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## ABOUT COVER

Editor-in-Chief of *Artificial Intelligence in Cancer*, Dr. Cedric Coulouarn has a long-standing expertise and track record in liver cancer with focus on TGF-beta signaling, non-coding RNA and functional genomics, including a 5-year experience at the National Cancer Institute. He currently heads a team at Inserm in France focused on studying the role of TGF-beta signaling in liver carcinogenesis. He is an active member of the French and European associations for the Study of the Liver (AFEF and EASL), International Liver Cancer Association, European Network for the Study of Cholangiocarcinoma. Dr. Coulouarn is also acting as a referee in scientific committees for evaluation of French and international Grants. He is teaching at University Paris-Diderot and University of Rennes 1, France.

## AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Cancer* (*AIC*, *Artif Intell Cancer*) is to provide scholars and readers from various fields of artificial intelligence in cancer with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*AIC* mainly publishes articles reporting research results obtained in the field of artificial intelligence in cancer and covering a wide range of topics, including artificial intelligence in bone oncology, breast cancer, gastrointestinal cancer, genitourinary cancer, gynecological cancer, head and neck cancer, hematologic malignancy, lung cancer, lymphoma and myeloma, pediatric oncology, and urologic oncology.

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EDITORIAL

# Artificial intelligence and omics in cancer

Cédric Coulouarn

**ORCID number:** Cédric Coulouarn 0000-0002-5692-9586.

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**Cédric Coulouarn,** Institut National de la Sante et de la Recherche Medicale (Inserm), Université de Rennes 1, Rennes F-35000, France

**Corresponding author:** Cédric Coulouarn, PhD, Senior Researcher, Principal Investigator, Team Leader, Institut National de la Sante et de la Recherche Medicale (Inserm), Université de Rennes 1, CHU Pontchaillou, 2 rue Henri Le Guilloux, Rennes F-35033, France. cedric.coulouarn@inserm.fr

## Abstract

Cancer is a major public health problem worldwide. Current predictions suggest that 13 million people will die each year from cancer by 2030. Thus, new ideas are urgently needed to change paradigms in the global fight against cancer. Over the last decades, artificial intelligence (AI) emerged in the field of cancer research as a new and promising discipline. Although emerging, a great potential is appreciated in AI to improve cancer diagnosis and prognosis, as well as to identify relevant therapeutics in the current era of personalized medicine. Developing pipelines connecting patient-generated health data easily translatable into clinical practice to assist clinicians in decision making represents a challenging but fascinating task. AI algorithms are mainly fueled by multi omics data which, in the case of cancer research, have been largely derived from international cancer programs, including The Cancer Genome Atlas (TCGA). Here, I briefly review some examples of supervised and unsupervised big data derived from TCGA programs and comment on how AI algorithms have been applied to improve the management of patients with cancer. In this context, *Artificial Intelligence in Cancer* journal was specifically launched to promote the development of this discipline, by serving as a forum to publish high-quality basic and clinical research articles in various fields of AI in oncology.

**Key words:** Omics; Big data; Artificial intelligence; Deep learning; Precision medicine



**Core tip:** Artificial intelligence (AI) emerged in the field of cancer research as a new and promising discipline to improve the management of patients with cancer, including more accurate and fastest diagnosis to facilitate the therapeutic decision. AI models are mainly fueled by multi omics data. Integrating omics data and clinical data of patients represents a challenging but fascinating task.

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## INTRODUCTION

Cancer is a public health problem worldwide[1]. Predictions suggest that 13 million people will die each year from cancer by 2030[2]. Tumor heterogeneity represents an important obstacle to establish efficient therapeutic strategies. Over the last decades, large-scale pan-genomic studies allowed to address tumor heterogeneity in multiple cancers and to provide a landscape of alterations occurring at multiple levels in tumor cells (*e.g.* at DNA, RNA and protein levels). Thus, international consortia have been initiated, including The Cancer Genome Atlas (TCGA) and its landmark cancer genomics program, which molecularly characterized over 84000 cases from 67 primary sites so far (https://portal.gdc.cancer.gov). Accordingly, TCGA and other cancer programs generated over 2.5 petabytes of genomic, epigenomic, transcriptomic, and proteomic data. This explosive growth of data represented a major driving force to develop innovative artificial intelligence (AI) methods, including deep learning algorithms, capable of analyzing large and multifaceted datasets in an integrated and comprehensive way[3]. By using algorithms that imitate the thinking process, deep learning allows computational models that are composed of multiple processing layers to learn representations of data with multiple levels of abstraction and to discover intricate structure in large data sets[4]. These automated methods, popularized in the society by image or speech recognition algorithms, are now moving into the field of health, including cancer research. Indeed, innovative algorithms are developed to extract meaningful genomic patterns and to translate this conceptual basic information into clinical applications, notably to improve cancer diagnosis, prognosis prediction and treatment efficacy (Figure 1). Here, I briefly review some examples of supervised and unsupervised big data derived from TCGA programs and comment on how AI algorithms have been applied to improve the management of patients with cancer.

## BIG DATA FROM TCGA

TCGA programs represented a major advance in the field of cancer research, allowing both supervised analysis of specific cancers and unsupervised analysis of pan-cancer datasets. Thus, supervised comparative and comprehensive analyses that distinguished clinically relevant molecular subtypes were reported in several cancers, including gastrointestinal (GI) cancers[5], gynecologic and breast cancers[6], pancreatic[7] or liver[8] cancers. Unsupervised analyses have been also performed using pan-cancer datasets. By analyzing mutation profiles, copy-number changes, gene fusions, mRNA expression, and DNA methylation in 9125 tumors profiled by TCGA, a detailed landscape of oncogenic pathway alterations was notably charted in 33 cancer types. Tumors were stratified into 64 subtypes, and patterns of co-occurrence and mutual exclusivity alterations were identified using SELECT, a method that infers conditional selection dependencies between alterations from occurrence patterns[9]. Importantly, using dedicated knowledge base of clinically actionable alterations, it was shown that 57% of tumors had at least one alteration potentially targetable and 30% of tumors had multiple targetable alterations, indicating opportunities for combination therapy[9]. This type of information will be crucial in the current area of cancer precision medicine to develop effective combination therapies that address or prevent resistance to initially successful single agent therapies. Pan-cancer supervised analyses were also performed to highlight frequent alterations in key signaling pathways involved in cancer progression. transforming growth factor beta (TGFβ) is a pleiotropic cytokine that harbors a functional duality in cancer, *i.e.* exhibiting tumor suppressive features at early stages but switching toward pro-metastatic activities at late tumor stages[10]. Interestingly, genetic alterations in TGFβ signaling, affecting mostly metastatic-associated genes, were observed in 39% of pan-cancer TCGA cases, and were particularly enriched in GI cancers[11]. Specific algorithms have been also used to characterize the immune tumor microenvironment across 33 cancer types analyzed by TCGA. By integrating major immunogenomics methods, including analysis of

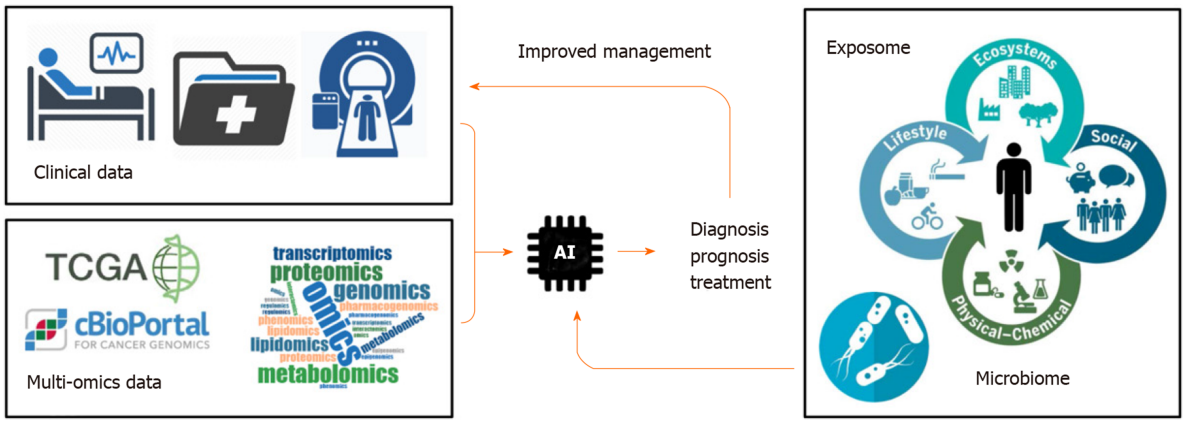


**Figure 1 Artificial intelligence and omics to improve the management of patients with cancer.** Actual artificial intelligence algorithms are mainly fueled with clinical data (*e.g.* clinical records, computed tomography scan, magnetic resonance imaging) and omics data, as exemplified by those from The Cancer Genome Atlas consortium (*e.g.* genetic, epigenetic, transcriptomic, proteomic, metabolomics profiles). They pave the way for future models that will integrate personalized clinical information related to lifestyle of each patient, including exposome and microbiome, in order to improve cancer diagnosis, prognosis prediction and treatment efficacy. AI: Artificial intelligence; TCGA: The Cancer Genome Atlas.

genomic profiles, hematoxylin and eosin stained tumor sections and deconvolution analysis of mRNA sequencing (mRNA-seq) data, six immune subtypes were characterized, spanning multiple tumor types, with potential therapeutic and prognostic implications for cancer management[12]. Interestingly, one so-called TGFβ dominant subtype, displayed the highest TGFβ signature and a high lymphocytic infiltrate. This observation is particularly relevant with the emergence of effective immunotherapies, including the recent development of an innovative immunotherapeutic that simultaneously blocks the PD-L1 checkpoint protein and the TGFβ signaling pathway[13].

From a basic point of view, several efforts have been made also to integrate multi omics data and to provide a better understanding of tumor biology. As an example, a deep learning-based predictive model using deep denoising auto-encoder and multilayer perceptron was developed to quantitatively capture how genetic and epigenetic alterations correlate with directionality of gene expression in liver cancer[14]. Similarly, an innovative one-class logistic regression machine-learning algorithm was used to identify stemness features associated with oncogenic dedifferentiation[15]. Interestingly, an unanticipated correlation of cancer stemness with immune checkpoint expression and infiltrating immune cells was highlighted in the tumor microenvironment[15]. The analysis of gene regulatory networks from available omics data is a challenging task given that biological data is prone to different kinds of noise and ambiguity. Soft computing tools, such as fuzzy sets, evolutionary strategies, and neurocomputing, have been found to be helpful in providing low-cost, acceptable solutions in the presence of various types of uncertainties[16].

