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# Applied machine learning in cancer research: A systematic review for patient diagnosis, classification and prognosis



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## ABSTRACT

Artificial Intelligence (AI) has recently altered the landscape of cancer research and medical oncology using traditional Machine Learning (ML) algorithms and cutting-edge Deep Learning (DL) architectures. In this review article we focus on the ML aspect of AI applications in cancer research and present the most indicative studies with respect to the ML algorithms and data used. The PubMed and dblp databases were considered to obtain the most relevant research works of the last five years. Based on a comparison of the proposed studies and their research clinical outcomes concerning the medical ML application in cancer research, three main clinical scenarios were identified. We give an overview of the well-known DL and Reinforcement Learning (RL) methodologies, as well as their application in clinical practice, and we briefly discuss Systems Biology in cancer research. We also provide a thorough examination of the clinical scenarios with respect to disease diagnosis, patient classification and cancer prognosis and survival. The most relevant studies identified in the preceding year are presented along with their primary findings. Furthermore, we examine the effective implementation and the main points that need to be addressed in the direction of robustness, explainability and transparency of predictive models. Finally, we summarize the most recent advances in the field of AI/ML applications in cancer research and medical oncology, as well as some of the challenges and open issues that need to be addressed before data-driven models can be implemented in healthcare systems to assist physicians in their daily practice.

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## 1. Introduction

Artificial Intelligence (AI) has recently made eminent progress in many areas, including medicine and biomedical research. AI, a branch of computer science, encompasses mathematical methods that enable the decision making or action, the rational and autonomous reasoning, and the effective adaptation to complex and unseen situations [1]. AI systems regroup several different algorithms originated from the subfield of Machine Learning (ML) to advance the automation of human experts' tasks leading to real and tangible results in healthcare. Given the digital acquisition of high-dimensional annotated medical data, the improvements in ML methods, the open ML data science and the evolving computational power and storage services, we could anticipate the tremendous progress of AI in the medical practice landscape [2,3].

Recently, the medical applications of AI have expanded to clinical practice, translational medicine and the biomedical research of various diseases, such as cancer [1,4]. Current AI systems, based solely on ML methodologies, have been applied to different aspects of clinical practice including: (i) the image-based computer-aided detection and diagnosis within many medical specialties (i.e. pathology, radiology, ophthalmology and dermatology), (ii) the interpretation of genomic data for identifying genetic variants based on high-throughput sequencing technologies, (iii) the prediction of patients prognosis and monitoring, (iv) the discovery of novel biomarkers through the integration of omics and phenotype data, (v) the detection of health status in terms of biological signals collected from wearable devices, and finally (vi) the development and application of autonomous robots in medical interventions [1].

Using AI/ML technologies in precision oncology and integrating them into clinical practice, however, raises technological challenges in model development [5,6]. Data curation and sanitization reduce the bias in collection and management preventing subsequently errors during the training and testing phases. These challenges along with social, economic and legal aspects should be considered before the deployment of AI/ML systems in medical practice to empower clinicians for better prevention, diagnosis, treatment and care in oncology. In addition, improving the performance, reproducibility and reliability of the AI/ML models would augment the work of clinicians by making better diagnostic decisions and tailoring the medical treatment to the patient's unique phenotype.

AI today is dominated by ML techniques capable of extracting patterns from large amounts of data as well as building reasoning systems for patient risk stratification and better decision making. For more accurate patient-level predictions and for modeling disease prognosis and risk prediction, data mining techniques and adaptive ML algorithms have consistently outperformed traditional statistical approaches [7]. ML-based techniques have the advantage of being able to automate the process of hypothesis formulation and evaluation, while assigning parameter weights to predictors based on correlates with the outcome prediction [6,8]. Despite this, the enormous promise of AI in cancer research should be carefully addressed alongside answers to the challenges of transparency and reproducibility [9–11]. To ensure the high potential of AI and ML in medicine and clinical trials, we need to adopt a

