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ORIGINAL ARTICLE

Why imaging data alone is not enough: AI-based integration of imaging, omics, and clinical data

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Abstract
Artificial intelligence (AI) is currently regaining enormous interest due to the success of machine learning (ML), and in particular deep learning (DL). Image analysis, and thus radiomics, strongly benefits from this research. However, effectively and efficiently integrating diverse clinical, imaging, and molecular profile data is necessary to understand complex diseases, and to achieve accurate diagnosis in order to provide the best possible treatment. In addition to the need for sufficient computing resources, suitable algorithms, models, and data infrastructure, three important aspects are often neglected: (1) the need for multiple independent, sufficiently large and, above all, high-quality data sets; (2) the need for domain knowledge and ontologies; and (3) the requirement for multiple networks that provide relevant relationships among biological entities. While one will always get results out of high-dimensional data, *all* three aspects are essential to provide robust training and validation of ML models, to provide explainable hypotheses and results, and to achieve the necessary trust in AI and confidence for clinical applications.

Keywords Precision medicine · Artificial intelligence · Machine learning · Decision support · Integrative computational biology · Network-based analysis · Radiomics

Data explosion and the vital need for high-quality data

First and foremost, the biggest problem in the AI world is the quality and sufficient volume of data. The most successful machine learning methods are data hungry [1], and extremely sensitive to poor data quality [2]. In the medical domain, data quality (i.e., completeness, correctness) is further extended by confidentiality requirements, and the need for comprehensive annotation. It is amazing how bad the standard data sets in the medical domain are (noisy, sparse, wrong, biased, etc.), which was already described by Komaroff in 1979, when he stated that "the taking of a medical history, the performance of the physical examination, the interpretation of laboratory tests, even the definition of diseases, are surprisingly inexact" [3]. Unfortunately, with the introduction of sophisticated electronic patient record systems this is often even worse today, as incorrect data escape routine checks and the errors are compounded across computational workflows, frequently increasing clinical errors [4]. Therefore, within a whole ML pipeline the aspect of data processing is of utmost importance. Consequently, for AI applications to be successfully applied to the medical domain, an *integrative machine learning* approach might be necessary [5], calling for the integration and fusion of heterogeneous data sets, e.g., images, physiological data, text (non-standardized"unstructure" and structured patient records), and diverse omics profiles (gene, microRNA, protein, metabolic, etc.) [6].

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Generally, in the health domain one can identify different areas of data volumes depending on the medical context in which they have been created [7]:

- Patient data from the electronic patient records (EPR), including clinical reports, mainly unstructured information in written clinical reports, but also lab test data, and all types of biomedical signals (ECG, EEG, EOG, etc).
- Imaging data, e.g., from radiology, pathology (whole slide images), dermatology (dermoscopy), but also sonography, etc.
- Biomedical research data, including clinical trial data and all sort of omics data, particularly from next-generation sequencing (NGS), etc. In addition to this data, which is produced in a clinical environment, more and more data is being generated outside the clinical sector, i.e.,
- Health business data, including management data, logistics, and accounting but also more and more prediction (e.g., resource planning);
- Private patient data, produced completely outside the clinical context, which is fostered by the possibilities of modern low-cost smartphones such as sport data, wellness and data for ambient assisted living (sensor data)

The US Department of Health and Human Services (HHS) created a taxonomy of health data with the following seven dimensions:

1. Demographics and socioeconomic data including age, gender, education, etc.
2. Health status data, including disabilities, diagnoses, and symptoms
3. Health resources data including the capacities of the health system, performance and operating data
4. Health-care utilization, including data about treatment and duration
5. Health-care cost and expenditure data, including charges, insurance status, etc.
6. Health-care outcomes of current and past prevention, treatments, etc.
7. Other data including omics data, but also environmental exposure data such as environmental impacts, etc.

Reproducibility is another recognized but still mostly ignored issue. Currently, there is a huge trend in the opposite direction: most scientific contributions are judged according to their novelty—rarely for their reproducibility, which would be the essential criteria of good science—see the recent debate in Science [8]. A typical example is that the data are considered as inaccessible due to ethical restrictions. Data protection is of course an issue but there must be solutions to publish data along with the results and the international scientific community should be invited to reproduce the results, for examples and a discussion see [9].