## AI AND OMICS FOR CANCER DIAGNOSIS AND PROGNOSIS

Cancer diagnosis using deep learning has been recently reviewed[17]. Soft computing techniques also provided solutions for cancer, regarding diagnosis, prediction, inference and classification[18,19,20]. The approaches are mainly based on segmentation processes using convolutional neural networks (CNN) in clinical images notably acquired from computed tomography (CT) and magnetic resonance imaging (MRI). AI allows integrating quantitative, multiparametric and functional imaging data to automatically recognize complex patterns and to provide quantitative, rather than qualitative, assessments of radiographic characteristics[21]. A classification of skin lesions using a single CNN, trained end-to-end from images directly, using only pixels and disease labels as inputs, nicely illustrates the interest and the power of AI algorithms[22]. Indeed, a CNN trained using a dataset of 129450 clinical images (2032 different cases) was capable of classifying skin lesions with a level of competence comparable to dermatologists[22]. By helping clinicians in characterizing early benign and/or malignant lesions, AI recently emerged as the next step towards precision pathology. Screening programs for early detection of colorectal cancer (CRC) have been shown to reduce mortality in multiple studies. Thus, a machine learning-based

algorithm (MeScore) was trained to predict the occurrence of CRC and to identify a group of individuals at a high risk for CRC. Remarkably, MeScore can help identifying individuals in the population who would benefit most from CRC screening, including those with no clinical signs or symptoms of CRC[23]. In another study, a total of 1970 whole slide images of 731 cases of nasopharyngeal carcinoma were divided into training, validation and testing sets. A CNN model was trained to classify images into three categories: Chronic nasopharyngeal inflammation, lymphoid hyperplasia and nasopharyngeal carcinoma. Remarkably, the model equals the senior pathologist when considered in terms of accuracy, specificity, sensitivity, area under the curve and consistency[24]. Thus, this couple of examples suggests that deep learning algorithms could potentially assist pathologists in clinical practice by providing a second opinion and thus increasing consistency on the diagnosis.

Gene expression profiling has been extensively used to derive prognostic signatures in multiple types of cancers. However, these signatures are usually derived from a single type of omics data (*e.g.* mRNA, miRNA, lncRNA profiling). Integration of multifaceted datasets with different levels of information appears relevant to better reflect the biology of a specific tumor. Accordingly, integrated genome-wide epigenetic and multi omics analyses using AI entered in the era of precision medicine with the burst of data generated over the last decades[25]. Thus, a deep learning multi omics model integrating RNA-seq, miRNA-seq, and methylation data from TCGA, was reported to robustly predict survival of patients with liver cancer[26]. A more aggressive subtype was associated with frequent TP53 inactivation mutations, higher expression of stemness markers, and activated WNT and AKT signaling pathways[26]. Pathway-based biomarker identification with crosstalk analysis has been also reported in liver cancer for efficiently differentiating patients into moderate or aggressive risk subtypes with significant differences in terms of survival[27]. Besides, deep-learning algorithms based on whole slide histological images were reported to predict prognosis of patients with liver cancer. By using a training set made of 390 slides from 206 tumors and a validating set made of 342 slides from 328 patients, a model was built for predicting the survival of patients after surgical resection of hepatocellular carcinoma[28]. Notably, the study highlights the importance of pathologist/machine interactions for the construction of deep-learning algorithms[28]. By processing 5202 digital pathology images from 13 cancer types, a deep-learning model established tumor-infiltrating lymphocytes maps correlated with molecular data, tumor subtypes, immune profiles and patient survival[29]. The application of deep learning in cancer prognosis has been shown to be equivalent or better than current approaches, as recently reviewed[30].

## AI AND OMICS FOR CANCER TREATMENT

Deep learning-based analysis of multi omics data finds its natural place for the development of personalized therapies in cancer, notably by linking molecular actionable alterations with specific drugs already developed for these alterations or through a drug repositioning process (also referred to as drug repurposing). Deep learning models also enable large scale virtual screening of compound databases for predictive activity profiling against targets important for multiple cancers. Such large scale screening facilitate the quick and cost-effective repurposing of existing drugs[31]. By using a pharmacogenomics database of 1001 cancer cell lines, deep neural networks were trained for predicting drug response and their performance was assessed on multiple clinical cohorts[32]. By integrating RNA-seq, copy number, and mutations from 33 different cancer types (TCGA PanCanAtlas project), a deep learning model was shown to successfully predict RAS activation across cancer types and to identify phenocopying variants (*e.g.* NF1 loss). The model represents a useful tool to predict response to MEK inhibitors and identify the best responders[33]. Specific algorithms for drug repurposing have been also developed, based notably on linking gene expression profiles of tumors with gene signatures of bioactive molecules. Thus, the L1000 Connectivity Map is a library of gene expression signatures established in cell lines after pharmacologic or genetic (knockdown or over-expression) perturbation (approximately 20000 compounds, 4500 knockdowns, and 3000 over-expressions)[34]. This approach has been successfully used to propose epigenetic modulators (*e.g.* HDAC inhibitors) as relevant innovative therapeutics to target several hallmarks of liver cancer[35]. Using the same approach, anthelminthic drugs were also identified as potential therapeutic candidates in liver cancer[36]. Thus, combined with a robust stratification of human tumors, AI would help predicting response to individual

therapy. Although translation between research and clinical practice requires to fully addressing the question of the reproducibility and interpretability of the developed algorithms, there is no doubt that AI will positively impact clinical decision-making, providing a more personalized management of patients[37]. Another aspect that needs to be fully appraised is the regulatory issue for AI technologies, including clinically approved algorithms (Software as Medical Devices, SaMD), *e.g.* in terms of personal data sharing[38].

## CONCLUSION

Over the last decades, cancer genomic programs generated a large amount of multi omics data. This information fueled the development of innovative algorithms to extract meaningful information possibly translatable into clinical practices. AI emerged only recently in the field of cancer research. However, specific studies demonstrated already the possibility of AI to improve diagnosis and prognosis of patients with cancer and to develop innovative targeted therapeutics. Although, the actual algorithms are fueled mainly with omics data and clinical images (*e.g.* genetic, epigenetic, transcriptomic, proteomic, metabolomics profiles, CT scan, MRI), they pave the way for future models that will also integrate personalized clinical information related to lifestyle of each patient, including environmental exposure (exposome) or microbiome composition that may influence response to treatment[39](Figure 1). As a promising future direction, research on exposome, genetic factors, microbiome, immunity, and molecular tissue biomarkers is needed using AI and omics technologies. This field referred to as molecular pathological epidemiology (MPE) aims at investigating those factors in relation to molecular pathologies and clinical outcomes by means of computational analyses. Thus, MPE represents a promising area of investigation to better understand how a particular exposure influences the carcinogenic and pathologic process[40,41].

In this context, *Artificial Intelligence in Cancer* journal was specifically launched to promote the development of this discipline, by serving as a forum to publish high-quality basic and clinical research articles in various fields of AI in oncology.

## REFERENCES


1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **The Lancet**. GLOBOCAN 2018: counting the toll of cancer. *Lancet* 2018; **392**: 985 [PMID: 30264708 DOI: 10.1016/S0140-6736(18)32252-9]

3 **Landhuis E**. Deep learning takes on tumours. *Nature* 2020; **580**: 551-553 [PMID: 32317799 DOI: 10.1038/d41586-020-01128-8]

4 **LeCun Y**, Bengio Y, Hinton G. Deep learning. *Nature* 2015; **521**: 436-444 [PMID: 26017442 DOI: 10.1038/nature14539]

5 **Liu Y**, Sethi NS, Hinoue T, Schneider BG, Cherniack AD, Sanchez-Vega F, Seoane JA, Farshidfar F, Bowlby R, Islam M, Kim J, Chatila W, Akbani R, Kanchi RS, Rabkin CS, Willis JE, Wang KK, McCall SJ, Mishra L, Ojesina AI, Bullman S, Pedamallu CS, Lazar AJ, Sakai R; Cancer Genome Atlas Research Network, Thorsson V, Bass AJ, Laird PW. Comparative Molecular Analysis of Gastrointestinal Adenocarcinomas. *Cancer Cell* 2018; **33**: 721-735.e8 [PMID: 29622466 DOI: 10.1016/j.ccell.2018.03.010]

6 **Berger AC**, Korkut A, Kanchi RS, Hegde AM, Lenoir W, Liu W, Liu Y, Fan H, Shen H, Ravikumar V, Rao A, Schultz A, Li X, Sumazin P, Williams C, Mestdagh P, Gunaratne PH, Yau C, Bowlby R, Robertson AG, Tiezzi DG, Wang C, Cherniack AD, Godwin AK, Kuderer NM, Rader JS, Zuna RE, Sood AK, Lazar AJ, Ojesina AI, Adebamowo C, Adebamowo SN, Baggerly KA, Chen TW, Chiu HS, Lefever S, Liu L, MacKenzie K, Orsulic S, Roszik J, Shelley CS, Song Q, Vellano CP, Wentzensen N; Cancer Genome Atlas Research Network, Weinstein JN, Mills GB, Levine DA, Akbani R. A Comprehensive Pan-Cancer Molecular Study of Gynecologic and Breast Cancers. *Cancer Cell* 2018; **33**: 690-705.e9 [PMID: 29622464 DOI: 10.1016/j.ccell.2018.03.014]

7 **Cancer Genome Atlas Research Network**. Integrated Genomic Characterization of Pancreatic Ductal Adenocarcinoma. *Cancer Cell* 2017; **32**: 185-203.e13 [PMID: 28810144 DOI: 10.1016/j.ccell.2017.07.007]

8 **Cancer Genome Atlas Research Network**. Comprehensive and Integrative Genomic Characterization of Hepatocellular Carcinoma. *Cell* 2017; **169**: 1327-1341.e23 [PMID: 28622513 DOI: 10.1016/j.cell.2017.05.046]

9 **Sanchez-Vega F**, Mina M, Armenia J, Chatila WK, Luna A, La KC, Dimitriadoy S, Liu DL, Kantheti HS, Saghafinia S, Chakravarty D, Daian F, Gao Q, Bailey MH, Liang WW, Foltz SM, Shmulevich I, Ding L, Heins Z, Ochoa A, Gross B, Gao J, Zhang H, Kundra R, Kandoth C, Bahceci I, Dervishi L, Dogrusoz U, Zhou W, Shen H, Laird PW, Way GP, Greene CS, Liang H, Xiao Y, Wang C, Iavarone A, Berger AH, Bivona TG, Lazar AJ, Hammer GD, Giordano T, Kwong LN, McArthur G, Huang C, Tward AD, Frederick

MJ, McCormick F, Meyerson M; Cancer Genome Atlas Research Network, Van Allen EM, Cherniack AD, Ciriello G, Sander C, Schultz N. Oncogenic Signaling Pathways in The Cancer Genome Atlas. *Cell* 2018; **173**: 321-337.e10 [PMID: 29625050 DOI: 10.1016/j.cell.2018.03.035]

10 **Papoutsoglou P**, Louis C, Coulouarn C. Transforming Growth Factor-Beta (TGFβ) Signaling Pathway in Cholangiocarcinoma. *Cells* 2019; **8**: 960 [PMID: 31450767 DOI: 10.3390/cells8090960]