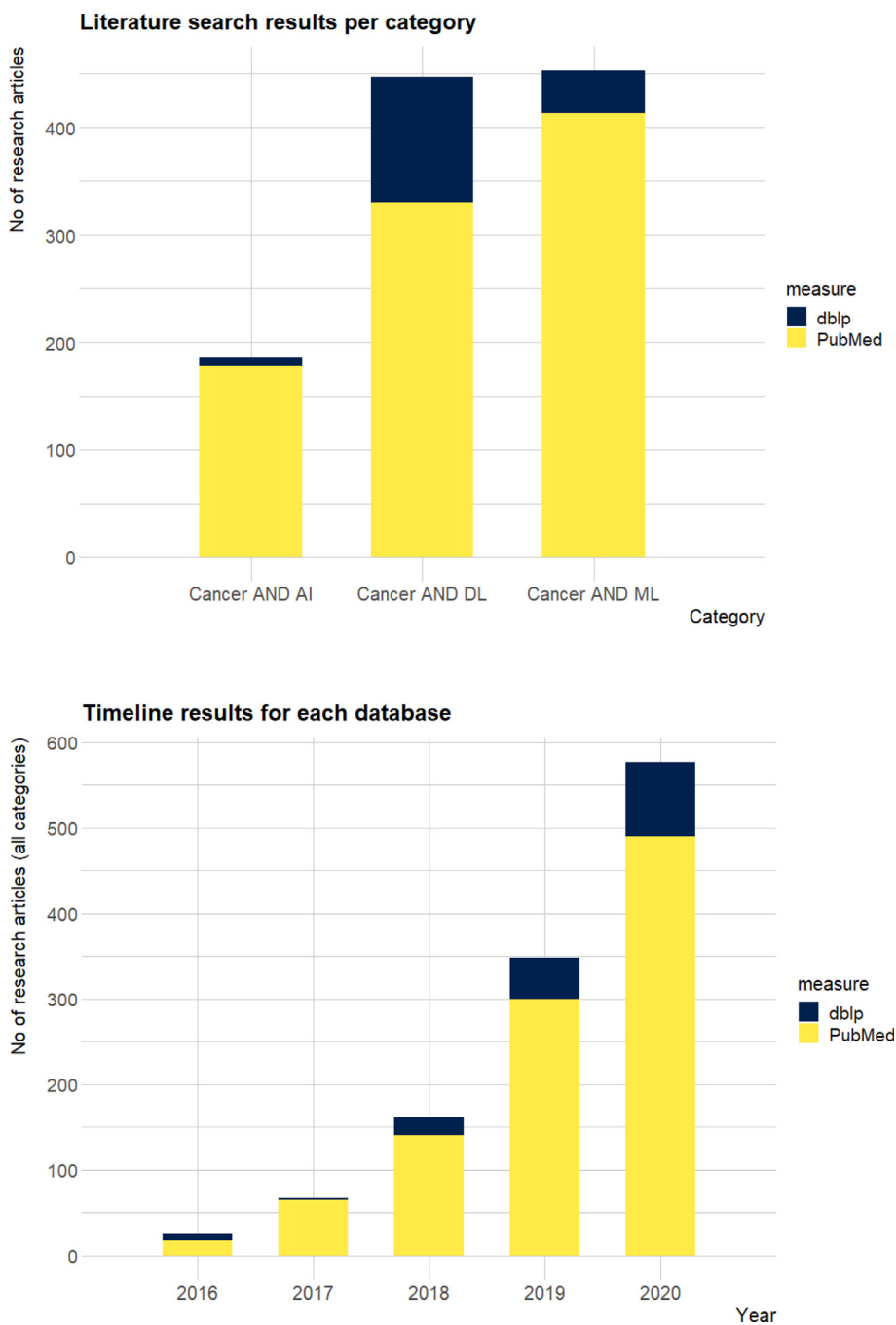
framework for making the scientific research more transparent and reproducible.

In cancer research and oncology, the successful application of Deep Learning (DL) techniques has recently demonstrated fundamental improvements in image-based disease diagnosis and detection [12,13]. Generally, DL architectures correspond to artificial neural networks of multiple non-linear layers. Over the last decade, a variety of DL designs have been developed based on the input data types and the study aim (s). Concurrently, the evaluation of the model's performance has shown that DL application on cancer prognosis outperforms other conventional ML techniques [14]. DL frameworks have been also applied towards cancer diagnosis, classification and treatment by exploiting genomic profiles and phenotype data [1,7,15].

In this review article, we focus on the ML aspect of AI-based applications in cancer research and medical oncology and present relevant studies that have been published the last five years (2016–2020) concerning the development of robust ML models towards patient diagnosis, classification and prognosis. The selection of the material was based on three clinical scenarios considering both the ML-based techniques and the heterogeneous data sources that were employed. We provide the search criteria of the literature review to obtain the most relevant studies, summarize the successful clinical scenarios towards applying robust and validated ML methods, discuss the state-of-the-art DL and Reinforcement Learning (RL) applications, present the impact of ML models in terms of robustness and explainability, identify the achievements and new challenges of ML-based systems in healthcare and discuss future research investigations along with the unsolved problems of reproducibility and transparency with possible solutions in the field. Systems biology and network-centered methods for computationally analyzing various sources of omics data and better comprehending the complex structures of biological processes and cellular components within cancer cells are also explained.