Integrative computational biology

Developing effective knowledge systems to support the governance, processing, inference, analysis and interactive visualization of integrated omics data is critical to maximize the impact on translational research. The importance of visualization is often underestimated, but it is the quality of the visualization that enables the experts end users to understand the data in the context of their problems [10]. Visualization enables more accurate and relevant modeling of healthy and disease states, and in turn support precision medicine [11].

Integrating layers of omics data

Understanding complex diseases (e.g., arthritis, brain disorders, cancer) requires computational analyses that integrate diverse layers of data—imaging data, omics profiles, clinical data, and annotations. Such complex data needs to be analyzed using scalable data mining, machine learning and statistical methods. In turn, comprehensive integration, further analysis and modeling requires detailed annotations and relationships among these entities (see Fig. 1). Such integrated network-based analyses help create and validate explainable disease models, and enable improved treatments strategies and patient outcomes.

Radiomics can aid this process (see Fig. 1), by providing additional features for the analysis, improved disease characterization and patient stratification. Radiomics enables more accurate disease classification than traditional disease grading; for example, it significantly improves sensitivity of identifying structural knee osteoarthritis [12]. Imaging data can provide integrated in the ”front end” by supporting cancer detection Cameron-2016, characterizing micro-environment [13], tracking tumor biology [14], cell proliferation, and blood vessel formation [15]. This can aid in more precise and earlier tumor detection and sybtyping [16], more accurate staging, treatment planning, prognosis [17], and non-invasive response monitoring [18–20]. From the machine learning perspective, this helps reducing noise and heterogeneity. Radiomics can also be integrated in the ”back end” by helping quantifying disease dynamics and predicting response to treatment [21] through series of “digital biopsies”.

From individual biomarkers to signatures

One of the central tasks in precision medicine is the identification of groups of markers for aiding diagnosis,

