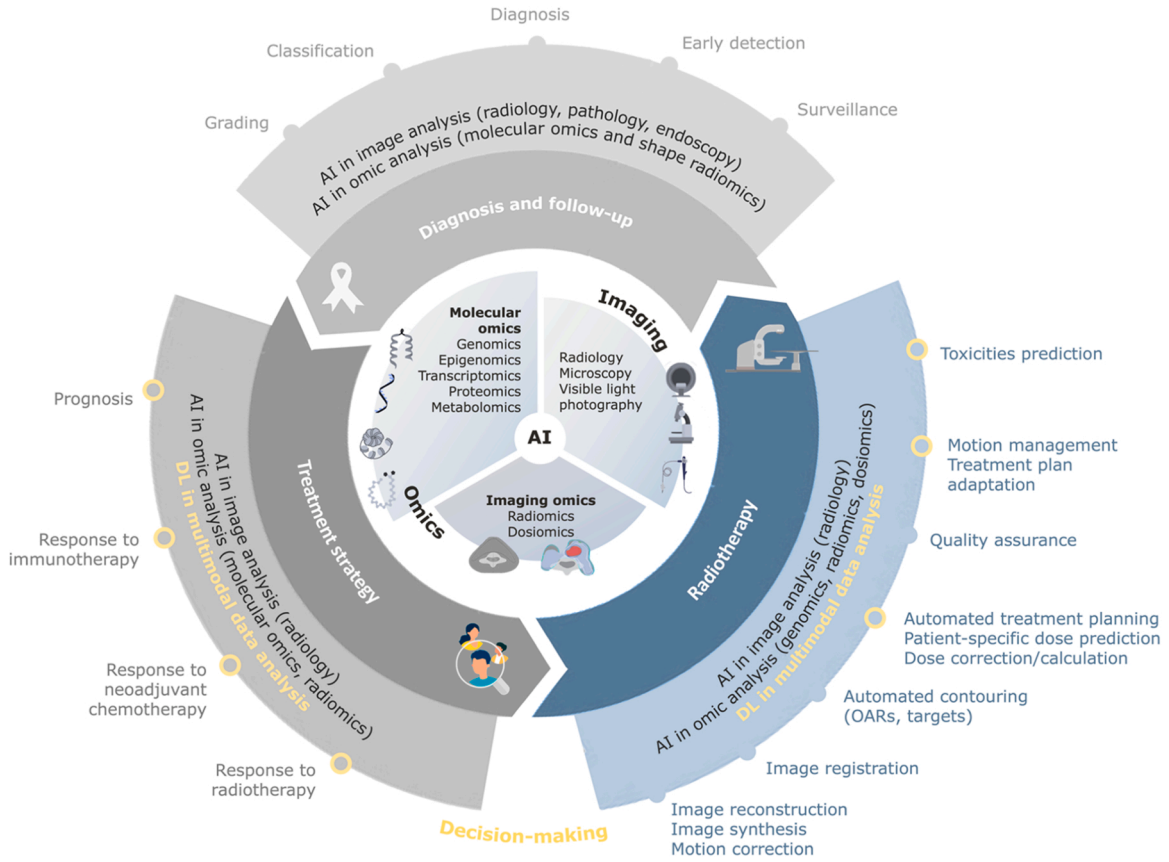

Fig. 2. . Currently investigated AI applications in cancer care. Artificial Intelligence (AI) applications in the three main domains of cancer care workflow: (1) diagnosis and follow-up, (2) multi-modal treatment strategy, (3) radiotherapy workflow. For each domain, AI is employed by different data analysis approaches: (I) imaging of different modality (radiology, microscopy, and visible light photography), and (II) omics, distinguished in molecular omics, excellent in high-dimensional data analysis but limited in spatial information and imaging omics, capable of rich spatial information but limited in capturing very fine molecular level detail. Omic approaches involve different data types: (a) genomics, single nucleotide polymorphism and copy number variations, (b) epigenomics, DNA methylation, (c) transcriptomics, microarray and RNA-seq (d) proteomics, protein expression, (e) metabolomics, metabolite abundances, (f) radiomics, texture analysis, shape features and first and higher order statistics data, and (g) dosiomics, dose metrics features, dose-volume histogram metrics, spatial dose features and dose shape features. Novel DL approaches provide tools to handle large amounts of different data types and play a key role to support decision-making tasks oriented to a precision oncology.

information available with image and omic data analysis, and whole-EHR data elements is orders of magnitude beyond the cognitive capacity of a single oncologist [16,70]. The multitasking and multimodal nature [71] of DL techniques have the potential to synthesize the amount and interdependence of diverse data that need to be explored to provide accurate interpretation of a patient's cancer features [16,69, 82].