## 2. Literature review

The PubMed biomedical repository [16] and the dblp computer science bibliography [17] were selected to perform a literature overview on ML-based studies in cancer towards disease diagnosis, disease outcome prediction and patients' classification. We searched and selected original research journal papers excluding reviews and technical reports between 2016 (January) and 2020 (December). In the PubMed's advanced search option, we added the query terms "Cancer AND machine learning", "Cancer AND artificial intelligence" and "Cancer AND deep learning", separately, in the title field and not in the abstract to obtain the relevant studies. The same strategy and keywords were followed and applied to the dblp query search. According to our search results a total of 921 and 165 studies were found in PubMed and dblp databases, respectively, for the three queries. Duplicate studies and review or technical reports within the search results were excluded. A total of 734 research studies were further compared to provide a comprehensive overview of the application of ML and DL techniques in oncology research. We systematically reviewed the methods and outcomes of these research works and compared them until we



**Fig. 1.** The results of our literature overview on cancer diagnosis, patients' classification and prognosis. The upper part of the figure presents the literature search results per category when considering each database. The bottom part of the figure depicts the timeline (last five years) results considering the total number of articles for the three search queries.

identified the main clinical scenarios where ML methods are widely applied to enhance the automated decision support systems, the selection of appropriate treatments and the explanation of clinical reasoning.

The Tables showing the total number of studies identified in the preceding year for each search query in PubMed [16] and dblp [17] are given as [supplementary material](#) (Tables I-III). In the current work, we selected the most representative research from each clinical setting and provided a quick review of their key findings. To summarize the most current computational methods and clinical investigations in connection to early disease diagnosis, prognosis, and clinical outcome prediction for patient monitoring, we

examined primarily preliminary studies published in the last year in both archives.

In Fig. 1, we present the results of our literature overview on cancer diagnosis, prognosis and patients' risk stratification the last five years on both databases. In Fig. 1 (upper part), a group-based barplot illustrates the number of articles that were identified when considering each search query in the databases. Fig. 1 (bottom part) illustrates the timeline results for each database. The total number of articles as regards to the total sum of the articles within the three queries is depicted per year.

In the sections that follow we present briefly the popular and rising techniques of DL and RL along with their successful

application and impact in oncology research and clinical practice. The clinical scenarios we have identified according to our literature overview are clearly presented along with the relative publications in the next sections. These clinical scenarios are among the most successful domains of biomedical ML-based applications in medical oncology. We provide details on the facets of robustness and explainability when ML-based models are employed in the healthcare systems. A summary and outlook presenting the recent advances and new challenges for the application of ML models for automated decision making in the clinical practice is also given in the last section.

### 2.1. Deep learning in oncology research

The potential of AI/ML techniques in biomedicine and precision oncology has become apparent with advances in new ML methods for computer-aided diagnosis [7]. These new technologies have been also integrated into the clinical practice for improving patient outcomes and accelerating clinical decision making [14]. DL approaches, a branch of ML, have recently showed great help to physicians in medical oncology with the development of medical-imaging diagnostic systems trying to improve disease diagnosis and the early detection of tumors [18,19]. With the availability of huge amounts of data and the parallel and distributed ML frameworks for their analysis, DL architectures have emerged and are categorized into three groups: (i) the deep neural networks (DNNs) [20–22], (ii) the convolutional neural networks (CNNs) [23,24] and (iii) the recurrent neural networks (RNNs) [25,26]. DL architectures are essentially artificial neural networks with numerous non-linear layers. The key distinguishing aspect of DL is that the feature layers are learnt from data using a general-purpose learning method rather than being created by the user.

ML can be roughly divided into three paradigms: (i) the supervised task that includes a label/class, (ii) the unsupervised task where no label is provided and (iii) the last category of RL techniques where an agent is trained to perform actions sequentially. Supervised techniques are mainly applied in today's use of ML in automated patient-centered decision making with the decision trees (DTs), support vector machines (SVMs) or linear regression being the most common algorithms [27]. Based on the traditional ML techniques the main descriptors or variables are used to train a model and extract patterns and reasonable representations of feature vectors relevant to the problem under study. Despite this, the ability of conventional machine-learning approaches to analyze natural data in its raw form is limited. On the other hand, nowadays, DL (i.e. the implementation of multi-layered neural networks) has gained a lot of attention for their potential to include multiple levels of representation of features as part of the learning process, increasing thereby the model's performance, computational feasibility and scalability [28,29]. DL approaches can be adapted to new representations of data allowing the different layers of features to be learned from more informative data using a complex learning procedure. DL outperforms in tasks related to perception problems (such as image analysis and sound recognition), while typical ML methods suffer from managing high dimensional datasets.

In cancer research and medical oncology, several DL architectures have been developed and applied for the classification and/or detection of cancer types [30]. The evaluation of DL models' performances have shown that this type of techniques outperform other conventional ML approaches. DL frameworks have been also developed and further utilized for cancer diagnosis and classification based on gene expression profiles [31–33]. Concerning cancer prognosis and treatment, DL methods have been proposed to tackle the problem of predicting the drug response in certain cancer types [12].

### 2.2. Reinforcement learning in oncology research

RL, a distinctive class of ML, has also found applications in cancer research and medical oncology towards finding the optimal treatment policies and computer-aided disease diagnosis [34,35]. In an RL model, an agent (i.e. the physician) learns from the interaction with his/her environment to achieve a goal based on the outcome that he/she wants to optimize (reward function). The learning process of an agent in a typical RL cycle is a continuous procedure. The interaction with the environment occurs at discrete time points. Once an environment's state is received the agent selects a certain action to interact with it. The environment responds then to the action and the reward that the agent will or will not receive is finally determined [36].

