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PERSPECTIVE

Cellular and Molecular Biology

High-dimensional role of AI and machine learning in cancer research

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The role of Artificial Intelligence and Machine Learning in cancer research offers several advantages, primarily scaling up the information processing and increasing the accuracy of the clinical decision-making. The key enabling tools currently in use in Precision, Digital and Translational Medicine, here named as 'Intelligent Systems' (IS), leverage unprecedented data volumes and aim to model their underlying heterogeneous influences and variables correlated with patients' outcomes. As functionality and performance of IS are associated with complex diagnosis and therapy decisions, a rich spectrum of patterns and features detected in high-dimensional data may be critical for inference purposes. Many challenges are also present in such discovery task. First, the generation of interpretable model results from a mix of structured and unstructured input information. Second, the design, and implementation of automated clinical decision processes for drawing disease trajectories and patient profiles. Ultimately, the clinical impacts depend on the data effectively subjected to steps such as harmonisation, integration, validation, etc. The aim of this work is to discuss the transformative value of IS applied to multimodal data acquired through various interrelated cancer domains (high-throughput genomics, experimental biology, medical image processing, radiomics, patient electronic records, etc.).

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BACKGROUND: THE ROLE OF INTELLIGENT SYSTEMS IN CANCER RESEARCH

Artificial Intelligence (AI) refers to functions and processes by which machines learn from data how to intelligently use the available information and establish associations between variables. In oncology, complex datasets reflect the presence of many quantifiable dimensions needing Machine Learning (ML) solutions to recommend, decide and especially predict over time while new data are accrued. Although AI and ML are often interchangeably used terms, they are complementary and can be reconciled under the term 'Intelligent Systems' (IS) ('learning health systems' has also appeared with clinical data in precision medicine [1]). A corresponding glossary appears at the end (see Table 1). In general, cancer researchers leverage IS for their ability to conduct inference by algorithmic rules which eventually lead to informed clinical decisions. These algorithms can analyse and integrate multiple data modalities facilitating the confluence of information from heterogeneous sources. Then, by combining computing power and mathematical thinking with domain knowledge and context-specific information, IS deals with scalability and generalisability. Therefore, IS solutions assist the cancer expert in key tasks such as identifying triggers for diagnosis, or intervention/treatment, and support the decisions taken under conditions of uncertainty. As this uncertainty can have many causes, and only some are controllable, efficiency is desired together with the applicability of principles such as stability and predictability, both necessary to ensure reproducibility metrics and establish high-quality predictions [2].

To better delineate what cancer patient outcomes can be inferred from all types of acquired information, the IS role is to design and implement strategies that assemble and engineer a wealth of data features. These features are used to define signatures and patterns carrying information at a molecular level and combining evidence obtained at cell biology, pathology and radiology levels. Then, to exploit the interdependence between these domains, the definition of suitable standards is required [3]. This is a major harmonisation effort, with three major impacts involved: (i) the identification of diagnostic markers, (ii) The monitoring of patients' response to treatment and (iii) the delivery of prognostication paths. In such regards, IS contribute to lower both infrastructural barriers (data management related costs, computational requirements for fast data processing, expertise needed to ensure quality processes, etc.) and ensure further developments toward:

A. *Easier access to Big Data database resources and repositories* (genes, ncRNAs, proteins, peptides, small molecules, monoclonal antibodies, bio-images, registries, etc.);
B. *Fast deployment of scientific findings* related to molecular profiles (including RNA), genetic information, electronic health records (EHR), medical imaging archives, etc.

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Table 1. Glossary.

AI = Artificial Intelligence
Digital tools able to perform tasks commonly associated with intelligent beings.
ML = Machine Learning
Methodological solutions that work algorithmically to find consistent patterns and reliable features in large amounts of data aimed at deciding and formulating predictions based on new data.
IS = Intelligent Systems
Software tools that support expert decision-makers in acquiring information from data, learning patterns from the processing of information and using the knowledge to facilitate the decisions.
EHR = Electronic Health Records
Digital version of the patient's paper chart and medical history.
EM = Ensemble Modelling
A computational process by which multiple diverse base models are used to predict an outcome.
DL = Deep Learning
Deep learning is a class of algorithms employing multiple layers to extract informative features from the raw input data and use them to learn and generalise.
TL = Transfer Learning
Family of techniques enabling researchers to infer about a problem by using the knowledge gained from a model applied to a similar problem.
RL = Reinforcement Learning
Algorithmic process of learning by doing to make a sequence of decisions based on rewarding desired behaviours and/or penalising undesired ones.
IoMT = Internet of Medical Things
The collection of medical devices and applications that connect to healthcare IT systems through online computer networks.
VoI = Value of Information
An analytic method that quantifies the potential benefits of additional information before making decisions under uncertain conditions.