11 **Korkut A**, Zaidi S, Kanchi RS, Rao S, Gough NR, Schultz A, Li X, Lorenzi PL, Berger AC, Robertson G, Kwong LN, Datto M, Roszik J, Ling S, Ravikumar V, Manyam G, Rao A, Shelley S, Liu Y, Ju Z, Hansel D, de Velasco G, Pennathur A, Andersen JB, O'Rourke CJ, Ohshiro K, Jogunoori W, Nguyen BN, Li S, Osmanbeyoglu HU, Ajani JA, Mani SA, Houseman A, Wiznerowicz M, Chen J, Gu S, Ma W, Zhang J, Tong P, Cherniack AD, Deng C, Resar L; Cancer Genome Atlas Research Network, Weinstein JN, Mishra L, Akbani R. A Pan-Cancer Analysis Reveals High-Frequency Genetic Alterations in Mediators of Signaling by the TGF-β Superfamily. *Cell Syst* 2018; **7**: 422-437.e7 [PMID: 30268436 DOI: 10.1016/j.cels.2018.08.010]

12 **Thorsson V**, Gibbs DL, Brown SD, Wolf D, Bortone DS, Ou Yang TH, Porta-Pardo E, Gao GF, Plaisier CL, Eddy JA, Ziv E, Culhane AC, Paull EO, Sivakumar IKA, Gentles AJ, Malhotra R, Farshidfar F, Colaprico A, Parker JS, Mose LE, Vo NS, Liu J, Liu Y, Rader J, Dhankani V, Reynolds SM, Bowlby R, Califano A, Cherniack AD, Anastassiou D, Bedognetti D, Mokrab Y, Newman AM, Rao A, Chen K, Krasnitz A, Hu H, Malta TM, Noushmehr H, Pedamallu CS, Bullman S, Ojesina AI, Lamb A, Zhou W, Shen H, Choueiri TK, Weinstein JN, Guinney J, Saltz J, Holt RA, Rabkin CS; Cancer Genome Atlas Research Network, Lazar AJ, Serody JS, Demicco EG, Disis ML, Vincent BG, Shmulevich I. The Immune Landscape of Cancer. *Immunity* 2018; **48**: 812-830.e14 [PMID: 29628290 DOI: 10.1016/j.immuni.2018.03.023]

13 **Lan Y**, Zhang D, Xu C, Hance KW, Marelli B, Qi J, Yu H, Qin G, Sircar A, Hernández VM, Jenkins MH, Fontana RE, Deshpande A, Locke G, Sabzevari H, Radvanyi L, Lo KM. Enhanced preclinical antitumor activity of M7824, a bifunctional fusion protein simultaneously targeting PD-L1 and TGF-β. *Sci Transl Med* 2018; **10**: eaan5488 [PMID: 29343622 DOI: 10.1126/scitranslmed.aan5488]

14 **Seal DB**, Das V, Goswami S, De RK. Estimating gene expression from DNA methylation and copy number variation: A deep learning regression model for multi-omics integration. *Genomics* 2020; **112**: 2833-2841 [PMID: 32234433 DOI: 10.1016/j.ygeno.2020.03.021]

15 **Malta TM**, Sokolov A, Gentles AJ, Burzykowski T, Poisson L, Weinstein JN, Kamińska B, Huelsken J, Omberg L, Gevaert O, Colaprico A, Czerwińska P, Mazurek S, Mishra L, Heyn H, Krasnitz A, Godwin AK, Lazar AJ; Cancer Genome Atlas Research Network, Stuart JM, Hoadley KA, Laird PW, Noushmehr H, Wiznerowicz M. Machine Learning Identifies Stemness Features Associated with Oncogenic Dedifferentiation. *Cell* 2018; **173**: 338-354.e15 [PMID: 29625051 DOI: 10.1016/j.cell.2018.03.034]

16 **Mitra S**, Das R, Hayashi Y. Genetic networks and soft computing. *IEEE/ACM Trans Comput Biol Bioinform* 2011; **8**: 94-107 [PMID: 21071800 DOI: 10.1109/TCBB.2009.39]

17 **Munir K**, Elahi H, Ayub A, Frezza F, Rizzi A. Cancer Diagnosis Using Deep Learning: A Bibliographic Review. *Cancers (Basel)* 2019; **11**: 1235 [PMID: 31450799 DOI: 10.3390/cancers11091235]

18 **Gambhir S**, Malik SK, Kumar Y. Role of Soft Computing Approaches in HealthCare Domain: A Mini Review. *J Med Syst* 2016; **40**: 287 [PMID: 27796841 DOI: 10.1007/s10916-016-0651-x]

19 **Bhatia A**, Mago V, Singh R. Use of soft computing techniques in medical decision making: A survey. Proceedings of the 2014 IEEE International Conference on Advances in Computing, Communications and Informatics (ICACCI); 2014 Sep 24-27; New Delhi, India. IEEE. **2014**: 1131-1137 [DOI: 10.1109/ICACCI.2014.6968460]

20 **Yardimci A**. A survey on use of soft computing methods in medicine. In: de Sá JM, Alexandre LA, Duch W, Mandic D, editors. Artificial Neural Networks – ICANN 2007 - Lecture Notes in Computer Science, vol 4669. Berlin, Heidelberg: Springer, 2007: 69-79 [DOI: 10.1007/978-3-540-74695-9_8]

21 **Hosny A**, Parmar C, Quackenbush J, Schwartz LH, Aerts HJWL. Artificial intelligence in radiology. *Nat Rev Cancer* 2018; **18**: 500-510 [PMID: 29777175 DOI: 10.1038/s41568-018-0016-5]

22 **Esteva A**, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, Thrun S. Dermatologist-level classification of skin cancer with deep neural networks. *Nature* 2017; **542**: 115-118 [PMID: 28117445 DOI: 10.1038/nature21056]

23 **Kinar Y**, Akiva P, Choman E, Kariv R, Shalev V, Levin B, Narod SA, Goshen R. Performance analysis of a machine learning flagging system used to identify a group of individuals at a high risk for colorectal cancer. *PLoS One* 2017; **12**: e0171759 [PMID: 28182647 DOI: 10.1371/journal.pone.0171759]

24 **Diao S**, Hou J, Yu H, Zhao X, Sun Y, Lambo RL, Xie Y, Liu L, Qin W, Luo W. Computer-Aided Pathological Diagnosis of Nasopharyngeal Carcinoma Based on Deep Learning. *Am J Pathol* 2020 [PMID: 32360568 DOI: 10.1016/j.ajpath.2020.04.008]

25 **Hamamoto R**, Komatsu M, Takasawa K, Asada K, Kaneko S. Epigenetics Analysis and Integrated Analysis of Multiomics Data, Including Epigenetic Data, Using Artificial Intelligence in the Era of Precision Medicine. *Biomolecules* 2019; **10**: 62 [PMID: 31905969 DOI: 10.3390/biom10010062]

26 **Chaudhary K**, Poirion OB, Lu L, Garmire LX. Deep Learning-Based Multi-Omics Integration Robustly Predicts Survival in Liver Cancer. *Clin Cancer Res* 2018; **24**: 1248-1259 [PMID: 28982688 DOI: 10.1158/1078-0432.CCR-17-0853]

27 **Fa B**, Luo C, Tang Z, Yan Y, Zhang Y, Yu Z. Pathway-based biomarker identification with crosstalk analysis for robust prognosis prediction in hepatocellular carcinoma. *EBioMedicine* 2019; **44**: 250-260 [PMID: 31101593 DOI: 10.1016/j.ebiom.2019.05.010]

28 **Saillard C**, Schmauch B, Laifa O, Moarii M, Toldo S, Zaslavskiy M, Pronier E, Laurent A, Amaddeo G, Regnault H, Sommacale D, Ziol M, Pawlotsky JM, Mulé S, Luciani A, Wainrib G, Clozel T, Courtiol P, Calderaro J. Predicting survival after hepatocellular carcinoma resection using deep-learning on histological slides. *Hepatology* 2020 [PMID: 32108950 DOI: 10.1002/hep.31207]

29 **Saltz J**, Gupta R, Hou L, Kurc T, Singh P, Nguyen V, Samaras D, Shroyer KR, Zhao T, Batiste R, Van Arnam J; Cancer Genome Atlas Research Network, Shmulevich I, Rao AUK, Lazar AJ, Sharma A, Thorsson V. Spatial Organization and Molecular Correlation of Tumor-Infiltrating Lymphocytes Using

Deep Learning on Pathology Images. *Cell Rep* 2018; **23**: 181-193.e7 [PMID: 29617659 DOI: 10.1016/j.celrep.2018.03.086]

30 **Zhu W**, Xie L, Han J, Guo X. The Application of Deep Learning in Cancer Prognosis Prediction. *Cancers (Basel)* 2020; **12**: 603 [PMID: 32150991 DOI: 10.3390/cancers12030603]

31 **Issa NT**, Stathias V, Schürer S, Dakshanamurthy S. Machine and deep learning approaches for cancer drug repurposing. *Semin Cancer Biol* 2020 [PMID: 31904426 DOI: 10.1016/j.semcancer.2019.12.011]

32 **Sakellaropoulos T**, Vougas K, Narang S, Koinis F, Kotsinas A, Polyzos A, Moss TJ, Piha-Paul S, Zhou H, Kardala E, Damianidou E, Alexopoulos LG, Aifantis I, Townsend PA, Panayiotidis MI, Sfikakis P, Bartek J, Fitzgerald RC, Thanos D, Mills Shaw KR, Petty R, Tsirigos A, Gorgoulis VG. A Deep Learning Framework for Predicting Response to Therapy in Cancer. *Cell Rep* 2019; **29**: 3367-3373.e4 [PMID: 31825821 DOI: 10.1016/j.celrep.2019.11.017]

33 **Way GP**, Sanchez-Vega F, La K, Armenia J, Chatila WK, Luna A, Sander C, Cherniack AD, Mina M, Ciriello G, Schultz N; Cancer Genome Atlas Research Network, Sanchez Y, Greene CS. Machine Learning Detects Pan-cancer Ras Pathway Activation in The Cancer Genome Atlas. *Cell Rep* 2018; **23**: 172-180.e3 [PMID: 29617658 DOI: 10.1016/j.celrep.2018.03.046]

34 **Duan Q**, Flynn C, Niepel M, Hafner M, Muhlich JL, Fernandez NF, Rouillard AD, Tan CM, Chen EY, Golub TR, Sorger PK, Subramanian A, Ma'ayan A. LINCS Canvas Browser: interactive web app to query, browse and interrogate LINCS L1000 gene expression signatures. *Nucleic Acids Res* 2014; **42**: W449-W460 [PMID: 24906883 DOI: 10.1093/nar/gku476]

35 **Allain C**, Angenard G, Clément B, Coulouarn C. Integrative Genomic Analysis Identifies the Core Transcriptional Hallmarks of Human Hepatocellular Carcinoma. *Cancer Res* 2016; **76**: 6374-6381 [PMID: 27634755 DOI: 10.1158/0008-5472.CAN-16-1559]

36 **Chen B**, Garmire L, Calvisi DF, Chua MS, Kelley RK, Chen X. Harnessing big 'omics' data and AI for drug discovery in hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 238-251 [PMID: 31900465 DOI: 10.1038/s41575-019-0240-9]