The incorporation of DL and RL systems into clinical practice with reference to available structured and unstructured biomedical and clinical cancer data will improve our understanding of cancer complexity and the role of risk factors and determinants in the development of effective treatment protocols.

### 2.3. Systems biology in oncology research

Systems biology concerns the integration of different components (i.e. genes, proteins and other cellular components) and how they interact in a dynamic environment. To facilitate our understanding on how cellular components function we need to elucidate in an integrated way how the system is organized with reference to dynamic networks of genes or proteins alongside their interactions with each other [37]. The development of AI models that predict the characteristics of large and interconnected networks found in living organisms would permit the thorough investigation of how signaling molecules produce functional cellular responses. In systems biology, mathematical descriptions of the processes during cancer progression and knowledge from network analysis and ML theories are used to identify the components and their interactions in a network-centered model and integrate them into an interconnected biological pathway. To this end, molecular or cellular associations and causal dependencies can be identified [38–40].

The last decade, different omics platforms have provided large cancer datasets concerning the biological and cellular processes that can be studied at both the gene and protein levels. Applying AI/ML tools on omics data, based on systems biology and network-based theory, we may be able to expose the intricate structure of biological processes, improving our understanding of cancer onset and progression. Network theory and analysis in oncology research could permit to decipher the organization of biological signals within the cells in terms of nodes (e.g. genes or proteins) and edges which represent the relationships among them allowing to quantify the strength, type and direction of these interactions based primarily on omics data. High-throughput technologies, such as DNA microarrays, facilitate the simultaneous assessment of many gene expression levels as they vary over time. The huge amount of available experimental data may be used to obtain a better understanding of how genes interact with one another, forming a network and allowing for integrative analysis of biological systems [37,38].

In the following sections, we clearly provide the clinical scenarios we found based on our literature review, along with the relevant papers published in the field of cancer research and clinical oncology.

### 2.4. Cancer detection and diagnosis

Arguably, automated cancer detection and diagnosis is one of the most important and successful domains of biomedical ML

applications. According to our search results in PubMed and dblp, the last five years 192 research studies proposed ML-based pipelines based on conventional or state-of-the-art techniques to perform diagnostic tasks in common cancer types such as breast, lung, colon and pancreatic cancers, among others. Most of the studies used imaging data acquired from computed tomography (CT), magnetic resonance imaging (MRI), X-ray radiography and positron-emission tomography (PET) to develop automated diagnostic models based mainly on DL architectures.

In this review article, we present the most recent and indicative studies of the last year using either imaging or clinical, genomic and other relevant medical data to develop ML-based models for disease diagnosis and detection. A large proportion of this comprehensive list corresponds to studies that handle the specific clinical scenario by utilizing solely imaging data as input to DL models (Table I in the [supplementary material](#)).

To this direction, automatic disease diagnosis was studied in terms of CNN models to early detect breast cancer by analyzing histopathological images [41–49]. More specifically, Zheng et al. [42] examined and proposed a CNN-based transfer learning method to early detect breast cancer by efficiently segment the ROIs. In comparison to other machine learning traditional approaches, promising results were obtained with high levels of accuracy (i.e. 97.2%) and a fair balance between sensitivity and specificity metrics (i.e. 98.3%, and 96.5%, respectively). Similar approaches were proposed by Benhammou et al. [43], Sha et al. [44], Kumar et al. [45], Krithiga et al. [46], Hameed et al. [47], and Li et al. [48] towards assessing the diagnostic capability of deep CNN architectures by analyzing imaging slides. Based on the models' preprocessing, training, and evaluation procedures, favorable results were suggested with an average percentage of accuracy equal to 90.0%, demonstrating the authors' contribution in assisting clinicians to their diagnostic processes. DL frameworks were also designed and developed in [50–54] based on the CNN architecture for the analysis of CT and dermoscopy images in liver and skin cancer, respectively. In the study of Das et al. [53] the Gaussian mixture model (GMM) algorithm was primarily used to effectively segment the lesions and deep neural networks were then employed for the automated diagnostic task. Furthermore, in [54] feature selection and optimization was performed to identify the most important determinants of skin cancer detection while deep CNN was employed for melanoma detection. Promising results were obtained by the studies with high performance in terms of classification accuracy (i.e. ~ 90.0%).