C. *Digitally annotated biobanks* with biological samples associated to clinical information and analyses performed on experimental data;
D. *Drug banks* with sophisticated semantic frameworks and efficient algorithms to facilitate repurposing and repositioning.

These resources suggest a rich research agenda. A few major directions are: (i) repurposing existing drugs for treatment decisions supported by multi-sourced protein–protein interaction networks [4], (ii) developing ML algorithms predictive of anticancer drug efficacy [5], (iii) advancing semantics to deploy public cancer genomic datasets as linked data and offer automated analytics and visualisation [6], in addition to other emerging applications [7]. Accessibility, especially concerning cloud-sourced data, and heterogeneity of independently created ontologies and vocabularies represent real bottlenecks. There is still limited and inconsistent data reuse, which calls for creating shared models and performance measures for efficient data warehousing approaches. It is worth mentioning that focusing mainly on the algorithmic performance of methods designed for diagnostic or therapeutic scopes may be a limiting factor. The ability to infer patient's outcomes depends on multidimensional decisions embedded within the IS-supported clinical workflow, for instance calibrating the measurement of under/overtreatment effects or identifying early detection or relapse to guide specialistic care (management of treatment intensity effects, reassessment of timing in monitoring toxicity, etc.) during follow-up or surveillance.

At the methodological level, a first critical issue is the training of algorithms over multiple datasets to build first descriptive and then predictive models aimed at generalisation. For example, Deep Learning (DL) may be blind to the underlying cancer biology but still offer (a) the power of digesting huge information from patient sample tissues via large volumes of digitised biopsy slides across many cancer types, (b) the alignment of such detailed maps with therapy factors, (c) the combination of tissue characteristics with treatment response and the correlation with identified patterns to tell what cancer drugs work best at the individual level or find clues in tissue microenvironment for establishing vulnerabilities to immunotherapy drugs. In general, cancer dynamics have inherent complexity that cannot be just algorithmically trained. The mechanisms governing such dynamics involve dysregulated cell signalling networks with crosstalk between many variables that operate at different time scales, which complicates data collection. Some variables may induce response due to reprogramming, for instance at the metabolic level. Mutations affecting treatment may require updates or corrections of earlier predictions, especially for personalising the cure or improve/accelerate trial practices with priority assigned to establishing synthetic control groups or modulating drug doses for prevention of resistance.

Precision medicine is gaining clear benefits from IS [8]. Immune profiling (IP) offers a good example. A recent study [9] on the PD-L1 biomarker to predict a patient's response to treatment was performed via tumour-immune cell interactions analysed spatially and computationally by AI-assisted multiplexing approaches. About the same marker, another study [10] identified factors explaining the success of target immunotherapy treatment in urothelial cancer by using information from tumour and immune cells together with patient clinical and outcome data [11]. An ML algorithm performed over 36 features from multimodal data to find the 20 most associated with a specific response to PD-L1 inhibitor and deliver predictive marks of potential tumour adverse immune cells in patients after treatment. The key factor was the integration of data types: without just one of these types, the predictive performance vanished.

SIGNIFICANCE FOR ONCOLOGY

The recent advances in radiology had strong impacts on early diagnosis and timely treatment, reducing the chances of misdiagnosis and therapy-related complications. Benefits involve less overtreatment in the short term and less mortality in the long term. IS contributed in various ways, measurable at prevention