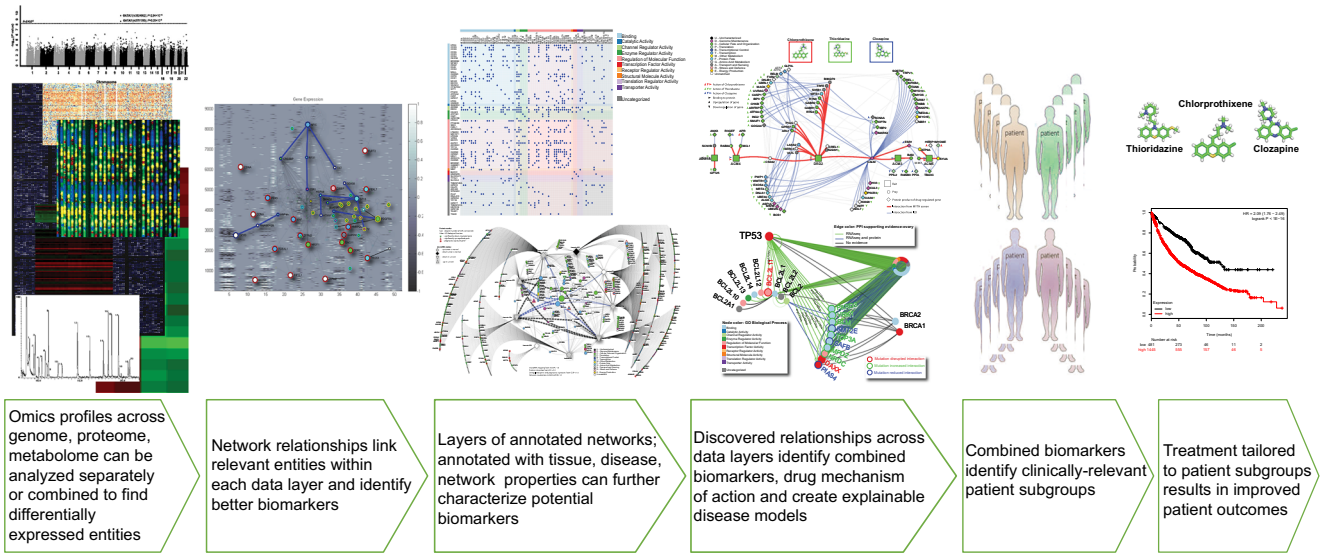

Fig. 1 Network-based omics data integration and analysis

and for predicting risk and treatment outcome. The discovery and validation of such biomarkers is a complex and computationally intensive process, utilizing advanced statistics and ML algorithms. Both unsupervised data exploration and pattern discovery methods are useful. An ideal approach is one that characterizes each sample on the basis of a small number of biologically relevant, pathway-related variables, integrating omics data with imaging and clinical data.

Current radiomics studies usually use smaller cohorts, extract many features, and have limited validation across different instruments, leading to overfitting and in turn overoptimistic results that do not generalize. An overfit signature or model contains more features than could be justified from the training data set. Recently, Phantom study [22] explored reproducibility and robustness of radiomic features for MRI, concluding that large fraction of imaging features lack robustness. Standardizing instruments and protocols will lead to ability for integrating larger datasets, and validating signatures and models on independent datasets. This will increase generalizability, and in turn will help increasing reproducibility and robustness. In turn, using robust features will result in better classifier performance Robinson-2019.

Many methods have been introduced to generate useful biomarkers from individual and combined layers of omics, imaging and clinical data, but results remain unsatisfactory; existing methods often suffer from overfitting due to small numbers of samples. Proposed biomarkers frequently do not validate using other biological assays or on a different cohort of patients [23–25]. Reasons for such failures include: (1) patient and sample heterogeneity, (2) range of biological assays with different technical and analytical biases, (3) diversity of statistical and bioinformatics algorithms and annotation databases used, (4) disproportionately many more variables than samples analyzed, (5) and existence of multiple, clinically equivalent biomarkers that basic statistical and ML algorithms cannot distinguish. A promising alternative to the brute-force approach that works in the space of expression levels of thousands of genes, microRNAs, metabolites or proteins takes advantage of relationships among these entities and identifies a small number of biologically relevant, network-structure or pathway-related variables, integrating high-throughput, imaging, and clinical data.

Successful biomarker discovery and building explainable models require integration of diverse and heterogenous databases, ontologies and biological networks. Ontologies and pathway/network annotations come from diverse, distributed repositories, including Gene Ontology (http://www.geneontology.org), Uniprot (http://www.uniprot.org), ProteinData Bank (http://www.rcsb.org), Disease Ontology (http://disease-ontology.org), Online Mendelian Inheritance in Man (http://www.omim.org), DrugBank (http://www.drugbank.ca), DisGeNET (http://www.disgenet.org), The Comparative Toxicogenomics Database (http://ctdbase.org), Integrated Interactions Database (http://ophid.utoronto.ca/iid), pathDIP (http://ophid.utoronto.ca/pathDIP), etc. (see http://omictools.com/ for extensive list).

Network-based computational biology

Successful network-based methods for class prediction take advantage of network modules to identify score-based sub-network biomarkers. This could take advantage of identifying network structures (complexes, graphlets, hubs and articulation points, etc.) or identifying overlap with curated pathway databases. Multiple studies have shown that resulting biomarkers are highly conserved across studies.

These analytics workflows have to integrate diverse heterogeneous data, comprising confidential and publicly available data, local and broadly distributed data and annotations. Some parts of the analysis may strongly benefit from GPU (graphical processing unit) accelerations (image feature extraction algorithms, deep neural networks, graph analysis algorithms), while others require multi-core CPU (central processing unit) and large bandwidth/storage. Implementing such discovery pipelines using automated workflows [26] support efficiency, increase validation rates and reproducibility [27]. Combining results of such analyses with diverse biological networks, including transcription regulatory, protein interaction and microRNA:target networks, and metabolic and signaling pathways, with transcriptional changes induced by drugs [28] enables modeling drug mechanism of action. In turn, radiomics can help predict [29] and measure treatment response [30].