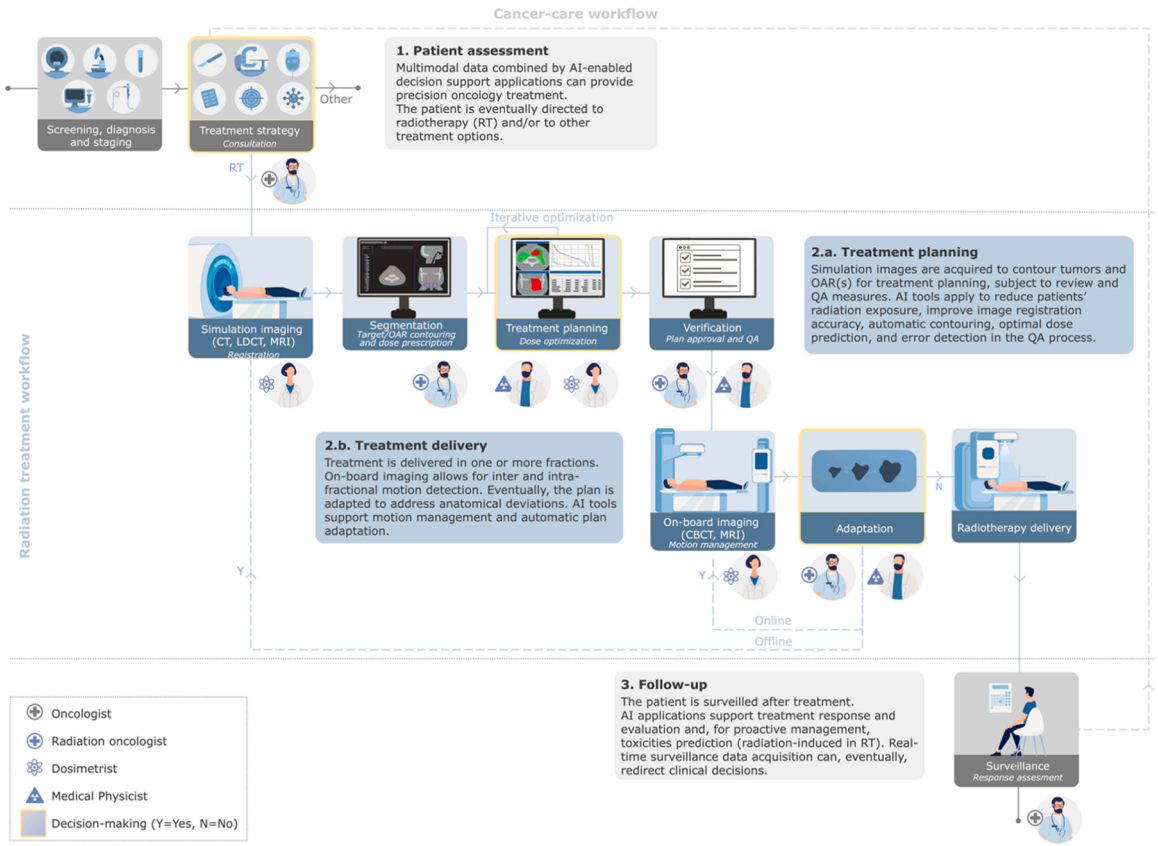

Fig. 3. AI in the cancer care workflow: radiation oncology here stands as an example of integrating AI into clinical practice, given its heavy reliance on human-machine interaction. Schematic overview conceptually divided into: (1) assessment, (2) treatment planning and delivery, (3) follow-up. The workflow begins with the patient consult: useful information derived from screening and diagnostic tools are evaluated. To assess the potential benefit and feasibility of a treatment, tumor stage, gene signatures, and overall patient status (e.g., age, comorbidities, functional status, tumor, and critical healthy tissues proximity) need to be considered. If the patient is directed to RT, simulation medical images are acquired for treatment planning. Subsequently, the treatment plan is created and subjected to approval and quality assurance (QA) measures prior to RT delivery. Finally, the patient receives follow-up care. Many clinical figures are involved, such as radiation oncologists, medical physicists, and dosimetrists. AI tools have the potential to shift their focus from repetitive and laborious tasks, such as tumor and organ segmentation, plan design, and QA, respectively, towards the management of non-routine, high-risk issues and the development and implementation of solutions that require human insight.