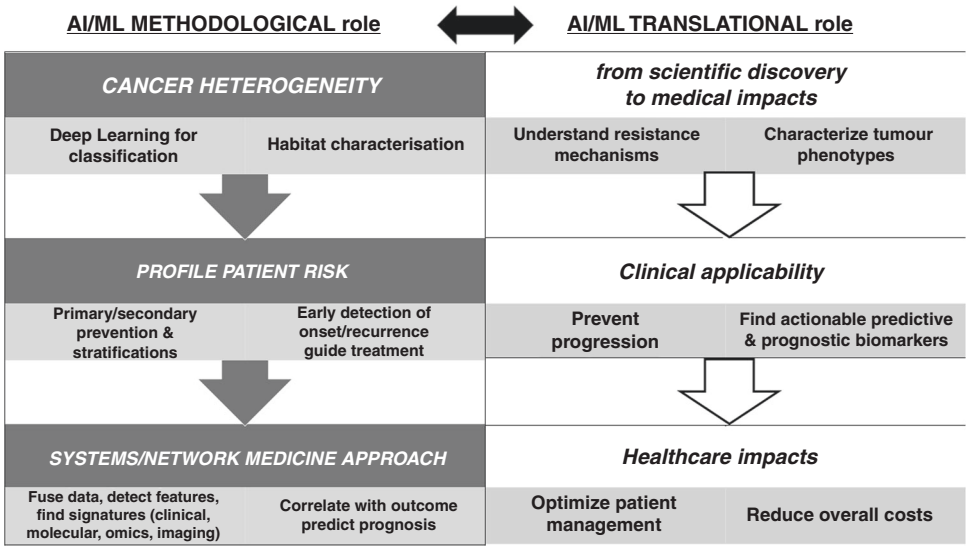

Fig. 1 Impacts Overview. AI and ML methodological and translational roles in Precision Oncology.

(primary and secondary), diagnostics, therapy and prognostication (see Fig. 1) levels.

Prevention

The stratification of patients according to their risk profile is often associated with the design of screening methods able to detect cancer at the early stage [12]. One reason for using IS approaches is to ensure the scalability of results to large-scale population screening. Most improvements in screening outcomes have been obtained from medical imaging, and this presents cost barriers. Although advanced learning with large complex datasets has become possible with various strategies and tools, often the limitation is in terms of the clinical applicability of the proposed solutions. These tend to leverage only some of the patients' characteristics and thus justify even more the need to profile large patient cohorts across many stratifying factors. Typically, an increased detection power of disease marks captured from multimodal data at an early stage leads to a much more accurate patients' classification. In the end, a full assessment of the actual capability of IS algorithms requires a demonstration of comparable performance with clinicians' interpretations, although an excess of focus on this aspect may diminish some potential gains. The reference goes to accuracy and efficiency achievable in triaging practices, for instance, for which more studies are needed [13].

Diagnosis

Medical imaging has gradually become the reference field for IS contributions [14–20]. Here, the spectrum of investigations in cancer covers primary versus metastatic lesion detection, image segmentation and classification, discrimination between benign and malignant nodules, histological subtyping, and many others. DL has established new standards through the learning of features directly computed from data. Complex solutions, typically Convolutional Neural Networks (CNN) or Recurrent Neural Networks (RNN), can execute training over large sets of labelled Regions of Interest (ROI) from where to learn the parameters useful to the generalisation of results. CNN applications and demonstrations have for instance covered skin cancer from a dataset of 12,940 clinical images [21] and metastatic breast cancer (BC) [22], and in BC it was also shown the feasibility of fusing CNN with other feature extractors [23].

DL is very effective in identifying variation by automatically inspecting complex patterns [24]. An application is provided by *ExPecto* [25], an experimentally validated tool that links genome-wide sequence data genetic mutations with disease prediction. In general, the ability to decrease variability depends on the heterogeneity of data and requires algorithmic training followed by testing and validation. This normally happens via accurate separation of tasks into independent datasets to optimise parameter tuning and performance assessment. With regards to imaging variation, the field of radiomics [26–30] currently inspires most of the algorithmic thinking toward predictive modelling for cancer detection, characterisation, and monitoring. This is because the imaging features extracted by ML algorithms are subject to sequential analysis steps aimed at prioritising their discrimination power and ensuring control of data redundancies, selection operated according to relevance and model tractability.

Therapy

Optimal therapeutic strategies are considered those able to overcome identified gaps and develop successful, sustainable and scalable interventions that improve the outcomes at the individual as well as population levels. IS present a wealth of methods that accurately measure response prediction and allow to develop and refine treatment options for cancer patients [31]. Correspondingly, they have revealed useful to advance drug discovery. IS may especially improve predictability, accuracy (with effects on effectiveness and safety), and speed/timeline of drug discovery [32]. It is possible to analyse large-scale AI-empowered and ML-driven drug discovery platforms centred on large warehoused data and predictive algorithms tailored to specific proteins with their structures as a target. An example is the scalable cloud computing ML-driven *SpliceCore* platform (https://www.envisagenics.com/) with a > 5 ml RNA splicing errors database supporting identification, testing and validation of hypothetical drug targets that specifically target RNA splice variants causing cancer (such as triple-negative breast cancer and other genetic diseases). To stress the importance of therapeutic targeting of splicing in cancer [33], another tool worth mentioning is *SpliceAI* (https://github.com/Illumina/SpliceAI), a 32-layer deep CNN operating on pre-mRNA sequences [34]. Then, the cloud-based platform *Ligand Express* (https://www.cyclicarx.com/) that screens small-molecule drugs against proteomes and determines poly-pharmacological profiles. Here, an AI-assisted identification of protein targets is operated by a structure-based drug-centric technology (*MatchMaker*, a DL engine) determining drug's effects and visualising predicted drug–protein interactomes with