37 **Ching T**, Himmelstein DS, Beaulieu-Jones BK, Kalinin AA, Do BT, Way GP, Ferrero E, Agapow PM, Zietz M, Hoffman MM, Xie W, Rosen GL, Lengerich BJ, Israeli J, Lanchantin J, Woloszynek S, Carpenter AE, Shrikumar A, Xu J, Cofer EM, Lavender CA, Turaga SC, Alexandari AM, Lu Z, Harris DJ, DeCaprio D, Qi Y, Kundaje A, Peng Y, Wiley LK, Segler MHS, Boca SM, Swamidass SJ, Huang A, Gitter A, Greene CS. Opportunities and obstacles for deep learning in biology and medicine. *J R Soc Interface* 2018; **15**: 20170387 [PMID: 29618526 DOI: 10.1098/rsif.2017.0387]

38 **Walradt T,** Glissen Brown JR, Alagappan M, Lerner HP, Berzin TM. Regulatory considerations for artificial intelligence technologies in GI endoscopy. *Gastrointest Endosc* 2020 [PMID: 32504697 DOI: 10.1016/j.gie.2020.05.040]

39 **Jim HSL**, Hoogland AI, Brownstein NC, Barata A, Dicker AP, Knoop H, Gonzalez BD, Perkins R, Rollison D, Gilbert SM, Nanda R, Berglund A, Mitchell R, Johnstone PAS. Innovations in research and clinical care using patient-generated health data. *CA Cancer J Clin* 2020; **70**: 182-199 [PMID: 32311776 DOI: 10.3322/caac.21608]

40 **Ogino S**, Chan AT, Fuchs CS, Giovannucci E. Molecular pathological epidemiology of colorectal neoplasia: an emerging transdisciplinary and interdisciplinary field. *Gut* 2011; **60**: 397-411 [PMID: 21036793 DOI: 10.1136/gut.2010.217182]

41 **Ogino S**, Nowak JA, Hamada T, Milner DA Jr, Nishihara R. Insights into Pathogenic Interactions Among Environment, Host, and Tumor at the Crossroads of Molecular Pathology and Epidemiology. *Annu Rev Pathol* 2019; **14**: 83-103 [PMID: 30125150 DOI: 10.1146/annurev-pathmechdis-012418-012818]

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*EVIDENCE REVIEW*

# Management of cancer patients during the COVID-19 pandemic: A comprehensive review

Ayun K Cassell III, Lydia T Cassell, Abdoul Halim Bague

**ORCID number:** Ayun K Cassell III 0000-0002-7977-6682; Lydia T Casssell 0000-0002-5673-4359; Abdoul Halim Bague 0000-0003-2428-053X.

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**Ayun K Cassell III,** Department of Urology and Andrology, Hopital General de Grand Yoff, Dakar 3270, Senegal

**Lydia T Cassell,** Department of Public Health, Cuttington University, Graduate School and Professional Studies, Monrovia 10010, Liberia

**Abdoul Halim Bague,** Unit of Surgical Oncology, Department of General Surgery, Yalgado Ouedraogo Teaching Hospital, Ouagadougou 160, Burkina Faso

**Corresponding author:** Ayun K Cassell III, MD, MPH, MFSTEd, FICS, Academic Fellow, Lecturer, Senior Researcher, Surgeon, Department of Urology and Andrology, Hopital General de Grand Yoff, Grand Yoff, Dakar 3270, Senegal. ayuncasselliii@gmail.com

## Abstract

The novel 2019 corona virus disease also called severe acute respiratory syndrome coronavirus 2 has caused a global pandemic and more than 2.5 million people have been affected globally with over 100000 deaths. The disease has caused an escalation in hospitalization with growing need for hospital beds and intensive care unit for severe cases. Recent evidence has shown that a significant proportion of cancer patients affected by the corona virus present with severe respiratory pneumonia-like illness with need for subsequent intensive care unit ventilation and higher mortality risk. This susceptibility may be due to the immunosuppressive state of patients with malignancy confounded by chemotherapy, immunotherapy and targeted therapy. Many solid tumors (lung cancer, pancreatic cancer) as well as hematological malignancies (leukemias) may require prompt diagnosis and treatment based on the disease aggression and progression. Many centers lack clear guideline on the management of cancer during the pandemic. The objective of this review is to synthesize the available literature and provide recommendations on the management of various soft tissue and hematological malignancies. The review will also assess the management guidelines for hospitalized cancer patients; cancer patients in the outpatient setting as well as available modalities for follow-up.

**Key words:** Cancer; Chemotherapy; COVID-19; Coronavirus; Pandemic; Transmission; Radiotherapy

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**Core tip:** Management of cancer patients during the novel 2019 corona virus disease pandemic is challenging. The need of surgery, chemotherapy or radiation therapy places the patients at risk of nosocomial transmission. The myelosuppressive effect of chemotherapy and radiation may increase the morbidity and mortality associated with the coronavirus. Therefore, cancer treatment should be stratified based on the benefits and risk of intervention. Avoiding unnecessary procedures, social distancing, hand hygiene and mask wear could reduce the associated disease burden.

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## BACKGROUND

The novel 2019 corona virus disease (COVID-19) also called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic and more than 2.5 million people have been affected globally with over 100000 deaths[1]. The corona virus is highly contagious and transmitted from person to person through direct contact of respiratory secretions from coughing or sneezing[2]. The disease has caused an escalation in hospitalization with growing need for hospital beds and intensive care unit for severe cases. During this period, the oncological practice has faced enormous challenges.

Recent evidence has shown that a significant proportion of cancer patients affected by the corona virus present with severe respiratory pneumonia-like illness with need for subsequent intensive care unit (ICU) ventilation along with higher mortality risk[3]. Study by Liang *et al*[4] revealed that cancer patients with corona virus progress more rapidly to severe disease than non-cancer patients. This susceptibility may be due to the immunosuppressive state of patients with malignancy confounded by chemotherapy, immunotherapy and targeted therapy[1]. Most cancers centers are now weighing the benefit of cancer treatment and risk of exposure to the corona virus.

Many solid tumors (lung cancer, pancreatic cancer) as well as hematological malignancies (leukemias) may require prompt diagnosis and treatment based on the disease aggression and progression[5]. However, low risk early-stage breast cancer, prostate cancer and cervical cancer may be amenable to some delay in treatment. The major risks to cancer patients remain the availability of hospital beds, changes of resource allocation and the lack of an appropriate guideline for cancer care during a pandemic[6]. Even if cancer treatment is to continue, the risk of nosocomial infection remains a concern during the pandemic.

Currently, many oncological societies and cancer networks have assessed the risk of COVID-19 infection for cancer patients and formulated practice recommendation for oncological care including neoadjuvant therapy, surgery, adjuvant therapy, immunotherapy, targeted therapy and palliative care. Several soft tissue malignancies have now been stratified according to priority or risk level predicting the need for either urgent intervention, delayed intervention or deferment of intervention after the pandemic.

The objective of this review is to synthesize the available literature and provide recommendations on the management of various soft tissue and hematological malignancies. The review will also assess the management guidelines for hospitalized cancer patients; cancer patients in the outpatient setting as well as available modalities for follow-up.

## LITERATURE SEARCH

A comprehensive literature search of COVID-19 was conducted using the PubMed database from December 2019 until the May 11, 2020. The keyword used was "managing cancer patients during the COVID-19 pandemic". A total of 71 articles were retrieved after using free full-text filter in the PubMed database. Both the English and French literatures were included for analysis. Duplicated articles on COVID-19 during the search were also excluded. All articles published in the Chinese language

were also excluded from the study. The title, abstract and full text of the retrieved publication were screened for eligibility. A snapshot of the search in PubMed data was presented in Figure 1.

## ELIGIBILITY

About 37 texts met the desired objective and were included in the review for analysis. All soft tissue malignancies with proposed management recommendation on neoadjuvant therapy, surgery, adjuvant therapy, immunotherapy, targeted therapy and palliative care were included in the study. All commentaries, editorials, reviews, group consensus and original article with recommendation on cancer management during the COVID-19 pandemic were considered for inclusion. All accepted articles, with published online proof reviewing recommendation of cancer management were included for analysis. A PRISMA flow chart was used to summarize the selection process (Figure 2).

## RESULT

Out of the 35 papers retrieved, 34 articles were published in the English language with only one in French. The result included review recommendations and guidelines, commentaries, editorials, letters and correspondence. The selected articles provided various recommendations for cancer care during this current corona virus crisis assessing the benefit of treatment against the risk of contracting the virus.

The qualitative analysis included articles with data on COVID-19 epidemiology, recommendations for hospitalized cancer patients, outpatient settings and oncological follow-up during the COVID-19 pandemic. There was also specific recommendation for specific types of malignancy during the pandemic including hematological cancers, sarcoma, breast cancer, urological cancers, thoracic cancers, neuro-oncology, head and neck cancers, gastrointestinal cancers and colorectal cancer (Figure 3). A qualitative analysis of the various 'malignancies is synthesized below.

## EVIDENCE SYNTHESIS AND DISCUSSION

### *Managing cancer patients during the COVID-19 pandemic*

Due to the immunosuppressive state of cancer patients most oncological practices are now informing all cancer patients about signs and symptoms of COVID-19 (fever, cough, dyspnea, fatigue)[7] and advocating strong adherence to social distancing principle[1,5]. Report from a Collaborative Cancer Network in the United States by Ueda *et al*[8] have demanded that all cancer patients are triaged for respiratory symptoms as part of a mandatory practice for this current outbreak. A systematic review by Moujaess *et al*[9] found that cancer patients may present with atypical clinical and radiological features that could be confused for SARS-CoV-2 infection causing a diagnostic dilemma.

**Management in outpatient settings:** An International Collaborative Group involving several cancer centers around the world have proposed that clinic visits should be restricted, and universal precaution is taken[6]. According to Al-Shamsi *et al*[6], clinic attendants should be limited as much as possible because the coronavirus could be asymptomatic in up to 33.3% of patients. To minimize occupational hazard, health care workers wear personal protection equipment (PPE) and maintain health protocols to ensure infection control and avoid nosocomial transmission[1]. Shankar *et al*[1] and Motlagh *et al*[2] recommended that patients with cancer could be selectively treated provided there is a guideline for risk stratification to prevent unnecessary infection from COVID-19 in hospital settings[5]. According to Al-Shamsi *et al*[6] and Gosain *et al*[7], patients on intravenous chemotherapy can be switched to appropriate oral chemotherapy if feasible. Decision should be considered on a case by case basis. Home drawn blood service is now being recommended to monitor side effect from chemotherapy[6]. For symptom management and chemotherapy supervision, telemedicine is being strongly advocated. The Gustave Roussy cancer center in France is now utilizing telemedicine for monitoring and organizing referrals for cancer patients with COVID-19[10]. According to Scotté *et al*[10] telemedicine is also being used