Conventional ML algorithms, such as DTs, Random Forests (RFs), Naïve Bayes (NB), k Nearest Neighbor (kNN), Artificial Neural Networks (ANNs), Gradient Boosting Machines (GBMs) and SVMs were also applied the last year in medical oncology for the automated detection and diagnosis of cancer. Indicative works include the studies of [55–62] where positive results were obtained by employing traditional ML techniques for the analysis of clinical, laboratory, genomic and epidemiological data to effectively diagnose prostate, lung, colorectal, breast and gastric cancers. In a separate work [63], supervised and unsupervised techniques were applied to transcriptomic data for the identification of potential candidate biomarkers (i.e. genes) with reference to pancreatic cancer onset. Preprocessing steps based on certain bioinformatics workflows were applied to detect the novel gene set that contributes to the extension of prostate cancer to adjacent lymph nodes with Area Under the ROC Curve (AUC) higher than 0.90.

The total number of published studies identified in the previous year based on our literature search results for cancer prognosis and survival prediction is shown in Table II in the [supplementary material](#).

## 2.5. Cancer patient classification

In medical oncology and cancer research the classification task of disease prediction has been studied thoroughly based on well-established ML algorithms for handling binary or multi-class learning problems. Patient classification into predefined groups would enable the development of ML-based predictive models able to assess risk stratification with generalizable performance. In this regard, numerous research papers were released last year that predicted the identification of key variables for cancer classification using traditional algorithms and DL methods. Most of the studies utilized DL architectures for the analysis of imaging and genomic data with respect to risk prediction and stratification. Indicatively, in [64–69] DL models were trained to classify and detect disease subtypes based on images and genetic data. These data-driven approaches demonstrated the superiority of ML-based frameworks towards exploiting heterogeneous datasets with respect to improved diagnosis and treatment.

Recently, a very interesting study was proposed by Li et al. [70] with regards to the assessment of pan-cancer Ras pathway activation and the identification of hidden key players during disease progression. RNA sequencing, copy number and mutation data were integrated in the DL model to provide insights into the pathway activity. The proposed model achieved superior performance in comparison to relevant studies concerning the classification of abnormal activity of the Ras pathway in tumor samples (i.e. AUC > 0.90) In an alternative study, a colorectal cancer (CRC) cohort [71] was analyzed based on whole-genome sequencing experiments of DNA samples to obtain an ML model with accurate generalization performance towards the early detection of the disease. A comprehensive ML-based pipeline was proposed to investigate the genomic profiles and cancer status and further identify the highly ranked covariates that discriminate control cases and early-stage CRC patients. According to the performance results a mean AUC of 0.92 with a mean sensitivity of 85.0% at 85.0% specificity were achieved.

Furthermore, well-known adaptive ML algorithms have been used widely in the literature for cancer classification by integrating different types of data [72–76]. Song et al. [77] proposed a predictive model for long-term prognosis of bladder cancer based on the learning ability of ML algorithms. The validated classification model was developed by utilizing clinical and molecular features able to distinguish cancerous from non-cancerous samples. Positive results were obtained in terms of classification performance with AUC higher than 0.70. Recently, similar works were published [60,78–81] aiming at applying data-driven methodologies to classify cancer data for prediction purposes. These studies correspond to ML-based models that improve the decision making process of physicians during patient monitoring and follow-up. Due to the availability of large amounts of heterogeneous data types in cancer research these studies utilized cancer data coming from patient registries, electronic health records, demographics, sequencing and imaging technologies.

Two distinct research studies [82,83] were published currently which use CT data integrated with radiomics features to classify cancer cases for improved prediction of lung cancer and in pulmonary lesions, respectively. The combination of radiomic features with clinical information in terms of ML algorithms empowered the extraction of potential patient characteristics that need to be considered thoroughly for disease screening. The performance metrics of the proposed ML-based methods were high with classification accuracy and AUC higher than 77.0% and 0.80, respectively.

The total number of studies identified in the previous year based on our indicative literature search results for cancer prognosis and survival prediction is shown in Table III in the [supplementary material](#).

## 2.6. Cancer prognosis and survival prediction

This is another important aspect of cancer research where AI is expected to provide significant insight in the management of patients diagnosed with cancer. Specifically, in this category we have gathered studies aiming to assess the prognosis of patients, i.e. predict approximate survival based on a set of features (clinical, imaging, genomic), evaluate response to treatment and consequently patient prognosis. Due to the volume of data and its complexity, such analyses would be inevitable without the employment of ML algorithms and especially DL techniques. Specifically, during the last year only, approximately 200 studies were published aiming to assess cancer prognosis. Among them, the considerable majority utilized DL techniques, whereas only a small percentage used traditional ML algorithms.

Same as in the previous scenarios as well, and in accordance with the cancer research overall, certain organ cancers are predominantly studied, such as breast, lung, prostate and colorectal. The types of data used vary across the studies, however, we observe propensity towards specific sources of data for each cancer type. Specifically, pathology data are used in prostate cancer, breast and colorectal cancer research utilize genomic data, and lung cancer is largely dependent on imaging data, especially CT scans. Despite those slight propensities per cancer type, we observe that all ML techniques, and especially DL techniques, are primarily used for the analysis of imaging data, indifferent to the type of imaging modality employed.