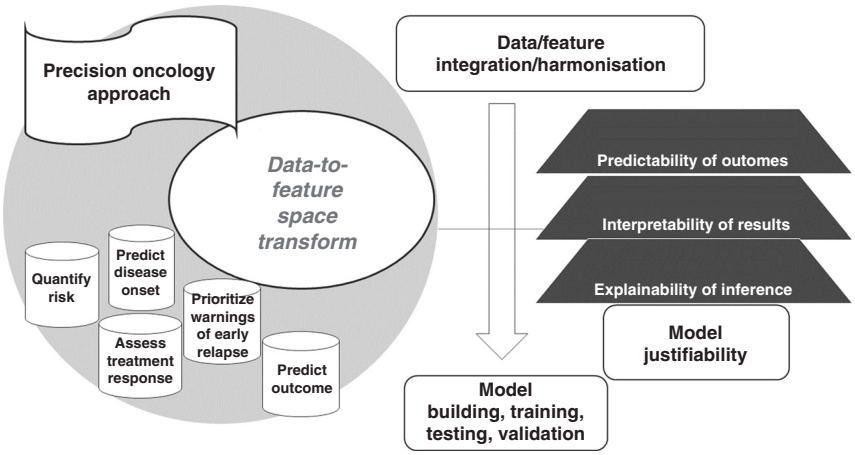

Fig. 2 Methodological Approach. Role of features in IS modelling.

coverage of both on- and off-target interactions (expected and unanticipated, respectively).

Computational drug development predictions face necessarily the validation stage to minimise the uncertainty about the efficacy with which any single drug or combination of drugs may eventually lead to better outcomes, something risky and demanding for new compounds or large-scale clinical trials. IS augment the possibility of diversifying drug pipelines [35, 36]. In addition, used drugs are increasingly investigated for repositioning/repurposing scopes, implying high computational demand for evaluating the possible application in new disease domains of libraries of approved drugs (about 1500 FDA-approved drugs can be potentially matched with about 10000 potential targets, numbers destined to change quickly anyhow). Some interesting in silico approaches refer to pharmacophore modelling and docking-based virtual screening for repurposing small-molecule drugs against multidrug-resistant cancers [37]. The role of resistance in cancer has stimulated research from prevention to control directions and effectively accelerated experimental and validation phases. The results have led to developing more targeted therapies to (i) identify neoantigens and immunotherapies [38, 39], (ii) understand toxicity from chemotherapy and radiotherapy and more automated planning of treatment programs in radiology [40–44], (iii) prioritise surgery [45].

Prognostication

Survival prediction determines how patient profiles match the available treatment options. A key characteristic in cancer is the inherent risk of metastasis that generates recurrence. Metastatic tumours, especially recurring ones with acquired resistance to therapy, influence cancer management because the probabilistic quantification of this type of risk is the most uncertain cancer management phase [46]. Usually, biomarkers determine this phase by looking at the disease at a molecular level. IS have increasingly leveraged the algorithmic processing of patient information inducing response to therapy under many influencing factors, from genetics and immune status to environment and lifestyle. In association with factors objectively measurable (histopathological characteristics or effects of adjuvant therapies) and crucial for determining disease markers, instruments such as risk scores and nomograms [47] may guide the therapy phases by quantifying chances of recurrence and prognostic assessment via various genetic and/or molecular markers and signatures. Recourse to DL (and other unsupervised algorithms) may offer black-box solutions with little insight into the processes determining their final output. Graph-based integrations may help integrate multi-omics data and improve the prediction accuracy of clinical outcomes [48]. In addition, beyond the problems of inaccurate, incomplete or biased data towards specific populations, a further complication is due to algorithms that may misrepresent the context without the necessary specificity. More importantly, the nonlinear complexity of biological processes indicates the necessity of matching quantitative modelling with the context-related complexities [49].