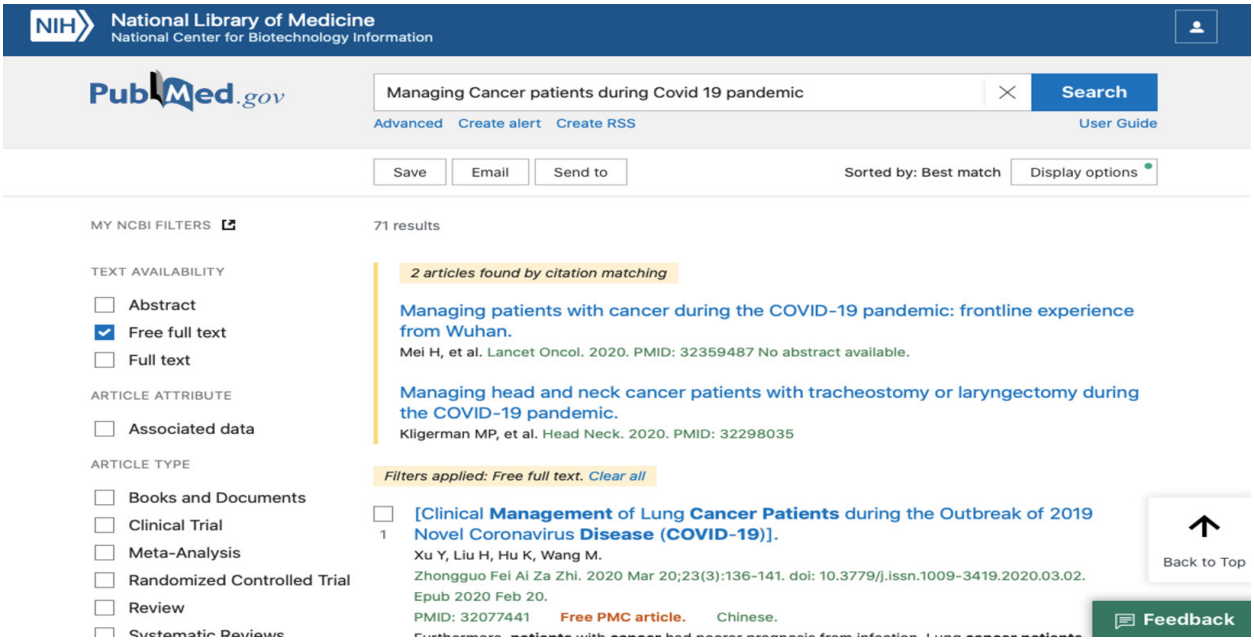


**Figure 1 Search strategy using PubMed database for free full text.**

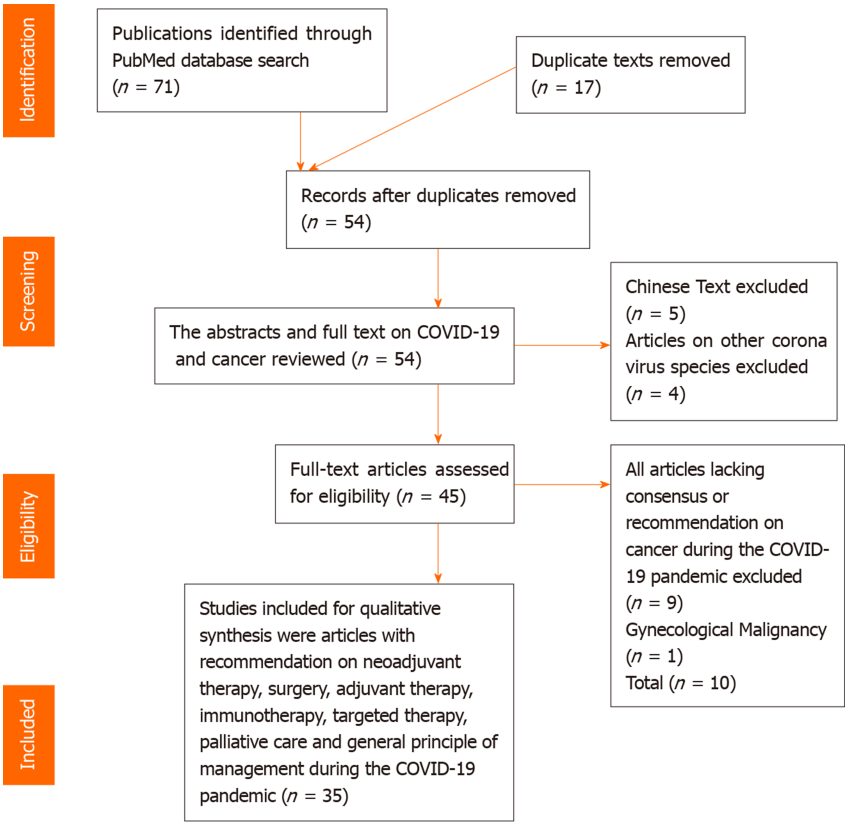


**Figure 2 PRISMA flow chart outlining the selection of articles for qualitative analysis.** COVID-19: Novel 2019 corona virus disease.

by other institution in France to monitor cancer patients on oral therapy. Mei *et al*[11] reported that the Cancer Center of Wuhan in China have now attended to more than 80000 cancer patients using the telemedicine platform. Nonetheless, the limitation of telemedicine remains the inability to perform a physical examination. Patients receiving curative radiation therapy are encouraged to continue[3]. Patients who have a known contact can continue treatment in a separate compartment.

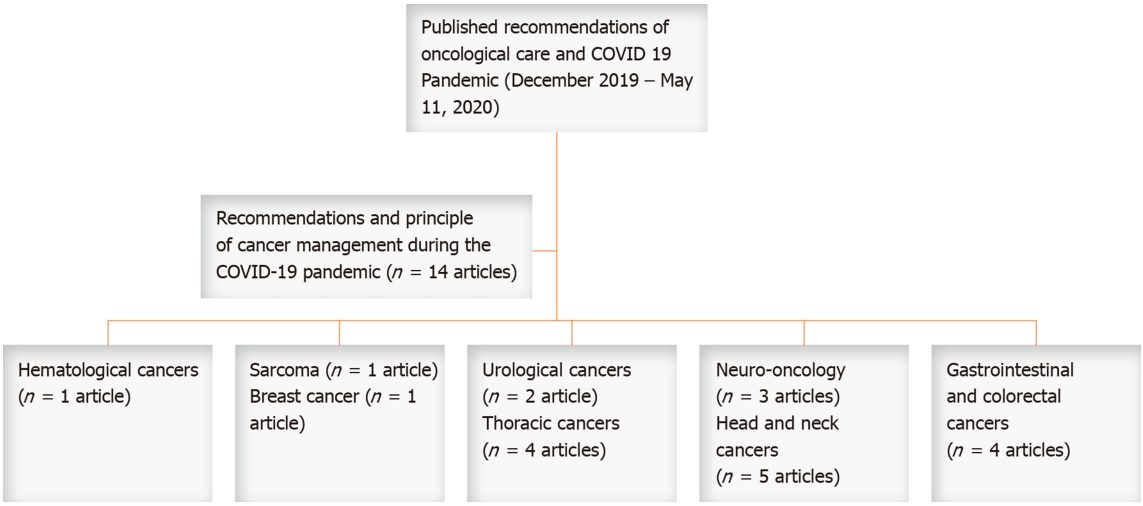


**Figure 3 Number of retrieved recommendations on each malignancy during the novel 2019 corona virus disease pandemic.** COVID-19: Novel 2019 corona virus disease.

**Hospitalized patients with cancer:** The management of hospitalized patients during the pandemic is complicated. Strict safety measures should be ensured by all health care provider to avoid nosocomial transmission[11]. The number of ward staff should be reduced as much as possible[12]. Patients that are symptomatic should be isolated and tested. If results are positive for SARS-CoV-2 infection, the patient should be moved to the COVID-19 disease treatment unit according to the safety protocols. According to Motlagh *et al*[2] cancer patients are at higher risk vascular thrombosis therefore, mobilizing the patients is crucial during these isolations. Delaying surgery and chemotherapy in these setting is reasonable due to the high demand of ICU beds and ventilation[3,4]. Conversely, an editorial by Peng *et al*[13] stated that the cessation or continuation of chemotherapy in the setting of COVID-19 infection remains debatable. This was based on reports that cancer patients coinfected with human immunodeficiency virus and hepatitis B did not experience viral reactivation during chemotherapy. A multi-center study by Tan *et al*[12] recommended risk stratification for cancer patients requiring surgery as either emergency or selective operation. Rapidly progressing and compressive tumors with imminent risk of rupture and hemorrhage should be operated as an emergency[12]. According to Gosain *et al*[7] patient who have received neoadjuvant therapy awaiting tumor resection can be addressed on a selective basis considering the hospital capacity, cancer stage and the burden of the prevailing coronavirus pandemic. Intervention for cancer can be avoided for patients that are clinically stable or those requiring palliative care during the peak of the virus epidemic.

**Cancer in older patients:** Data have shown that older cancer patients have higher risk of respiratory complications and death following a viral infection therefore increase barrier methods, mask wearing, and hand hygiene should be provided for this population[3,4,14]. The report by Falandry *et al*[14] from France was inconclusive whether older cancer with COVID-19 infection should be offer resuscitation when needed considering the high demand of ICU beds and ventilation. This calls into question ethical issues that differs across center based on the disease burden and available resources for treatment. However, it is being advocated that older cancer patients should not become systemically excluded from oncological care with the theory of their impending risk of severe disease when infected with the coronavirus[3,14].

**Specific recommendation for hematological malignancies:** A multi-center review in Brazil by Perini *et al*[15] provided recommended management algorithm for patients with lymphoid malignancies during the coronavirus outbreak. All lymphoid malignancies in remission are advised to be postponed with virtual follow-up and counseling. Patients with aggressive non-Hodgkin lymphoma like Burkitt's lymphoma, plasmoblastic lymphoma, lymphoblastic lymphoma, mantle cell lymphoma and peripheral T-cell lymphoma are recommended immediate treatment using the appropriate regimen[15]. Granulocyte stimulating agents (G-CSF) should be considered strongly to avoid febrile neutropenia during the COVID-19 pandemic.

Nonetheless, patients with indolent lymphoma like chronic lymphocytic lymphoma and follicular lymphoma can benefit from watchful waiting or a less intense regimen including oral chemotherapies can be considered. Patients with relapse and refractory diseases can be managed on an outpatient basis. Treatment should not be delayed for patients with Hodgkin lymphoma, but less intensive chemotherapeutic regimen should be initiated.

**Specific recommendation for sarcoma:** The French Sarcoma in collaboration with the European Society for Medical Oncology (ESMO) by Penel *et al*[16] proposed several management recommendations for sarcoma patients during the COVID-19 crisis. Operable patients with soft tissue sarcoma, visceral sarcoma and bone sarcoma without symptoms of coronavirus infection should not have their surgery delayed[16]. Patients with Ewing's sarcoma, osteosarcoma, alveolar sarcoma and embryonal rhabdomyosarcoma without symptoms of COVID-19 infection should proceed with standard treatment including neoadjuvant chemotherapy, surgery and adjuvant chemotherapy[16]. Patients with advanced soft tissue sarcoma should receive standard chemotherapy along with G-CSF to avoid neutropenia.

**Specific recommendation for breast cancer:** Based on the challenges of cancer care during the recent coronavirus outbreak, the Commission on Cancer, the National Accreditation Program for Breast Centers, American Society of Breast Surgeons, the National Comprehensive Care Net-work, and the American College of Radiology have stratified patients with breast cancer into priority categories[17]. These recommendations were based on individual patient's disease, comorbidities and treatment benefits.

Priority A category are patients that are clinically unstable with life threatening disease like breast abscess and sepsis or expanding breast hematoma. Immediate operative drainage is warranted for breast abscess; breast tumor hematoma should be evacuated with control of the bleeder.