4. AI in the radiation treatment workflow

If the multidisciplinary team directs the patient to RT, a precise workflow follows. To design the RT plan, the radiation oncologist prescribes radiation doses that balance tumor coverage and control, contextualized in established dose constraints for normal structures (i.e., organs-at-risk, OARs), guided by imaging and radiobiological principles [6,7,83] (Fig. 3). AI approaches in image analysis provide applications for the required tasks of multimodal image simulation and onboard imaging [84–96], image registration [97–99], and tumor-organ segmentation [100–110] (Fig. 2).

As for image simulation, AI platforms have been developed to reduce the imparted dose to the patient's healthy tissues. In computed tomography (CT) imaging, AI tools timely act on the image reconstruction timeline of LDCTs to guarantee suitable image quality for treatment planning, degraded by increased noise due to reduced exposure. Either denoising after image reconstruction (*image-to-image* approaches) or during the reconstruction process (*iterative-learning* approaches) are performed [83]. Among image-to-image approaches, deep CNN methods have been used to map LDCT images toward their corresponding normal-dose counterparts [84,85]. In iterative-learning approaches, prior functions for image smoothness and edge maintenance are learned for iterative reconstruction from sinograms [86]. Currently, prior functions are manually designed or learned with conventional ML algorithms, assuming that reconstructed images lie within a linear manifold model trained from normal-dose images; however, the manifold is usually highly non-linear. Recently, DL methods have been adopted for appropriate modeling, improving the LDCT image reconstruction quality [86,87]. Also, commercial DL-based solutions, such as Precise Image [111], True Fidality™ [112], and AiCE [113], have already been integrated into diagnostic imaging devices.

In contrast to CT, magnetic resonance imaging (MRI) does not involve additional radiation exposure for the patient but lacks electron density information for direct dose calculation. In MRI, AI has been investigated to create synthetic CT (sCT) images [114]. Novel DL algorithms have outperformed conventional voxel, atlas, or hybrid-based methods, limited in terms of nonstandard sequences, atypical anatomies, and related complex workflow, respectively. Architectures such as encoder-decoder (ED) networks, U-Net, and generative adversarial networks (GANs) proved improved accuracy and computation speed [91,92]. Notable, cycle-GANs, a particular derivation of GANs, opened the era of sCT generation from unpaired image dataset [93]. Furthermore, many DL methods have been employed for image motion correction [94–96]. Namely, Moco-SToRM is a motion-compensated reconstruction approach for high-resolution free-breathing lung MRI data, which models the deformation map at each time instant (0.1 s interval) as the output of a CNN-based generator driven by a motion vector [96].

Next, medical physicists and dosimetrists carry out image registration to optimize alignment of multimodal data (simulation images) in

the treatment planning stage or, later on, of longitudinal data in the pre-delivery steps and in computing dose accumulation through the course of the treatment (on-board images) (Fig. 3). To deal with image modality variability, some investigational DL methods employ learning algorithms either to construct a shared latent representation of anatomical structures across different modalities, or to synthetize cross-modal images (e.g., sCTs), reducing the task to a monomodal registration [115]. In the context of quantifying registration error for treatment margins definition, DL models in *area-based* methods allow for superior similarity metrics by learning the patch-wise correspondences of registered images [97]. To address the image content variability, DL models in *feature-based* methods allow for deformable image registration (DIR) [98,116]. DL approaches have been adopted to rapidly predict the deformation field that aligns the images to be registered: VoxelMorph proved a DIR accuracy comparable to state-of-the-art methods, while operating up to 150 times faster [99].