LEVERAGING DATA FEATURES IN MODELLING CANCER

Among the tools traditionally used in quantitative cancer research, it is common to find those modelling mechanistically and predicting tumour progression/growth. Growth, and resilience to survive, suggest that tumours are complex adaptive systems facing heterogeneous environments and dealing with variables measurable at various length and time scales (oncogenes, tumour suppressor genes, cell–cell communication, etc.). Models of the dynamics of growth in tumours have mostly followed principles of statistical physics and dynamical systems accounting for both inter-tumour processes and host–tumour interactions. This way, inference on cancer heterogeneity (and evolution) has been mainly explorative of the likelihood that different advantageous and deleterious mutations survive in the tumour cell population. Outstanding open questions remain and refer to multiscale nonlinear model parameterisations, the role of resistance, subclone detection among various other factors that might limit predictability [50]. At a methodological level, it is interesting to address the IS developments that occurred in two major areas of clinical impacts in cancer: (1) data science analytics to manage issues such as aggregation, augmentation, imbalance issues, etc. (2) algorithmic treatment of the complexity that affects the dimensions of data, with *reinforcement learning* deserving special attention (see the next section) when a dynamic rather than a static treatment of the data is necessary.

Ensemble models

IS have emphasised the potential significance of a more integrative use of multitype omics evidence. For instance, more accuracy is gained in assessing the cancer metastatic potential, in prioritising the patient-specific variables that once quantified may help the clinicians individualise the treatment options, in increasing the depth of risk profiles and the precision of outcome estimates, in planning cost-effective follow-up actions. Data integration is a critical structural component that calls for adaptive strategies at the algorithm level. Ensemble modelling (EM) is for example an approach that engages multiple models to predict outcomes by the means of different algorithms and/or different training sets. Then, EM aggregates the results in a prediction with reduced generalisation error.

Substantial criticism points to the ability of learning strategies to explain the results they achieve, beyond converging to optimality.

As a rule, highly complex models can lead to low interpretability and poor explanation of what mechanisms underlie predictions. In oncology, data modalities may reveal the insufficient size, and model results may present limited interpretability [51]. This means that data integration must be contextualised at the level of input raw data, features (extraction, selection and combination) and finally model outcome predictions. These levels are more or less convoluted, therefore characterising the strategies for data-to-feature-to-prediction transforms that enable IS performance assessment through measures and scores associated with the risk of disease onset, relapse, treatment response (Fig. 2).

Transfer learning

The bottleneck of data significance is often insufficiency of information. This problem calls for alternative learning approaches aimed to augment the space of features using, for instance, surrogate datasets. Such practice is foundational in Transfer Learning (TL) approaches [52]. TL algorithms reuse a model pre-trained over a new problem to improve its predictive performance by transferring knowledge about a related problem learned from auxiliary data. Examples are provided by drug sensitivity prediction [53], cancer classification [54], automatic lung CT image segmentation [55], etc. Domain-specific models can use importance/attribution methods to estimate the feature's contribution to the predictions (using prior or context knowledge).

DIFFERENTIATING FEATURES IN CANCER DOMAINS

The processing of NGS datasets has become increasingly time effective and routinely assisted by ML tools for executing accurate read alignment and robust variant calling tasks discriminating coding and non-coding bioentities (mRNA and ncRNA) by sophisticated multiplexed omics strategies. In terms of characterisation, a typical investigation target is subtyping, as this might affect treatment. A recent study [56] discovered patterns characterised by feature similarity and used to computationally classify five new subtypes within primary luminal A-type breast tumours. The impacts involve further development of targeted drugs and potential improvement of therapies/immunotherapies at an individualised patient level. Another pan-cancer study [57] used DL with multimodal data to find molecular subtypes, together with genetic mutations, gene expression signatures, and pathology biomarkers, by exploiting histology from tissue slides of >5000 patients across multiple solid tumours. In addition, a key aspect is timely monitoring to track progression or regression or target the emergence of resistance. This goes beyond traditional metrics (RECIST) to assign a central role to the interplay between different tumour cells and the immune response in the tumour microenvironment (TME). Emerging DL applications in digital pathology treat this domain to better stratify patients and identify relevant biomarkers predictive of clinical outcomes and treatment response [58].