An interesting approach was recently proposed by [84] where an automated deep learning system was trained to grade prostate biopsies following the Gleason grading system. Similar approaches have been presented in the literature for assessing prostate cancer prognosis [85,86]. In the same manner, a DL approach is proposed in [87] to discern between benign and malignant lesions of the skin, resulting in an overall AUC = 0.91. Another commonly used purpose of ML for cancer prognosis, is the assessment of approximate survival of the patient based on a set of features, from the baseline; encompassing information from subsequent follow-up visits achieves higher accuracy. Such studies have been presented in the literature for several types of cancer, e.g. lung cancer [88], breast cancer [89], bladder cancer [90], etc. For a similar end purpose, ML algorithms have also been used for predicting response to treatment and consequently assessing the patient's overall prognosis and survival [91].

The total number of relevant studies identified in the preceding year based on our literature search results for cancer prognosis and survival prediction is shown in Tables I-III in the [supplementary material](#).

## 2.7. Robustness and explainability of AI/ML models

The recent advances in AI/ML raised the issue of vulnerabilities that affect the predictive models and strongly impact their robustness. To this direction, a set of principles for trustworthy and secure use of ML techniques in the digital society have been drawn to augment innovation while protecting fundamental human rights [92]. Although ML techniques could extract complex patterns and correlations from large datasets, there is a severe lack of understanding considering the causal relationships and the explicit rules [93].

To ensure the right deployment of ML models in the clinical practice in accordance with a sound regulatory framework, three main topics need to be highlighted and addressed. Firstly, the transparency of the models, which relates to the technical requirements and the data used, should be achieved. To obtain a complete view of a ML model the levels of implementation (i.e. technical principles), specifications (i.e. details about the training and testing

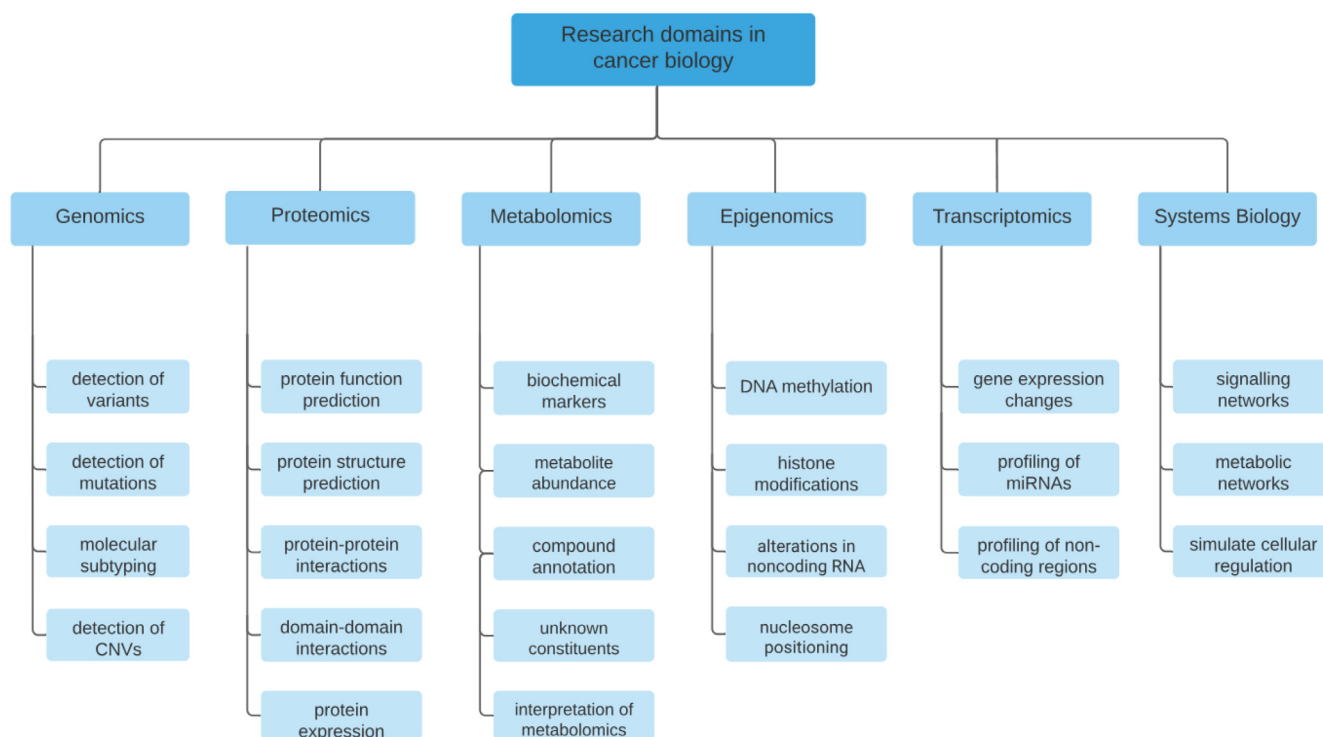
phase) and interpretability (understanding model's reasoning) must be fulfilled. The second topic concerns the reliability of the models along with the technical solutions that need to be clarified and adopted to prevent failures of autonomous systems in specific conditions. To assess the reliability of a model its performance and vulnerabilities need to be evaluated. Poor performance and existence of malfunctions indicate that a learned ML model is not reliable. Hence, the approaches of: (i) data sanitization, (ii) robust learning and (iii) extensive testing have been proposed to increase the reliability of ML models. The protection of sensitive data in ML systems is the third point that needs to be encountered for ensuring a good regulatory framework towards building and making use of automated systems. The implementation of data protection principles will guarantee the compliance to the privacy and data protection laws. Nevertheless [94], the use of anonymization and pseudonymization techniques on sensitive data in accordance with the General Data Protection Regulation (GDPR) in Europe [95] and the guidelines on how the information may be used or shared in accordance with the Health Insurance Portability and Accountability Act (HIPAA) in the United States [96] may increase model's complexity and impact its explainability.