Regarding delineation of targets and structure avoidance, the radiation oncologist delineates tumor and OARs on the aligned simulation images (Fig. 3). Semi-automatic segmentation methods for OARs in clinical practice, such as atlases, integrate prior knowledge from segmented reference images and are affected by associated uncertainties in the registration procedure, selection strategy, and required subsequent manual iterations. AI methods more efficiently incorporate prior knowledge in the form of parameterized models by considering each voxel contribution in the learning process [83]. Current DL-based approaches mainly rely on U-Nets, a CNN architecture characterized by an encoding path to capture context, a decoding path to generate high-resolution segmentations, and skip connections to retain fine-grained structural information [117]. Many AI-based commercial tools have already been adopted to support a more efficient and standardized RT workflow [118] and several more have been announced [119]. Lately, VBrain, an ensemble NN based on DeepMedic and 3D U-Net architecture for brain metastases segmentation on CT and MR images, has received the Food and Drug Administration (FDA) clearance as the first AI-powered tumor auto-contouring solution [120,121]. VBrain proved improved sensitivity in lesion detection (12.2% increase in sensitivity), contouring accuracy (0.028 increase in dice similarity coefficient) and efficiency (30.8% decrease in treatment planning time) with respect to unassisted clinicians' performance [100]. AI applications in genomic analysis provide prescription doses based on genomic-adjusted tumor radiosensitivity [122]. Moreover, AI methods in image analysis can predict patient-specific dose distributions [123–127] and, by means of optimization approaches, offer tools to automate treatment planning [128,129] (Fig. 2).

Manual treatment planning is a time-consuming task, influenced by the operator's expertize: the physician selects an appropriate treatment technique and fractionation schedule and, with a trial-and-error approach based on clinical guidelines and personal experience, the dosimetrist iteratively adjusts positioning, distribution, and other machine parameters to optimize the dose trade-offs between the target and OARs, according to approved dose prescriptions (Fig. 3).

Automated rule implementation and reasoning techniques implement clinical guidelines as hard-coded rules, by means of a binary logic ("if-then"), to simulate manual treatment planning and allow for iterative adjustments after performance evaluation [130]. To assist the adjustment process, *knowledge-based (KB)* planning considers a selection of successful previous treatment plans defined with best clinical knowledge for cases with similar OARs/target geometry, to predict suitable planning parameters to incorporate in the planning process of the current case. Recently, multicriteria optimization approaches have been implemented to generate, instead of a single plan, multiple plans simultaneously (so-called Pareto surface), allowing real-time evaluation of results for different planning parameters [83,130]. While these approaches lack spatial information and remain suboptimal, AI techniques can implement a voxel-based prediction for optimal patient-specific dose distribution [123–127]. For instance, HD U-net, a hierarchically densely connected U-Net architecture, has been proposed for 3D dose distribution prediction of H&N RT[127]. During its initial clinical deployment on over 840 patients, the model significantly improved the percentage of first plan acceptance from 63% to 90%[131]. Moreover, DL methods have been explored to predict dosimetrically suitable machine parameters for clinical treatment plan generation [130,132,133]. Finally, reinforcement learning and GANs algorithms have been suggested to simulate the decision-making process for the dosimetric trade-off definition, forecasting AI-enabled fully automated treatment planning in the near future [128–130].

AI approaches have been applied in expediting the current iterative treatment planning process, which involves evaluation of simulations based on dose calculation algorithms that trade speed (e.g., pencil-beam) with accuracy (e.g., Monte Carlo, MC). DL-based models have been applied to either correct fast dose calculations to improve the simulation accuracy [134,135], or to replace dose calculations with fast and accurate simulations [136–139]. Recently, DoTA, a DL-based calculation algorithm combining CNN and transformers, has been implemented to predict proton doses with MC-level accuracy (1%, 3 mm gamma pass rate of 99.37 $\pm$ 1.17%) while operating even faster than pencil-beam algorithms (around 100 times, speed of 5 $\pm$ 4.9 ms)[139].

The plan is then sent to the radiation oncologist for approval and then finalized together with the medical physicist, who's also responsible of QA activities to ensure proper setting and performance of elements involved in the treatment delivery stage (Fig. 3). AI applications address repetitive manual tasks to expedite QA procedures, detecting rare errors and potential contributing factors, which would otherwise require further investigation [140,141].

In the treatment delivery phase, AI methods in image analysis for on-board image guidance can support motion management [142–148] and treatment planning adaptations [149–154] to ensure a correct treatment plan delivery (i.e., image-guided radiotherapy, IGRT) (Fig. 2). Patient or organ motion during treatment delivery (i.e., *intra-fractional motion* [155]) is assessed to preserve precision. Current motion management methods either limit or monitor the respiratory and abdominal motion range in a passive or active (i.e., gating techniques) manner to continuously adapt the beam delivery[156]. AI-based methods have been applied in patient-specific markerless target tracking [142–144] and motion modeling for real-time motion estimation [145–148].