Cancer immunograms [59] describing the interactions between cancer and the immune system, and in general, the integrated picture of immune oncological profiling [60], are present among the IS research developments. Gene expression signatures are ideally either prognostic (telling about patient prognosis with therapy or not) or predictive (telling about treatment benefit, typically within randomised controlled clinical trials). However, the fact of being non-specifically immune-related can bring to the loss of important information associated with patient outcomes. Other data augmentation strategies can be supported by supplementary patient data points provided from new data sources (patient-generated outcomes, sensors, wearables, implantable electronic devices, etc.). Here, the risk is learning features from data with some types of imbalance (skewed distributions force classifiers to be trained with bias). The problem is what model should be used, considering that both under- and over-sampling approaches can, respectively, downsize or upsize the classes depending on their large or small size. Clustering methods can mitigate under-sampling effects in data while common solutions to over-sampling are considered SMOTE [61] and ADASYN [62]. Selection and collider biases are also problems. Associations between risk factors and outcomes can be induced at the individual versus sample level, thus affecting the likelihood of an individual being sampled and distorting the associations between the variables in the sample. Of relevance here are a double negative effect, lack of generalisation (beyond the sample), and inaccurate inference (within the sample), especially with collider bias (various tools are nevertheless available [63]).

Predictive analytics

Predictive analytics holds great promises for clinical decisions and genomic-driven risk stratifications but crucially needs prospective validation and bias control to become an automatically embedded feature of any IS learning approach. Data heterogeneity, although highly informative, plays against a comprehensive coverage of endpoints. Support may come from EHR capturing multifaceted data, identifying patients that meet inclusion-exclusion criteria and delineating reachable endpoints. Within omics, data integration strategies try to process data both horizontally (same omics across different studies, thus automatically reducing the patient stratification depth), and vertically (different omics applied to the same samples to directly deal with multidimensionality, genotype-phenotype correlation, and biomarker discovery). However, the applicability of these strategies is ultimately cancer type-dependent and particularly challenging when inference is conducted at a pan-cancer level. Here, some form of control of complexity should be reflected onto models extracting features to verify significant associations across cancers and/or estimating the effects of perturbed conditions. For example, to uncover latent molecular signatures, integrative omics approaches should aim at profiling specific omics-related data with harmonised criteria. As cancer heterogeneity remains in large part undeciphered, it is worth considering approaches able to balance the role of influential variables that are either partially observable/measurable or latent. These variables potentially trigger early detection in cancer and are usable in latent variable models to provide accurate quantifications of risk of relapse and warning signals of emerging resistance [64].

Reinforcement learning

Harnessing cancer data for clinical translation has guided IS toward emerging directions [65]. IS development represents an inherently elastic process that adapts rapidly to contextualised data structures and targets the salient characteristics helping the models to be efficient and accurate. A trade-off between structural data and algorithmic complexity guides model selection depending on the relevance of the needed information and experiments. In such regards, the value of information (VoI) inherent to the context is an important factor defined in principle by a ratio of benefits over costs, i.e., survival or quality of life gains versus costs of discovering biomarkers, administering therapy, avoid side effects and similar criteria. VoI tends to correlate value also with data volumes (genomics, proteomics, histopathology, radiology, etc.) due to the analyses needed by them (say, tissue diagnostic analysis [66], informed decision-making, optimal trial design, etc.) [67, 68].

Among their scopes, IS allow to better prioritise modifiable factors and accelerate the identification of patients at high risk of adverse events. This is the area in which *reinforcement learning* (RL) approaches may support the development of personalised treatments. RL aims at optimising the prediction performance by processing a series of trial and error moves while considering the feedback received from the environment (or context) and the rewards assigned to the trials. As the goal is to learn adaptively

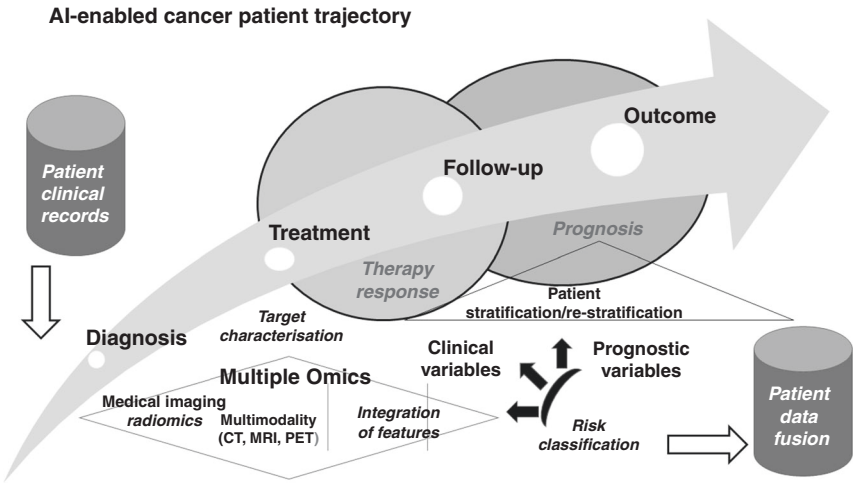

Fig. 3 Integrated View. The patient trajectory within the cancer data workflow.