Patients priority B category do not have life threatening conditions, but their surgery should not be deferred after the pandemic. A short delay of 6-12 wk may not adversely affect treatment outcome in this group. Patients in this group include hormone receptor positive patients, mastectomy flap ischemia, patients completing neoadjuvant therapy and suspected local recurrences[17].

Individuals in priority C category are patients whose intervention can be deferred indefinitely till after the epidemic without adversely affecting treatment outcome. These include hormone receptor +/- ductal carcinoma *in situ*, clinical stage I breast cancers, benign breast lesions, prophylactic mastectomies and discordant benign biopsies[17].

**Specific recommendation for urological cancers:** The Cancer Committee of the French Association of Urology (CCFAU) published a report by Méjean *et al*[18] with formulated guidelines for the management of urological malignancies during the COVID-19 pandemic.

Localized renal cancer along with renal cyst Bosniak I and II should be postponed and undergo quarterly surveillance. Patients with locally advanced renal cancer or symptomatic tumor with pain and hematuria should have their surgery prioritized. Good prognosis metastatic renal cancer can benefit from immunotherapy with virtual follow-up from home. Poor prognosis metastatic renal cancer can receive immunotherapy, but the benefit should be balanced against the risk of toxicity[18]. Otherwise, palliative care is a reasonable alternative.

According the CCFAU guideline, transurethral resection for low-grade, low volume, non-muscle invasive bladder tumor without out evidence of carcinoma in situ from urine cytology can be delayed for 3 mo. Patients with muscle invasive bladder cancer or non-muscle invasive disease refractory to bacille Calmette-Guerin therapy should have radical cystectomy within 3 mo following diagnosis[18]. Neoadjuvant chemotherapy is discouraged in this setting.

According to Méjean *et al*[18] low risk localized prostate cancer should preferably undergo surveillance during the outbreak. A systematic review by radio-oncology groups in the United Kingdom (UK) and the United States of America (USA) by Zaorsky *et al*[19] recommended that radiotherapy for low risk prostate cancer can be delayed until safe. The CCFAU recommended that patients with intermediate risk localized prostate cancer, treatment can be delayed within 2 mo. These include radical prostatectomy, extremal beam radiotherapy and brachytherapy. For patients with high risk and localized advanced prostate cancer, surgery cannot be delayed more than 2 mo and hormonotherapy should not be delayed. The radio-oncology group in UK and USA[19] recommended a delay of 1-3 mo for intermediate risk prostate cancer, high risk

prostate cancer, postprostatectomy and nodal cancer requiring radiation therapy. The initiation of androgen deprivation therapy (ADT) for high risk prostate cancer can help in the delay of intervention. However, if delay is not feasible, external beam radiotherapy is preferred with the shortest fractionation schedule. Nevertheless, the benefit of treatment, the toxicity of treatment as well as the risk of contracting COVID-19 infection are important parameters to assess to limit morbidity and mortality.

Patients with hormone sensitive metastatic prostate cancer can continue ADT and newer generation hormonotherapy (apalutamide or enzalutamide)[18]. Patients with castrate resistant metastatic prostate cancer treated who did not receive second generation hormonotherapy can continue ADT with enzalutamide. Chemotherapy and steroid should be avoided to prevent unwanted toxicity. For patients with castrate resistant metastatic prostate cancer who received second generation hormonotherapy, the risk and benefits of initiating chemotherapy can be discussed (docetaxel, carbazitaxel)[18]. G-CSF should be considered to avoid neutropenia in patient on chemotherapy. According to Zaorsky *et al*[19] radiotherapy for low volume metastatic cancer and oligometastases can be delayed up to 6 mo for patients on ADT.

**Specific recommendation for thoracic cancers:** A consensus statement from the Thoracic Surgery Outcomes Research Network formulated several recommendations for thoracic cancers based on the high usage of ICU beds, ventilators and PPE during the COVID-19 pandemic. Lung cancer ≥ 2-cm, node positive lung cancer, high risk chest wall tumors, symptomatic mediastinal tumors and invasive esophageal cancer should have surgery prioritized in the soonest possible time[20]. Yet, lung cancer less than 2-cm, indolent histology, asymptomatic thymoma, pulmonary oligometastases, bronchoscopy, upper endoscopy and tracheostomy can be deferred for up to 3 mo[20].

An ESMO publication by Banna *et al*[21] also stratified non-small cell lung cancer and small cell lung cancer for treatment intervention. For locally advanced resectable non-small cell lung cell, neoadjuvant chemotherapy, chemotherapy + radiotherapy and immunotherapy should not delay treatment when possible[21]. Nonetheless, Chemotherapy should be withheld in patients at significant risk of COVID-19 infection. Patients with locally advanced to advanced small cell lung cancer should continue with standard treatment. Treatment should be delayed in patients at risk of COVID-19 infection or those requiring long period of immunotherapy. According to Zhao *et al*[22], immunotherapy is associated with significant pulmonary toxicity as such should be suspended or postponed in patients with stable disease.

Study by Mazzone *et al*[23] also provided a consensus statement on the management of lung nodule during the epidemic. There was almost a unanimous agreement that evaluation should be delayed for pulmonary nodule discovered incidentally or during screening that are likely indolent[23]. The expert group from this study generally agreed that surgery for localized non-small cell lung cancer can be postponed if there no evidence of an aggressive disease or progression.

**Specific recommendation for brain cancers:** A correspondence by Zacharia *et al*[24] stratified patients with brain tumor needing surgery into emergent, urgent and semi-urgent. In the setting of a brain tumor with impending herniation or hydrocephalus, surgery should be performed as soon as possible[24]. All patients should be considered COVID-19 positive until otherwise. Enhanced PPE is required for all operating staff and health care providers. High grade malignancies or tumor presenting with progressive neurological deficits should be operated urgently between 2 to 7 d. Attempt COVID-19 testing preoperatively if possible.

Patients with asymptomatic or benign brain lesions can have their surgery delayed up to 4 wk. Patient should be properly screened, and every health precaution should be maintained including self-quarantine for 14 d before surgery. Studies by Mohile *et al*[25] and Bernhardt *et al*[26] also formulated guidelines for patients with gliomas during the COVID-19 pandemic. According to Mohile *et al*[25] newly diagnosed glioma should continue with their standard of care but with precaution to avoid nosocomial transmission. Therapy for recurrent glioma should be delayed and certain chemotherapeutic agents avoided[25,26].

**Specific recommendation for head and neck cancers:** The French consensus on the standard of care of head and neck surgery by Fakhry *et al*[27] stratified patients into 3 groups. Cancer patients with life-threatening emergencies (dyspnea, hemorrhage) where classified as Group A and required immediate treatment. The SARS-COV-2 swab test along with a chest CT-san in 24 h is advisable before surgery.

Aggressive cancer of the salivary gland and aerodigestive tract for whom treatment postponement for a month will adversely affect outcome of the disease were considered as Group B. If tracheostomy is not required, the surgery should be delayed,

and all necessary investigation done[27].

Well differentiated thyroid cancer, non-progressive skin cancer and slow growing salivary gland tumor were considered as Group C for which treatment can be postponed for 6 to 8 wk without adversely affecting outcome.

A review by a head and neck oncology group Day *et al*[28] proposed that hospitals should provide preoperative, intraoperative and postoperative management algorithm to ensure patient and staff safety. They proposed several reasons for strict precautions by head and neck surgeons. The coronavirus replicates in the nasal cavities, nasopharynx and oropharynx which are sites for routine head and neck surgery[28]. The coronavirus is aerosolized for at least three hours. Most head and neck surgeries require general anesthesia which entail aerosol generating procedures like bag-valve mask ventilation and intubation. The team recommended that most high-risk procedures should be performed with an N95 mask or a powered air-purifying respirator. The disadvantage is that these masks are uncomfortable to surgeons for long standing procedures.

A guideline consensus from the European Society for Radiotherapy and Oncology and the American Society of Radiation Oncology agreed that patients with locally advanced squamous cell carcinoma of the oropharynx and larynx scan continue radiation therapy with concurrent chemotherapy[29].

According to Sharma *et al*[30] the management of head and neck cancer in elderly patient during the COVID-19 pandemic is very challenging. About 70% of death from head and neck cancer occur in patients over 70 years. Moreover, 95% of COVID-19 death occur in patients over 60 years and about 50% in patients over 80 years alone[30]. Therefore, treatment decision for this group should be individualized considering disease severity, comorbidity and risk of coronavirus infection (Figure 4).

Report by Salari *et al*[31] conveyed that multidisciplinary meeting for head and neck cancer in Iran have now been moved to a virtual platform, since the COVID-19 pandemic. During these virtual meetings, cancer surgeons, head and neck surgeons, maxillofacial surgeons, medical oncologists, radiologist, radiotherapist and nuclear medicine specialist discuss the benefit and risk of treatment and patient are prioritized for the appropriate treatment[31].

**Specific recommendation for gastrointestinal and colorectal cancers:** An editorial by Patel *et al*[32] recently outlined three groups prioritizing the treatment of cancer patient during the COVID-19 pandemic. This stratification had been previously released by the American Society of Clinical Oncology. Group 1 were patients who completed treatment or patients with controlled disease. Clinics visits were recommended to be delayed and telemedicine platform are to be used for follow-up. Group 2 were patients undergoing active neoadjuvant or adjuvant treatment with curative intent. Patients were encouraged to continue treatment while minimizing the risk of nosocomial transmission with hand hygiene, PPE for staff and social distancing[32]. Patients undergoing treatment for metastatic disease were considered as Group 3. Delaying treatment in this group was considered reasonable if it did not adversely affect the disease outcome. Another multi-center radio-oncology report by Tchelebi *et al*[33] classified the provision of radiotherapy during the pandemic for several gastrointestinal cancers including esophageal cancer, gastric cancer, hepatocellular cancer, cholangiocarcinoma, pancreatic cancer, rectal cancer and anal cancer. The group recommended that operable esophageal cancer, advanced gastric cancer, locally advanced operable rectal cancer and hepatocellular cancer can receive radiation therapy reducing the period of fractionation. Radiotherapy was not recommended in operable or resected gastric cancer, operable cholangiocarcinoma and resectable pancreatic tumor[33]. These recommendations were made to guide treatment decision; to either reduce disease progression or avoid unnecessary exposure to the COVID-19 infection. A report by Romesser *et al*[34] from the Memorial Sloan Kettering Cancer Center suggested that short course radiation therapy (SCRT) can provide quality and efficient oncological care for patients while reducing the risk of exposure to the COVID-19 infection. A report from a multinational colorectal cancer group in Europe by Di Saverio *et al*[35] proposed that surgery during the COVID-19 pandemic should be aligned by clear perioperative protocols. The group advocated safe transfer of patients between the ward and the operating theater with the proper use of PPE by staffs and coordinated transport system between the theater staff and ward staff[35].