Additionally, anatomical changes between simulation imaging and delivery of treatment fraction (i.e., *inter-fractional motion*[155]) need to be considered (adaptive RT, ART)[83]. AI-based approaches have been implemented to improve the image quality of on-board cone-beam CT (CBCT) images to CT level for treatment planning adaptation [157–159]. Also, DL has been adopted to automatically adapt the treatment plan based on daily changes in anatomy (i.e., online ART, oART) in CBCT-guided[151] and MR-guided [152–154] RT. For instance, Ethos is a novel commercially available CBCT-guided and AI-driven solution for oART [160]. In a pre-release study, automated treatment planning of 39 pelvic treatment cases proved clinically acceptable AI-segmentation (no further editing for 75% of cases) and auto-planning (selected for 88% of the cases instead of the pre-treatment plan) with reasonable adaptive procedure duration for the first 5 treated patients[151]. Importantly, defining whether a re-planning stage is beneficial in the treatment is a pivotal aspect in the RT workflow. Such a decision should consider not only the anatomical deviation range, but also patient-specific characteristics and, on the other hand, the impact of a treatment delivery delay. Finally, DL methods can be investigated to combine a multitude of data and automatically adapt dose according to individual responses, defined as KB response-ART[161]. With a reinforcement learning-based approach, a set of algorithms can be trained to learn the RT environment and search for the optimal adapted dose based on their knowledge of clinical, dosimetric and radiomics data [162].

5. Challenges and adoption barriers of AI models in oncology

Despite the AI applications proposed, the transition to clinical practice poses challenges. Large, top-notch datasets for training models, along with rigorous validation, are prerequisite to improve performance in clinical settings [163]. Conversely, substantial investments of time and resources are imperative to acquaint clinicians with this technology – both in terms of utility and limitations – and ensure safe and appropriate clinical use [164].

5.1. Database construction

The reliability of AI hinges on extensive data training to prevent overfitting, which can otherwise compromise model performance when applied to external validation datasets [16,70]. The modernization of the healthcare setting is already promoting a full digitalization of patient medical information, with the volume of data to be collected and managed rapidly growing. To effectively leverage these datasets for research purposes [16,17,163], it is crucial to establish translational research platforms that ensure secure storage, anonymization, and regulated access [17].

However, different challenges need to be addressed. First, the plethora of generated data often requires laborious curation and cleaning, particularly for unstructured EHRs that may contain substantial noise and inconsistencies [7]. In this context, data standardization plays a pivotal role in generating high-quality data and facilitating the integration of diverse features for automatic multicentric data extraction and integration. The Observational Medical Outcomes Partnership (OMOP) and the Common Data Model (CDM) are actively working to provide standardized disease codes and vocabulary to structure observational health records into easy-to-use databases [82]. Approximately 440 biomedical ontologies, such as SNOMED, NCI Thesaurus, CTCAE, the ROO, and the UMLS meta-thesaurus have already been established to regulate terminology in EHR, treatment procedures, RT, and genomic annotations [17,165]. Moreover, the multi-institutional Image Biomarker Standardization Initiative has made efforts to define nomenclature and pre-processing image workflow for 172 important radiomic features, providing a benchmark dataset for calibration of radiomic softwares and guidelines for radiomic studies publication [166]. Second, given the concerns of real data protection and patient control over their sensible medical records, data are usually confined as property of individual institution, with limited adoption of data-sharing platforms.

The restricted data availability leads to smaller training datasets, increasing chances of model overfitting, especially for DL architectures based on a huge number of features. Moreover, the significant heterogeneity in medical data across institutions decreases model's performance and generalizability across different centers and populations [16,17,82,163,167]. To avoid biases related to data collection, data-sharing solutions that enable contributions and learning across institutional borders should be promoted in view of a medical and scientific interest. Some progress is on course with the establishment of privacy-preserving distributed DL (DDL) [165,168] and multicenter data-sharing agreements [169,170]. DDL, for instance, allows multiple research groups to cooperatively implement a common DL model without actually sharing local datasets [171].

Efforts have also been made to develop open-source and open-access archives for cancer-related data collections, such as The Cancer Imaging Archive and TCGA. However, inherent biases toward certain minoritized racial and ethnic groups persist, with databases like TCGA being predominantly composed of individuals of European ancestry, mainly featuring primary tumors, and having limited representation of metastatic tumors [82]. Addressing these biases is an ongoing challenge in the pursuit of more inclusive and representative healthcare data.