(policy) how to maximise a reward function (health), the target with treatment becomes a dynamic process (drug administration, how it evolves and how personalised is the policy). Examples come from adaptive radiotherapy in synergy with immune modulators [69], with AI assisting with the adaptive planning process, or dynamic treatment regimes [70–72]. In both cases, a nonlinear feedback control problem is manifested and the support to decisions comes from selected actions for inferring the outcomes given the uncertainty of their interactions with the environment and possible delayed effects (feedback). RL has been evaluated in cancer screening [73] and to enable clinical decision systems at the point of care aligned with evidence-based data. In general, RL responds to the need of achieving superior reproducibility, quality control, interpretability, and generalisability standards (toward different endpoints within the same patient cohort, different patient cohorts within same cancer, different cancers). Hence, comparing datasets through benchmarks for assessing robust validation, even with deficient data, is a crucial issue [74].

EMERGING APPLICATIONS

Integrative radiomics

Radiomics represents a natural complement to radiology in the assessment of early prediction of response to treatment. By characterising non-invasively intratumor heterogeneity by a myriad of features, radiomics adds value integrable with clinical information when assessing treatment outcomes. A main goal of radiomics is correlating the radiomic phenotypes with the genomic profile. Radio-genomics [75, 76] goes in this direction to better predict genotypic traits based on raw images and transformed features. Similar principles hold for radio-metabolics [77] and theranostic [78] and other hybrid approaches like pathoradiomics (a recent study [79] differentiates NSCLC subtypes and novel tumour-immune response pathomics-based DL classifications in TME [80]). There are challenges associated with the clinical translation of radiomic results (as per the recommendations related to applications that come from the National Clinical Trials Network [81]), although the potential discoveries have been only weakly validated so far and need to be consolidated. Other major problems are summarised in a few needed actions: (i) standardisation of the image acquisition parameters, (ii) harmonisation of results, (iii) share of pre-/post-processing steps in image analyses. In such regards, fused radiomics [82] (especially multimodality [83, 84]) and integrated radiomics (joint profiling with genomics, metabolomics, pathomics, holomics, etc. [85]) are the domains that promise to progress in the next future.

Of general interest is the variation problem [86]. Problems of a technical nature, together with the inherent aspect of patient variability, call for statistics and signal processing techniques that can deliver stable feature indexes and robust models. The features with explainable variability are considered the most informative for inference and predictive for generalisability. In such regards, *habitat delineation* [87–89] is a strong direction of study aimed to identify subregions with distinct characteristics, such as radio resistance. After the initial focus on image mining [90] and the significance established for delta radiomics [91–93], the delineation of habitats has gained popularity because of the specificity assigned to the tumour partitioning targeted to TME studies and impacting future immunotherapy. Standard validation strategies and multiple approaches are needed to prove performance quality and reproducibility aspects at the level of previously adopted standards, such as the *radiomic quality score* (checklist to ensure the quality) and the *phantoms* used to investigate reproducibility and stability of CT, PET or MRI radiomic features at single or multiple sites.

Internet of medical things

Internet of Medical Things (IoMT) [94, 95] is strongly connected with ML and in particular DL concerning fine-tuning segmentation and sub-type identification problems for which joint radio-pathomic signatures are sought [96]. Here, imaging findings have been useful to predict response to treatment via DL algorithms offering increased efficiency (speed and cost reduction) and accuracy (improved quality of images and their interpretation). What is still lacking is the generalisability of the approaches and the ability to translate the high-tech content results of these studies into clinically valid applications. Both discriminative and generative DL models are employed and network refinements are implemented by a mix of feature engineered methods (mathematically transformed to reduce error in modelling the target) and non-engineered methods, both types finding utilisation also in distributed radiomics (e.g., multicentre studies [97–99]).