Understanding the mechanisms and reasoning of a ML system in the digital society could guarantee its reliability. Introducing standardized approaches to assess the robustness of predictive models with respect to the data used for training, promoting model's transparency through explainability-by-design principle for ML-based systems and designing methodologies to address vulnerabilities ensuring thereby the reliability will promote an effective and secure use of AI/ML systems. Furthermore, the successful establishment of good practices towards the right development and deployment of automated ML-based systems will ensure a regulatory framework for strengthening the trust in AI/ML systems.

Explainable AI (XAI) provides a framework to facilitate the understanding why an AI system or ML model have produced a given result. Interpreting the output of a model and giving the explanations at the local and global levels would benefit the improvement of clinical decision support systems. Model-specific and model-agnostic analysis could be implemented for black-box models' explanations (such as SVM models) increasing thereby their trustworthiness and transparency in clinical trials [97]. Model-specific explanations are common but not well-adapted for two models with different structures. Once a new architecture for a predictive model is obtained a new method for model exploration and diagnostics should be searched. On the contrary, model-agnostic techniques could enhance models' exploratory analysis with instance-level exploration methods for better understanding on how a model yields a prediction for a particular single observation. Apart from instance-level explanations, dataset-level-explainers for ML-based predictive models help to understand how the model's predictions perform for the entire dataset and not for a certain observation [97]. Concerning the explanations of network-based models and tree-based classifiers (e.g. DTs and RFs), XAI techniques related to local and global explanations could benefit more the output interpretation concerning their less complex structure and hyper-parameters tuning. Although, DL techniques have been proved very efficient and effective regarding their performance, explanations on how a DL model has produced a result should be based on more comprehensive techniques with reference to model-specific and model-agnostic analysis.

## 2.8. Summary and outlook

In the previous review article [98], we provided a comprehensive overview of ML applications for cancer prognosis and prediction by explaining the main aspects of ML and their clinical implications. On this basis, we analyzed the most representative



**Fig. 2.** The most widely researched study topics in cancer biology, where ML-based techniques are frequently used. The six major features are illustrated, as well as the major biological issues they may address. CNVs: Copy Number Variations, DNA: Deoxyribonucleic acid, RNA: Ribonucleic acid, miRNAs: microRNAs

studies published between 2010 and 2015 which used traditional ML approaches to predict cancer susceptibility, recurrence, and survivability in cancer patients. In this work, we conduct a thorough and complementary literature search on the application of ML-based models in cancer research and oncology the last five years (2015–2020). According to our search results in both the PubMed [16] and dblp [17] databases, a comprehensive list of publications was obtained. In comparison to our previous review article, three different clinical scenarios were identified according to their clinical outcomes regarding disease diagnosis, patient classification and prognosis. To highlight the most recent achievements in the subject, we included the most representative studies from the previous year in each category. Furthermore, we investigated the contrasts between recent research works in terms of data used and cutting-edge ML approaches for addressing each clinical situation in the data-driven era of precision oncology.

AI and ML approaches may be utilized to explore many aspects of cancer biology and extract new insights given that any disruption to the genetic material causes the beginning and development of carcinogenesis. Apparently, a massive quantity of genetic information on neoplasia has now been gathered, and it is rapidly increasing. This knowledge has significantly aided two key goals in cancer research: (i) a better understanding of the processes and mechanisms of oncogenesis, and (ii) their direct use in clinical practice as markers of diagnosis, prognosis, prevention, and cancer treatment. Fig. 2 depicts the major subject themes in cancer biology that have been extensively explored in terms of ML applications during the last decade. We classified the main topics according to the well-established research domains in oncology research and provide indicative paradigms where ML-based methods can be employed.