Interaction networks underlie the genotype to phenotype relationship, understanding of which is the prime goal for a system's view of the cell, tissue or organism. While each omics data layer can be analyzed separately, integrating findings across data layers using biological networks enables discovering new results through these relationships. Integrated data and network models reduce biases, improve coverage and quality by eliminating noise and using reinforcement learning strategy to strengthen the signal [31].

Applications of "integrative radiomics" include combining radiomics features from MRI with peak area features from MR spectroscopy (prostate cancer), integrating histomorphometric features with protein MS features for predicting 5-year recurrence (prostate cancer), or integrating volumetric measurements on MRI with protein expression features (Alzheimers' diagnosis) [32]. Importantly, fMRI data analysis helps creating complex network structures, such as structural brain network [33], neuro-connectivity after brain injury [34], or schizophrenia characterization by functional connectivity [35]. All such application would benefit from all the graph theoretical algorithms developed mainly for protein interaction network analysis and characterization (e.g., [36, 37]).

Resulting multi-modal data can be further analyzed and visualized using algorithms from graph theory, and identify patterns characterizing graph structure-function relationship. Linking network structure to properties of genes and proteins that form it provides powerful method for predicting function [36, 38–40], identifying robust biomarkers [41, 42], and modeling drug mechanism of action [43, 44].

Integrated network-based analyses will lead to improving data interpretation, help generating testable hypotheses, and creating biologically meaningful models with clinical relevance [6, 45]. Importantly, broad imaging modalities and diverse image data analysis algorithms will lead to robust biomarkers for diagnosis and prognosis, but especially non-invasive monitoring of response to therapy [21]. Examples include molecular, functional and anatomical imaging and image feature extraction [46], including CT, ultrasound, magnetic resonance imaging, magnetic resonance spectroscopy, positron emission tomography, etc. Imaging helps to identify subregions for further omics studies [47]. Networks bring individual data layers together, help de-noise individual data sets, validate models, and explain results [31].

Despite noise present in interaction data sets, their systematic analysis uncovers biologically relevant information: lethality and synthetic lethality, functional organization, hierarchical structure, modularity, and network-building motifs. Synthetic lethality has been first explored by synthetic genetic arrays to study genetic interaction in yeast [48], then highly explored using graph theory algorithms (e.g., [36–38, 49]), and understanding of these principles resulted in applications for predicting drug combinations (e.g., [44, 50]. As such, network-based analysis of patient data is essential for developing stratified and patient-centric treatment strategies. Besides improved analytics and scalability, medical applications also require reliability, robustness, and explainability. This allows transitions from patterns and correlations to causation and explainable models [51]. As such, they will provide "an intellectual prosthesis" for the domain experts, striving for augmented rather than just "artificial" intelligence.

AI for precision medicine

AI holds great promise to revolutionize cancer care and bring precision medicine closer to reality [52–54]. There is an urgent need to invest in collecting, curating and annotating the data and developing the algorithms necessary to implement AI tools to optimize research and care [55]. We describe below the opportunities provided by AI for precision medicine.

Biomarker discovery

Developing biomarkers for cancer diagnostic, prognosis and prediction of therapy response or adverse side effects constitutes one of the main challenges in precision medicine. Combining the established clinical parameters with other non-invasive measurements from radiological images, blood or urine samples, would allow us to develop better predictors of clinical outcome and improve monitoring of treatment effects over the course of the therapy. Deep neural networks have recently been used to extract more information from radiological images, a relatively new field referred to as radiomics [56], and intense research is being pursued to further integrating multiple data modalities for higher accuracy [57].

Imaging and genomic data have been shown to carry redundant and complementary information to develop biomarkers. For instance, Sun et al. showed that it is possible to develop a radiomics signature from CT images as a surrogate for the level of CD8 cell tumor infiltration quantified using RNA-sequencing [58]. This is an important finding, as it provides a non-invasive way to quantify the level of tumor infiltrated lymphocytes (TILs), an important pathological measurement during immunotherapy). However, molecular profiling from tumor biopsy or blood draw may reveal genomic aberrations that are undetectable from images, supporting their complementary value with image-based features.