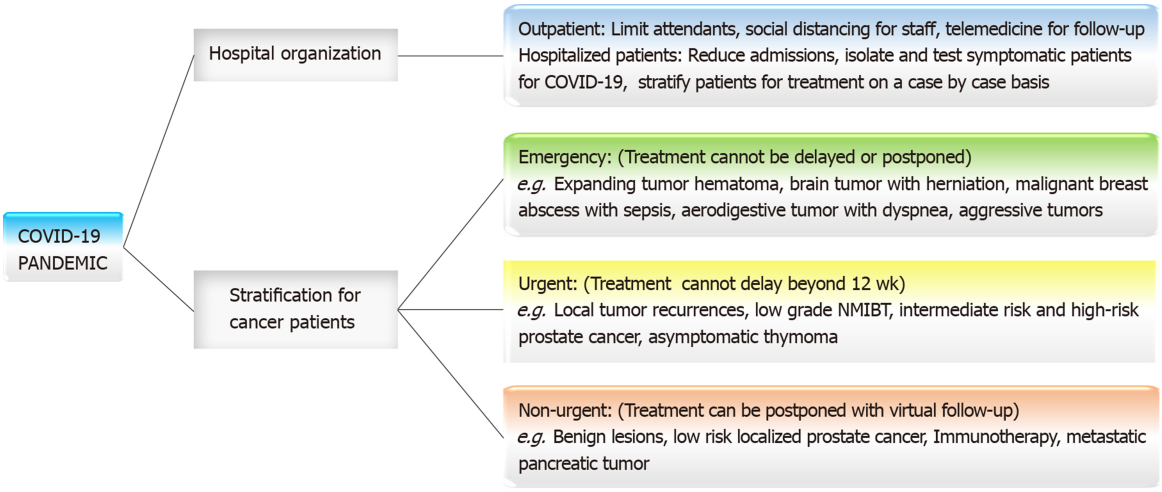


**Figure 4 Organizational structure and risk stratification of cancer patient for management during the novel 2019 corona virus disease pandemic.** COVID-19: Novel 2019 corona virus disease.

## CONCLUSION

Management of cancer patients during the COVID-19 pandemic is challenging. The need of surgery, chemotherapy or radiation therapy places the patients at risk of nosocomial transmission. The myelosuppressive effect of chemotherapy and radiation may increase the morbidity and mortality associated with the coronavirus. Therefore, cancer treatment should be stratified based on the benefits and risk of intervention. Avoiding unnecessary procedures, social distancing, hand hygiene and mask wear could reduce the associated disease burden.

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## REFERENCES

1 **Shankar A**, Saini D, Roy S, Mosavi Jarrahi A, Chakraborty A, Bharti SJ, Taghizadeh-Hesary F. Cancer Care Delivery Challenges Amidst Coronavirus Disease - 19 (COVID-19) Outbreak: Specific Precautions for Cancer Patients and Cancer Care Providers to Prevent Spread. *Asian Pac J Cancer Prev* 2020; **21**: 569-573 [PMID: 32212779 DOI: 10.31557/APJCP.2020.21.3.569]

2 **Motlagh A**, Yamrali M, Azghandi S, Azadeh P, Vaezi M, Ashrafi F, Zendehdel K, Mirzaei H, Basi A, Rakhsha A, Seifi S, Tabatabaeefar M, Elahi A, Pirjani P, Moadab Shoar L, Nadarkhani F, Khoshabi M, Bahar M, Esfahani F, Fudazi H, Samiei F, Farazmand B, Ahmari A, Vand Rajabpour M, Janbabaei G, Raisi A, Ostovar A, Malekzadeh R. COVID19 Prevention & Care; A Cancer Specific Guideline. *Arch Iran Med* 2020; **23**: 255-264 [PMID: 32271599 DOI: 10.34172/aim.2020.07]

3 **Al-Quteimat OM**, Amer AM. The Impact of the COVID-19 Pandemic on Cancer Patients. *Am J Clin Oncol* 2020; **43**: 452-455 [PMID: 32304435 DOI: 10.1097/COC.0000000000000712]

4 **Liang W**, Guan W, Chen R, Wang W, Li J, Xu K, Li C, Ai Q, Lu W, Liang H, Li S, He J. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; **21**: 335-337 [PMID: 32066541 DOI: 10.1016/S1470-2045(20)30096-6]

5 **Kutikov A**, Weinberg DS, Edelman MJ, Horwitz EM, Uzzo RG, Fisher RI. A War on Two Fronts: Cancer Care in the Time of COVID-19. *Ann Intern Med* 2020; **172**: 756-758 [PMID: 32219410 DOI: 10.7326/M20-1133]

6 **Al-Shamsi HO**, Alhazzani W, Alhuraiji A, Coomes EA, Chemaly RF, Almuhanna M, Wolff RA, Ibrahim NK, Chua MLK, Hotte SJ, Meyers BM, Elfiki T, Curigliano G, Eng C, Grothey A, Xie C. A Practical Approach to the Management of Cancer Patients During the Novel Coronavirus Disease 2019 (COVID-19) Pandemic: An International Collaborative Group. *Oncologist* 2020; **25**: e936-e945 [PMID: 32243668 DOI: 10.1634/theoncologist.2020-0213]

7 **Gosain R**, Abdou Y, Singh A, Rana N, Puzanov I, Ernstoff MS. COVID-19 and Cancer: a Comprehensive Review. *Curr Oncol Rep* 2020; **22**: 53 [PMID: 32385672 DOI: 10.1007/s11912-020-00934-7]

8 **Ueda M**, Martins R, Hendrie PC, McDonnell T, Crews JR, Wong TL, McCreery B, Jagels B, Crane A, Byrd DR, Pergam SA, Davidson NE, Liu C, Stewart FM. Managing Cancer Care During the COVID-19 Pandemic: Agility and Collaboration Toward a Common Goal. *J Natl Compr Canc Netw* 2020; 1-4 [PMID: 32197238 DOI:

10.6004/jnccn.2020.7560]
9 **Moujaess E**, Kourie HR, Ghosn M. Cancer patients and research during COVID-19 pandemic: A systematic review of current evidence. *Crit Rev Oncol Hematol* 2020; **150**: 102972 [PMID: 32344317 DOI: 10.1016/j.critrevonc.2020.102972]
10 **Scotté F**, Minvielle E, Mir O, André F, Barlesi F, Soria JC. A patient reported outcome platform, a useful tool to improve monitoring and effective management of Covid-19-positive patients with cancer. *Eur J Cancer* 2020; **132**: 1-4 [PMID: 32294611 DOI: 10.1016/j.ejca.2020.03.020]
11 **Mei H**, Dong X, Wang Y, Tang L, Hu Y. Managing patients with cancer during the COVID-19 pandemic: frontline experience from Wuhan. *Lancet Oncol* 2020; **21**: 634-636 [PMID: 32359487 DOI: 10.1016/S1470-2045(20)30238-2]
12 **Tan J**, Yang C. Prevention and control strategies for the diagnosis and treatment of cancer patients during the COVID-19 pandemic. *Br J Cancer* 2020 [PMID: 32313215 DOI: 10.1038/s41416-020-0854-2]
13 **Peng L**, Zagorac S, Stebbing J. Managing patients with cancer in the COVID-19 era. *Eur J Cancer* 2020; **132**: 5-7 [PMID: 32302754 DOI: 10.1016/j.ejca.2020.03.028]
14 **Falandry C**, Filteau C, Ravot C, Le Saux O. Challenges with the management of older patients with cancer during the COVID-19 pandemic. *J Geriatr Oncol* 2020; **11**: 747-749 [PMID: 32273247 DOI: 10.1016/j.jgo.2020.03.020]
15 **Perini GF**, Fischer T, Gaiolla RD, Rocha TB, Bellesso M, Teixeira LLC, Delamain MT, Scheliga AAS, Ribeiro GN, Neto JV, Baiocchi OCCG, Abdo ANR, Arrais-Rodrigues C, Fogliatto LM, Bigni RS, Schaffel R, Biasoli I, Pereira J, Nabhan SK, Souza CA, Chiattone CS; Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular (ABHH). How to manage lymphoid malignancies during novel 2019 coronavirus (CoVid-19) outbreak: a Brazilian task force recommendation. *Hematol Transfus Cell Ther* 2020; **42**: 103-110 [PMID: 32313873 DOI: 10.1016/j.htct.2020.04.002]
16 **Penel N**, Bonvalot S, Minard V, Orbach D, Gouin F, Corradini N, Brahmi M, Marec-Bérard P, Briand S, Gaspar N, Llacer C, Carrère S, Dufresne A, Le Cesne A, Blay JY. French Sarcoma Group proposals for management of sarcoma patients during the COVID-19 outbreak. *Ann Oncol* 2020; **31**: 965-966 [PMID: 32278878 DOI: 10.1016/j.annonc.2020.03.308]
17 **Dietz JR**, Moran MS, Isakoff SJ, Kurtzman SH, Willey SC, Burstein HJ, Bleicher RJ, Lyons JA, Sarantou T, Baron PL, Stevens RE, Boolbol SK, Anderson BO, Shulman LN, Gradishar WJ, Monticciolo DL, Plecha DM, Nelson H, Yao KA. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. the COVID-19 pandemic breast cancer consortium. *Breast Cancer Res Treat* 2020; **181**: 487-497 [PMID: 32333293 DOI: 10.1007/s10549-020-05644-z]
18 **Méjean A**, Rouprêt M, Rozet F, Bensalah K, Murez T, Game X, Rebillard X, Mallet R, Faix A, Mongiat-Artus P, Fournier G, Neuzillet Y; le comité de cancérologie de l'Association française d'urologie (CCAFU). [Recommendations CCAFU on the management of cancers of the urogenital system during an epidemic with Coronavirus COVID-19]. *Prog Urol* 2020; **30**: 221-231 [PMID: 32224294 DOI: 10.1016/j.purol.2020.03.009]
19 **Zaorsky NG**, Yu JB, McBride SM, Dess RT, Jackson WC, Mahal BA, Chen R, Choudhury A, Henry A, Syndikus I, Mitin T, Tree A, Kishan AU, Spratt DE. Prostate Cancer Radiotherapy Recommendations in Response to COVID-19. *Adv Radiat Oncol* 2020 [PMID: 32292839 DOI: 10.1016/j.adro.2020.03.010]
20 **Thoracic Surgery Outcomes Research Network, Inc**. COVID-19 Guidance for Triage of Operations for Thoracic Malignancies: A Consensus Statement from Thoracic Surgery Outcomes Research Network. *Ann Thorac Surg* 2020 [PMID: 32278755 DOI: 10.1016/j.athoracsur.2020.03.005]
21 **Banna G**, Curioni-Fontecedro A, Friedlaender A, Addeo A. How we treat patients with lung cancer during the SARS-CoV-2 pandemic: *primum non nocere*. *ESMO Open* 2020; **5**: e000765 [PMID: 32245904 DOI: 10.1136/esmoopen-2020-000765]
22 **Zhao Z**, Bai H, Duan J, Wang J. Recommendations of individualized medical treatment and common adverse events management for lung cancer patients during the outbreak of COVID-19 epidemic. *Thorac Cancer* 2020; **11**: 1752-1757 [PMID: 32291968 DOI: 10.1111/1759-7714.13424]
23 **Mazzone PJ**, Gould MK, Arenberg DA, Chen AC, Choi HK, Detterbeck FC, Farjah F, Fong KM, Iaccarino JM, Janes SM, Kanne JP, Kazerooni EA, MacMahon H, Naidich DP, Powell CA, Raoof S, Rivera MP, Tanner NT, Tanoue LK, Tremblay A, Vachani A, White CS, Wiener RS, Silvestri GA. Management of Lung Nodules and Lung Cancer Screening During the COVID-19 Pandemic: CHEST Expert Panel Report. *Chest* 2020 [PMID: 32335067 DOI: 10.1016/j.chest.2020.04.020]
24 **Zacharia BE**, Eichberg DG, Ivan ME, Hanft S, Boockvar JA, Isildak H, Mansouri A, Komotar RJ, D'Amico RS. Letter: Surgical Management of Brain Tumor Patients in the COVID-19 Era. *Neurosurgery* 2020; nyaa162 [PMID: 32347942 DOI: 10.1093/neuros/nyaa162]
25 **Mohile NA**, Blakeley JO, Gatson NTN, Hottinger AF, Lassman AB, Ney DE, Olar A, Schiff D, Shih HA, Strowd R, van den Bent MJ, Ziu M. Urgent Considerations for the Neuro-oncologic Treatment of Patients with Gliomas During the COVID-19 Pandemic. *Neuro Oncol* 2020; noaa090 [PMID: 32277236 DOI: 10.1093/neuonc/noaa090]
26 **Bernhardt D**, Wick W, Weiss SE, Sahgal A, Lo SS, Suh JH, Chang EL, Foote M, Perry J, Meyer B, Vajkoczy P, Wen PY, Straube C, Pigorsch S, Wilkens JJ, Combs SE. Neuro-oncology Management During the COVID-19 Pandemic With a Focus on WHO Grade III and IV Gliomas. *Neuro Oncol* 2020; noaa113 [PMID: 32369601 DOI: 10.1093/neuonc/noaa113]
27 **Fakhry N**, Schultz P, Morinière S, Breuskin I, Bozec A, Vergez S, de Garbory L, Hartl D, Temam S, Lescanne E, Couloigner V, Barry B; French Society of Otorhinolaryngology, Head and Neck Surgery (SFORL); French Society of Head and Neck Carcinology (SFCCF). French consensus on management of head and neck cancer surgery during COVID-19 pandemic. *Eur Ann Otorhinolaryngol Head Neck Dis* 2020; **137**: 159-160 [PMID: 32303485 DOI: 10.1016/j.anorl.2020.04.008]
28 **Day AT**, Sher DJ, Lee RC, Truelson JM, Myers LL, Sumer BD, Stankova L, Tillman BN, Hughes RS, Khan SA, Gordin EA. Head and neck oncology during the COVID-19 pandemic: Reconsidering traditional treatment paradigms in light of new surgical and other multilevel risks. *Oral Oncol* 2020; **105**: 104684 [PMID: 32330858 DOI: 10.1016/j.oraloncology.2020.104684]