The last decade, AI and its technologies has made tremendous progress helping clinicians to automate tasks, detect the disease earlier while obtaining more real and tangible results for tailoring treatments. In comparison to the traditional statistical approaches,

ML-based techniques have the inherent ability to identify patterns from high-dimensional datasets while automating the decision-making process by developing reasoning systems for disease early diagnosis, prognosis and risk stratification.

In the light of the recent advances in DL and RL methods for building ML-oriented systems we herein discuss their main characteristics alongside their major applications in the field of cancer research. Regarding the robustness and explainability of AI/ML systems we provide a brief overview of the standard points that need to be addressed when building ML models towards establishing a trustworthy regulatory framework while ensuring reliability, data protection and transparency as well as understanding of models.

ML methodologies have raised concerns in automated decision making tools and personal data regarding the lack of reasoning and explicit rules in black-box models. Hence, technical solutions need to be adopted for the design of standardized principles to increase the robustness and explainability of AI/ML systems as well as face the challenges of transparency and reproducibility of AI-based solutions. Transparency and reproducibility in AI are paramount for prospectively validate and implement in clinical practice such technologies and models [9,10]. Several frameworks and reproducible research practices have been implemented to ensure that the methods and code underpinning a research publication are adequately documented. Transparency is handled in terms of common code, software dependencies, and parameters required to train a model, allowing thereby the research study to be reproducible [99,100]. Practical and pragmatic recommendations for the effective documentation of research experiments and results have been proposed in the scientific community towards reproducible research and open science [100]. The degrees of reproducibility that are introduced concern the: (i) experiment reproducible, (ii) data reproducible and (iii) method reproducible. Different set of factors need to be documented within a publication to validate and reproduce the research results. Encouraging the research community to follow the best practices and recommenda-

tions for (i) data in publications, (ii) source code implementing AI/ML, (iii) AI methods and (iv) experiments described in scientific publications would be the steppingstone to accelerate transparency and reproducibility in the era of AI research. Several research groups cited replicable and clinically validated results in accordance with the oncology context, as well as transparency and validity in AI/ML-based solutions, concerning the clinical scenarios we addressed in this study and the indicative publications of 2020 described in each case [57,67,84].

Furthermore, transparent and reliable predictive models can protect the sensitive data according to anonymization and pseudonymization approaches that have been assessed by the GDPR [94,95]. Nowadays, ML-based systems are not yet considered reliable enough to avoid any malfunction without the human supervision. Identifying the vulnerabilities of ML models would foster the predictions of the given input and output in the learning process of a predictive model enhancing its robustness. According to the guidelines for the ethical development of ML-based systems [101], an ethics by design approach has been proposed for trustworthy AI/ML for GDPR-compliant, ethical and robust systems. Certain ethics and trustworthy aspects are outlined along with possible tools to self-assess an automated decision support system based on cutting-edge ML methodologies.

In addition to the standard technical solutions regarding the trustworthiness of autonomous ML-based systems in clinical practice we should also take into consideration the FAIR (Findable, Accessible, Interoperable and Reusable) data principles [102]. Thinking of the complex nature of cancer and the multistep process of tumorigenesis, one can easily presume that not enough data can be obtained from single centers regarding cancer research. Tailoring treatments to patients according to their status at both the phenotype and genotype levels would accelerate the automated decision process in disease management in the era of precision oncology. Moreover, the rise of omics data and their integration in precision oncology will promote a global and integrative analytical approach. Therefore, the adherence to the FAIR (Findable, Accessible, Interoperable and Reusable) principles when developing computational models leverages the adoption of data quality guidelines, data integration procedures and GDPR-compliance data sharing and access.

Dealing with multiple data modalities, i.e. multimodal frameworks, when building a ML-based framework for cancer prediction and classification, poses a new challenge in the field of cancer research. The development of integrative predictive models by combining the output from different algorithms is an innovation but also a challenge for the interpretation and reliability of the models implications in clinical practice.

To achieve our mission towards precision oncology and better understand the complex mechanisms of cancer, intervention actions should be designed by means of evidence-based decision support tools to prevent what is preventable, optimise diagnostics and treatment and support the quality of life of patients and caregivers. Furthermore, considering the COVID-19 pandemic in the last two years and the situation in the public healthcare systems, we can admit that cancer patients faced a severe and anxious period of follow-up visits trying to avoid a possible COVID-19 diagnosis which resulted in reduced hospitalizations and procedures [103,104]. As a result, we can foresee the influence of the COVID-19 pandemic on cancer early detection, on top of worsening prognosis and patient screening.

#### CRediT authorship contribution statement

**Konstantina Kourou:** Conceptualization, Writing – original draft, Visualization, Writing – review & editing. **Konstantinos P.**

**Exarchos:** Conceptualization, Writing – review & editing. **Costas Papaloukas:** Conceptualization, Writing – review & editing. **Prodromos Sakaloglou:** Visualization. **Themis Exarchos:** Conceptualization. **Dimitrios I. Fotiadis:** Conceptualization, Supervision.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.csbj.2021.10.006>.

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