In addition to biomarkers developed from data directly measured in clinical settings, the massive amount of imaging and genomics data generated in the pre-clinical and research settings can be used to build novel predictors of therapy response. Images and genomic data collected during drug testing *in vitro* (e.g., established cancer cell lines or patient-derived organoids) [59–61] and *in vivo* (e.g., genetically-engineered mouse models or patient-derived xenografts) [62] is a prime example of the richness of data that can be analyzed using AI methodologies to improve clinical predictors.

Image segmentation

Imaging technologies are omnipresent in cancer research and healthcare. AI, especially deep neural networks, already demonstrated superior performance in image classification and segmentation of natural images compared to other machine learning approaches [63]. AI tools are being developed to optimize the current workflows in radiology and pathology [64]. Tumor and lymph node delineations are complex and lengthy tasks performed by radiologists and radiation oncologists and represent bottlenecks for radiation therapy and monitoring of treatment effects, which can be overcome by the use of AI tools for (semi-)automated segmentation of radiological images [65]. AI-based segmentation will not only save time but will also decrease the inter-observer variance that is currently high in clinical settings, enabling clinicians to better identify and monitor lymph nodes that either benign or at risk of being invaded during tumor progression. Cardenas et al. outline the most recent deep learning approaches using in radiology showing unprecedented performance but also poses serious challenges for their clinical deployment [66]. Notably, these challenges include the retraining of the deep learning model on new data for calibration and performance improvement, as described in the recent FDA while paper on this topic.[1] Similarly, AI can help pathologists speed up and increase the reliability of the diagnosis based on histo-pathological slides. Moreover, AI-based tools can be developed to go beyond current diagnostic capabilities and allow for more comprehensive identification of cell types and their associations with aggressive phenotypes or response to targeted and chemotherapies.

Natural language processing

Rich clinical data are embedded into dictated and transcribed clinical notes. Recent advances in AI for natural language processing (NLP) allows for automated and efficient extraction of discrete data elements from these clinical notes [67]. NLP methods can be used to parse the large amount of physicians' notes, pathology reports, radiology reports and other free-form clinical documentation sources generated in clinical trials and standard-of-care. This is essential to provide context to other data types, such as radiological, histo-pathological images and genomics.

Ontology learning

While vast amounts of heterogeneous data are collected in administrative, clinical and research databases, integration and classification of these rich data sets are challenging due to the use of different systems involved in data collection and storage. Data across these various systems are often coded inconsistently, and lack the defined context required to fully understand the relationship between different data concepts. Increasing use of coding standards and the application of ontologies to these heterogeneous data sets will help ensure the data is optimally classified and integrated to enable advanced analytics. AI-based methodologies can be used in NLP and ontology learning

[1] https://www.regulations.gov/document?D=FDA-2019-N-1185-0001

to build and apply ontologies to better annotate and connect data assets across the institution. Ontology learning is the (semi-)automatic creation of ontologies, extracting the domain's terms and the relationships between the concepts that these terms represent from a corpus of natural language text, and encoding them with an ontology language for easy retrieval [68]. As building ontologies manually is extremely labor-intensive and time-consuming, there is a great need to automate the process using recent AI-based ontology learning applied to oncology, allowing us to annotate and connect data at the scale of multiple institutions.

Patient-reported outcomes

Learning more about the phenotypes of the patients (disease, treatment response, adverse side effects, survival) is crucial enable more relevant analyses of biomedical data [69]. AI enables collection of health-related data from the patients through the use of healthcare bots able to mimic human conversations, incorporate NLP, sentiment analysis, and perform image recognition tasks to analyze photos, handwritten notes and barcodes related to the patients' diseases, medications or treatment side effects [70]. AI-based solutions can be used to better engage the patients and collect high-quality patient-reported outcomes in a systematic way. Such patient-reported outcomes can then be used as output variables to predict from imaging and/or other data types, therefore enriching the pool of clinical questions that can be addressed using machine learning approaches.