5.2. Model commissioning

Beside dataset-related limitations, a rigorous experimental design is mandatory when developing AI models. Commissioning of a model involves two stages: an initial algorithm training and (*internal*) validation phase to tune the model to the clinical necessity, followed by a test phase (*external* validation) to ensure reproducibility prior to clinical use [164]. The training/validation phase implies a partition of the available dataset into a training set and a validation set (typically 80–20%, respectively). The test phase involves an independent evaluation of the final performance to investigate model's robustness.

To prevent model development from introducing biases, the datasets should reflect the population the model will serve, considering demographical, genotypical and socio-economical diversities [163,172]. Neglecting representativeness might have hazardous consequences, as in the case of a hypertrophic cardiomyopathy genetic test built on a dataset characterized by mostly White Americans [173,174]. With mutations being significantly more common among Black Americans than White Americans, the test misclassified benign variants as pathogenic for patients of African ancestry [173]. It turns out that instead of disease features, the model might learn the dataset distribution (i.e., shortcut learning) [175]. Detecting these shortcuts and removing disparities in race and subsequent patterns of health service utilization to ensure not codified or exacerbated algorithms is not an easy task. Even balancing dataset classes (e.g., majority class down-sample or minority class up-sample) might not be sufficient and lead to poor performance, since included cohorts might not reflect populations that did not access the healthcare system at all. The problem is not only AI-related, and local practices need to be considered.

Additionally, in the current status quo, despite great improvements in internal validation practices, external validation is still infrequent and limited by huge costs and lack of proper protocols and regulation. Usually, single-institution clinical data, limited in confounder information, are employed. Biases cannot be detected in such a test set, and the model fails when applied to different clinical setting (i.e., out-of-distribution data) during the test phase [172].

The reproducibility of the model output is challenging even within the same clinical environment it was developed for: AI models are subject to data drift over time, caused by changes in data formatting, clinical practice (equipment and protocols) [164] or natural drift not present during model commissioning, and change in features' relationship (covariate shift) [16,17,82,172]. A feedback system is required to monitor models' validity and advise for the necessity of model re-training [16,164,172]. For what concerns the employed dataset, precision medicine demands the integration of diverse data types (e.g., clinical, laboratory, imaging, and epidemiological data) [82,167], along with follow-up data collection to support treatment decisions and to predict and manage adverse events [17].

Beside dataset-related aspects, the patient-per-feature ratio is another critical factor in model commissioning, particularly in DL models combining thousands of information (e.g., genomics). A small ratio might result in model overfitting and training dataset noise description [17]. In addition, algorithm selection is essential, with the best-performing ML techniques to be preferred. Only about 17% of the published AI studies in oncology were estimated to compare the outcome of more than one ML method [17].

As a last note, a collaborative ecosystem systematically reporting algorithm source codes and training conditions is crucial to ensure transparency, reproducibility and quality-checks in similar healthcare systems and populations, ultimately supporting novel algorithm development and best practices refinement [82,172]. Therefore, the data-sharing agreements for publicly available datasets, should also require users to share their queries, git hubs, collabs, and Jupiter notebooks upon publication of their work.

5.3. Clinical implementation

Despite advancements, many AI tools remain at the proof-of-concept stage. Improved resolving power comes at the cost of our understanding capacity and ability to predict failures, especially for DL algorithms, which rely on convoluted hidden layers of data interaction and numerous parameters ("black box") [163,172]. AI systems urges the need for trust through *interpretability* (understanding what an algorithm is doing) and *explainability* (elucidating the underlying mechanics) of models. *Explanatory AI* is an evolving field striving to provide some level of transparency to the decision process beneath complex algorithms. Although research is still ongoing, there is promising progress in explanation of deep network data processing and representation, and in creating explanation-producing systems [176]. While challenges related to interpretability exist, a rigorous model implementation based on active monitoring of model's performance and regular assessment of suitable training data can prevent errors and systematic biases. Implementation into clinical reality would also require a dedicated multidisciplinary team of experts, with insight into the specific model, including the target patient cohorts. This team's responsibilities include conducting a risk analysis of the model and identifying potential malfunctions, ultimately improving model's robustness. Additionally, they would take on the crucial role of providing training and instructions to end-users on the appropriate utilization and interpretation of the model's output [164].