OUTLOOK

Building systems-level value of information

Methods' specificity can concretise into data overfitting when the performance is measured for new data over which the results should be generalised. Being the use of DL pervasive, until this suffers from a certain lack of full interpretability due to the black-box learning paradigm, a good part of data-intensive cancer research can have only a reduced impact. The data integration strategies aimed to gain statistical power do not follow standard

solutions yet. In principle, the VoI of integrated datasets may be summed linearly or combined in more sophisticated ways depending on the systems' uncertainty level, thus driving decisional processes to take advantage of decision trees and similar model structures.

Discovery is usually leveraging hypothesis generation that iterates through an automated cycle (measuring, validating, and automating) ending with predictive modelling for decision support. The IS added value in this cycle is ultimately defined in terms of better outcomes obtained at a lower cost, which implies the fusion of streams of information over time (Fig. 3). In radiomics, for instance, focusing on signatures and profiles requires detection of 'hard data' vulnerabilities [100], which might be amplified when searching for robust gene expression programs through multiple normalisations [101], elucidation of phenotype transitions, insights into therapy resistance, characterisation of TME, etc. These factors motivate an increased use of systems and network approaches for future applications. On the other hand, 'soft data' such as EHR, personalised and dynamic treatment data, disease trajectories, risk profiles, and scores for patient stratification are products of dynamical processes centred on patients. As such, the data distributions are subject to drift over time, causing the ML model to lose predictive power.

The sketch in Fig. 3 represents the complexity underlying the process of assembling various data types for stratification purposes at both population and individualised scales. The data distributions depend on factors that are endogenous and exogenous to the patient. Therefore, full reliability of data through the process requires continuous testing. Explaining the possible ways uncertainty can affect models remains quite difficult as well as it is problematic the interpretability of results through the usual metrics. In perspective, support to clinical decision systems in oncology will require dynamic IS calibration strategies for uncertainty control.

Impacts in clinical practice

Two main factors limit the impact of big data and IS in clinical practice. First, in view of the multiple data dimensions associated with novel drug discovery strategies and therapies, changes may be expected in the clinical trials [102–104]. Second, an increased input heterogeneity tends to make inference more convoluted and requiring specialised methodologies assigning specific roles to various types of intervention solutions (coming from software engineering, analytics, decision processes, etc.) in support of clinical evidence [105, 106]. With few exceptions [107–109], most translational studies are retrospective and not prospective [110]. This limits the ability to measure the IS generalisation performance and calls for high-quality reporting to mitigate potential problems related to data and algorithmic biases, confounders, etc. [111]. In turn, this further stimulates the adoption of model confidence measures to facilitate cross-domain applicability and reproducibility of findings [112].

Important initiatives are TRIPOD-ML [112, 113], SPIRIT-AI and CONSORT-AI [114, 115]. Algorithm-related aspects like quality control, model recalibration and retraining performances should be checked under varying conditions but also account for features reassessment with evolving clinical and operational practices. FDA guidelines were recently introduced with a regulatory framework for software-guided medical devices that must include predetermined change control plans. The sphere of opacity or ambiguity in IS models is also involved with the DL processing of unstructured data that represents an additional complex step toward inference (like multiple hidden layers or special optimisation functions). Some promising models have mitigated the overfitting effects: for instance, *Deep Forest* (or *gcForest*), applied to lung cancer staging with a decision-fusion strategy conservative in the parameters used over multimodal genetic data [116].

The clinical feasibility of large data IS studies depends on the generalisability of results across different populations (due to age, gender, ethnicity factors), despite the effects of biases (from training over historical data with size gaps and disparities) and confounders on the model outcomes. Consequently, validation concerns (choice of the dataset, selected criteria for significance assigned to variables, model discrimination, etc.) emerge. The usefulness or expected performance of sound algorithms is not sufficient to justify adoption and integration into clinical workflows. Accepting less accuracy from a 'black-box' learning machine may lead to gains in terms of transparency and interpretability, but assuming this balance is achieved, the risk is to rely on oversimplified models guiding the complex decision. Ultimately, the key question remains whether model results are beneficial to patients. Therefore, any adopted metric should prioritise and quantitatively measure the net benefit of using a certain model to guide actions and decisions with an appropriate outcome-driven model design. The continuous expansion of phenotypic knowledge bases of reference clinical datasets across populations and open software analytics platforms allowing reproducibility of results support this direction offering opportunities for testing and validating models by cross-referencing the findings over independent datasets while fine-tuning the methods (i.e., by ranking performance factors and applying standards for algorithm fairness and best practice recommendations to train-retrain and calibrate). Such developments will be likely inducing a revision of the model prediction paradigm [117, 118] and exerting effects on effective translation to clinical practice together with further propelling prospective studies.

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