Monitoring patients with wearable devices

Wearable devices hold the promise to complement patient-reported outcomes with longitudinal data streams for a more comprehensive assessment of symptom progression, requiring minimal patient interventions to inform their physician on their health status [71]. These devices are becoming increasingly popular among the healthy population and cancer patients. Although the current sensors are limited to a few vital signs and are still pending regulatory approvals, the technology is evolving fast and are being applied in clinical trials for a variety of diseases. AI methods have the potential to efficiently integrate these new data streams in clinical applications, while important challenges remain to be addressed regarding possible artifacts due to noisy sensors or incorrect use by the patients, and issues about patient privacy. Wearable devices can supplement current patient information to provide clinicians with a more accurate view of the habits and needs of their patients, allowing for treatment to be more tailored and effective.

Future challenges and opportunities

One of the grand objectives of the AI community is to develop algorithms that can automatically learn from data and to provide predictions—without any human interaction, called automatic or autonomous machine learning (aML). A close concept is automated ML (AutoML), which focuses on end-to-end automation of ML and helps, for example, to solve the problem of automatically producing test set predictions for a new data set - without any human interaction [72]. Such automatic approaches are currently very successful in daily routine and can solve already a number of problems in an sufficient manner. Standard best-practices include the advances achieved with deep learning models in automatic speech recognition, autonomous driving or game playing without human intervention. Here the current best example is the mastering of the game of Go, which has a long tradition in the AI community and is indeed a good benchmark for progress in automatic approaches [73].

However, all these approaches are limited to certain tasks in a very narrow field of specialization and totally lacking human-centered aspects, e.g., emotion, which is influencing cognition, perception, learning, communication and decision making [74]. Such approaches are not yet applied in the medical domain or on very specific small-scale problems. The currently best performing working examples are in automatic image classification, which are on par with medical doctors or even outperforms them [75]. However, bio-medical applications are diverse and as such, there will only be some parts fully automated, while other will require human experts involved in the decision-support process – one size will not fit all. Importantly, considering the complexities of medical decisions and liability, we will get further and faster by empowering/augmenting experts with AI-technology rather than replacing them, using the human-in-the-loop concept [76] or at least put the human-in-control. Using AI/ML solutions as an augmenting/assistive technology [77] has the benefit that both can complement each other, the human and the machine. To date, only human experts are able to understand the overall context [78].

Definitively the future will be in integrative approaches: Integrative omics will link biopsy or liquid biopsy to provide time-course view of disease progression and treatment response, effective and efficient analytic pipelines will ensure scalable and reproducible results, diverse networks will help link relationships among measured entities across multiple data layers and build explainable models, which in turn will provide improved hypothesis generation, validation and translation into clinical practice. A look further is in bringing wearable devices, which will enable a true "patient-centric" approach—as each patient's data over

time will be compared not to other patients with a similar condition/symptoms; rather, to their own, long-term data.

Finally, reproducibility, cost-efficiency, acquisition time, resolution and resulting confidence and precision are vital. AI and ML will become mainstream in the medical field, but cohort differences, instrument and protocol variations, overall data quality, integrity and relevant annotation are paramount. The goals of comprehensively integrative systems are not just classification; instead, the most useful application will be helping human experts discover new knowledge, form new questions and help explain and comprehend complex biological states and processes.

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Compliance with Ethical Standards

Conflict of interest Author AH declares no conflict of interest. Author BHK declares no conflict of interest. Author IJ declares no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Appendix: Abbreviations

AI ...	Artificial Intelligence
CPU ...	Central Processing Unit
CT ...	Computer Tomography
ECG ...	Electrocardiography
EEG ...	Electroencephalography
EOG ...	Electrooculography
EPR ...	Electronic Patient Record
fMRI ...	Functional Magnetic Resonance Imaging
GPU ...	raphical Processing Unit
ICD ...	International Classification of Diseases
ML ...	Machine Learning
MRI ...	Magnetic Resonance Imaging
NGS ...	Next-Generation Sequencing
SNOMED CT ...	Standard Nomenclature of Medicine Clinical Terms
TILs ...	Tumor Infiltrated Lymphocytes

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