From a regulatory standpoint, both the FDA and the European Union currently classify AI technologies as "software as a medical device", providing regulations and draft guidance for medical practice and clinical workflows [177,178]. Ethically, AI applications are grappling with inherent issues of racial bias. Legally, patients' right to explanations of algorithms' output and data protection compliance are points to be addressed [179]. Moreover, the ever-increasing reliance on AI may turn the patient-doctor relationship into a patient-healthcare system relationship, necessitating a reevaluation of the doctor's personal responsibility and the liable party for incorrect AI-based decisions [7167]. Some frameworks have recently been established by the Medical Device Regulation (MDR) on liabilities related to in-house created models and the 2013/59/EURATOM directive on obligation to perform risk analysis for AI-based software [164]. Also, the General Data Protection Regulation (GDPR) provisions on preventive measures concerning privacy compliance [180] and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule provides standards for maintaining patient confidentiality [181]. To ensure the regulatory observance, secure data storage systems with encryption protocols are being adopted as on-premises, cloud-based or hybrid solutions.

6. Conclusions and future perspectives

AI gains in accuracy, reproducibility, and consistency are poised to redefine the roles of clinical figures involved in the cancer treatment workflow (Fig. 1). The automatization of repetitive tasks requiring labor-intensive input is expected to unhamper the clinical workforce and transfer their responsibilities to quality control of AI output and high-value activities, such as complex decision-making tasks and clinical management [7]. To assist the implementation of AI solutions, the training of some physicians will need to shift from lengthy apprenticeships, meant to gain expertize in performing manual activities, to education in integrating and interpreting information from extensive datasets [7,16,17,163]. An example is the Information Exchange and Data Transformation (INFORMED) Fellowship in Oncology Data Science [182,183]. Furthermore, promoting extracurricular engagement in datathon competitions, which team up clinicians and data scientists to analyze real-world health-related data, can provide clinicians with valuable insights into data curation and model development and foster a deeper understanding of the clinical context among data scientists. Of note, novel generative AI tool such as ChatGPT show great potential in further streamlining the cancer care workflow [184,185]. However, considering the chatbox was (so far) not programmed as a medical bot, strict guidelines on appropriate use need to be established.

These benefits hold significant value in the current global health scenery, especially for resource-constrained clinical settings [6,7,16]. While more than half of all cancer patients live in low- or middle-income countries, according to the World Health Organization comprehensive treatment is available in less than 15% of low-income countries [186]. AI may address shortages by providing specialized knowledge across disease sites and by optimizing the utilization of available devices.

The enthusiasm around AI and big data is justified, but many challenges need to be stressed. The little inclination for multi-institutional data sharing must be surmounted to benefit from the use of *distributed learning*. Well-intentioned privacy-preserving policies turn into detrimental procedures for marginalized and under-represented populations when neglecting the risk of data privatization [16,82,172,187]. Efforts in the current legal framework need to be reinforced for the purpose of privacy, equity, and safety. To promote health equity, the FDA should ask developers of AI solutions to transparently disclose the patient dataset composition and mandate, rather than recommend, validation on diverse patient populations [187]. Besides, model performance needs to be continuously monitored and recalibrated to address shifts in dataset caused by changes in clinical practice, patient demographic variation, and advancements in data capture technology. In this regard, the FDA announced the need for a regulatory approach that spans the entire lifecycle of AI-based software [188]. To guarantee a safe operation of AI-based medical devices, re-evaluation plans which address differences in outputs from those reviewed prior to approval need to be clearly defined. A list of safe allowable changes for models' adjustment to new data should be established, either through safeguards or periodic reviews [189]. Equally important, algorithm retraining on patient status changes, either in real-time or scheduled slots (e.g., nightly runs), should be envisioned [16,17]. Finally, clinical evidence supporting initial approvals should be made publicly accessible in plain language and distributed through peer-reviewed literature [189].

In conclusion, the oncology field is highly algorithmic and data centric. AI-based models can fail during multiple phases of the AI lifecycle: biases might be introduced during data collection, model development, evaluation and test, implementation. Model's fairness requires clinicians, AI engineers, data scientists, social scientists, and industry partnership in a common goal-oriented cooperation [172,190]. In a time marked by socio-economic disparities, benefits of AI solutions can shift the healthcare model from fee-for-service to a quality-based care approach. To realize the full potential of AI, a synergy of the international oncology community is necessary for coordination of talent, training, investment, and resources. The road ahead is challenging, but the transformation of cancer care holds significant promise.

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