29 **Thomson DJ**, Palma D, Guckenberger M, Balermpas P, Beitler JJ, Blanchard P, Brizel D, Budach W, Caudell J, Corry J, Corvo R, Evans M, Garden AS, Giralt J, Gregoire V, Harari PM, Harrington K, Hitchcock YJ, Johansen J, Kaanders J, Koyfman S, Langendijk JA, Le QT, Lee N, Margalit D, Mierzwa M, Porceddu S, Soong YL, Sun Y, Thariat J, Waldron J, Yom SS. Practice Recommendations for Risk-Adapted Head and Neck Cancer Radiation Therapy During the COVID-19 Pandemic: An ASTRO-ESTRO Consensus Statement. *Int J Radiat Oncol Biol Phys* 2020; **107**: 618-627 [PMID: 32302681 DOI: 10.1016/j.ijrobp.2020.04.016]

30 **Sharma A**, Crosby DL. Special considerations for elderly patients with head and neck cancer during the COVID-19 pandemic. *Head Neck* 2020; **42**: 1147-1149 [PMID: 32343444 DOI: 10.1002/hed.26216]

31 **Salari A**, Shirkhoda M. COVID-19 pandemic & head and neck cancer patients management: The role of virtual multidisciplinary team meetings. *Oral Oncol* 2020; **105**: 104693 [PMID: 32291153 DOI: 10.1016/j.oraloncology.2020.104693]

32 **Patel R**, Saif MW. Management of Pancreatic Cancer During COVID-19 Pandemic: To Treat or Not to Treat? *JOP* 2020; **21**: 27-28 [PMID: 32377176]

33 **Tchelebi LT**, Haustermans K, Scorsetti M, Hosni A, Huguet F, Hawkins MA, Dawson LA, Goodman KA. Recommendations for the use of radiation therapy in managing patients with gastrointestinal malignancies in the era of COVID-19. *Radiother Oncol* 2020; **148**: 194-200 [PMID: 32342878 DOI: 10.1016/j.radonc.2020.04.010]

34 **Romesser PB**, Wu AJ, Cercek A, Smith JJ, Weiser M, Saltz L, Garcia-Aguilar J, Crane CH. Management of Locally Advanced Rectal Cancer During The COVID-19 Pandemic: A Necessary Paradigm Change at Memorial Sloan Kettering Cancer Center. *Adv Radiat Oncol* 2020 [PMID: 32322758 DOI: 10.1016/j.adro.2020.04.011]

35 **Di Saverio S**, Pata F, Gallo G, Carrano F, Scorza A, Sileri P, Smart N, Spinelli A, Pellino G. Coronavirus pandemic and colorectal surgery: practical advice based on the Italian experience. *Colorectal Dis* 2020; **22**: 625-634 [PMID: 32233064 DOI: 10.1111/codi.15056]

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*MINIREVIEWS*

# Application of artificial intelligence in clinical non-small cell lung cancer

Yong Liu

**ORCID number:** Yong Liu 0000-0002-4048-5837.

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**Yong Liu,** Department of Thoracic Surgery, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430011, Hubei Province, China

**Corresponding author:** Yong Liu, MD, PhD, Surgical Oncologist, Department of Thoracic Surgery, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, No. 26, Shengli Street, Wuhan 430011, Hubei Province, China. liuyong7575@163.com

## Abstract

Lung cancer is the most common cause of cancer death in the world. Early diagnosis, screening and precise individualized treatment can significantly reduce the death rate of lung cancer. Artificial intelligence (AI) has been shown to be able to help clinicians make more accurate judgments and decisions in many ways. It has been involved in the screening of lung cancer, the judgment of benign and malignant degree of pulmonary nodules, the classification of histological cancer, the differentiation of histological subtypes, the identification of genomics, the judgment of the effectiveness of treatment and even the prognosis. AI has shown that it can be an excellent assistant for clinicians. This paper reviews the application of AI in the field of non-small cell lung cancer and describes the relevant progress. Although most of the studies to evaluate the clinical application of AI in non-small cell lung cancer have not been repeatable and generalizable, the research results highlight the efforts to promote the clinical application of AI technology and influence the future treatment direction.

**Key words:** Artificial intelligence; Machine learning; Non-small cell lung cancer; Diagnosis; Prognosis; Therapy



**Core tip:** Artificial intelligence has been shown to help clinicians make more accurate judgments and decisions in non-small cell lung cancer screening and preliminary evaluation of lung nodules, histological differentiation and diagnosis, genomic identification, decision-making of therapy, prognosis of overall survival, metastasis or recurrence. Electronic medical records could be used as a source of artificial intelligence

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to help clinicians. This manuscript reviews the state of art artificial intelligence applications in clinical non-small cell lung cancer for those who will be interested in this field.

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## INTRODUCTION

The global tumor statistics report released in 2018 shows that lung cancer is the malignant tumor with the highest morbidity and mortality in the world. The incidence of lung cancer accounts for 11.6% of the incidence of all tumors, and the mortality rate accounts for 18.4% of the deaths of all tumors[1]. Due to the late onset of clinical symptoms and limited screening procedures, a large number of patients are diagnosed as advanced[2]. Histologically, about 85% of new lung cancer cases are classified as non-small cell lung cancer (NSCLC), 10% are small cell lung cancer, and 5% are other variants[3]. Most NSCLC can be divided into three categories: squamous cell carcinoma, adenocarcinoma and large cell carcinoma[4]. Patients need the most accurate personalized treatment from doctors. Therefore, doctors need to obtain genomics, proteomics, immunohistochemistry and imaging data, in addition to histological, clinical and demographic information in order to develop precise treatment plans for patients. There are many factors, such as high cost of testing and treatment discontinuity, which will limit the timely access to data. This has aroused people's interest in developing artificial intelligence.

Artificial intelligence (AI) is an important product of the rapid development of computer technology. It has a profound impact on the development of human society and the progress of science and technology through communication and cooperation with multidisciplinary and multifield, especially the organic combination with medicine, which is one of the most promising fields. John McCarthy first proposed the concept of AI: To develop machine software with human thinking mode, so that computers can think like humans[5]. Machine learning (ML) is a method to realize AI, which belongs to a subfield of AI. It analyzes and interprets data through machine algorithms, learns from it, and then makes decisions or predictions about something. Therefore, unlike manually writing software routines to complete specific tasks with a specific set of instructions, machines use a large number of data and algorithms to "train", which give machines the ability to learn how to perform tasks. ML comes directly from the idea of the early artificial intelligence crowd. For many years, algorithm methods include decision tree learning, inductive logic programming, clustering, reinforcement learning and Bayesian network, *etc*. These algorithms allow information to be classified, predicted and segmented to provide insights that are difficult to obtain by the human eye or cognitive system.

Deep learning is a technology to realize ML. There are two key aspects in the description of advanced definition of deep learning: (1) A model composed of multilayer or multistage nonlinear information processing; and (2) A supervised or unsupervised learning method for feature representation at a higher and more abstract level[6]. There are many kinds of network learning models for deep learning, such as convolutional neural networks (CNN), recurrent neural networks, bi-directional long-term and short-term memory cyclic neural networks, multilayer neural networks, *etc*. Among them, the CNN is one of the representative algorithms of deep learning, which is a kind of feed forward neural networks with deep structure and convolution calculation. It consists of a series of layers. Each layer performs specific operations, such as convolution, pooling, loss calculation, *etc*. Each middle layer receives the output of the previous layer as its input and finally extracts the high-level abstraction through the fully connected layer. In the process of back propagation in the training stage, the weights of neural connection and kernel are optimized continuously. A CNN has the ability of representation learning, which can classify input information according to its hierarchical structure. Therefore, it is also called "translation invariant artificial neural network (ANN)".

There are two main methods of data processing in ML: Supervised learning and

unsupervised learning. Supervised learning specifically refers to the use of labeled data learning process to assist, so as to achieve learning objectives. The advantage is that the generalization ability of the machine itself can be given full play, and problems such as classification and regression can be effectively solved. Unsupervised learning does not need to be marked, and it explores the similarity between instances according to specific indicators and methods or the value relationship among features. The algorithms commonly used in unsupervised learning are as follows: Deep confidence network, automatic encoder, *etc*. The most important research problems of unsupervised learning include clustering, correlation analysis and dimension reduction. Other learning methods include reinforcement learning, which optimizes the model to get the best decision by giving different feedback to different choices in the iterative process, semisupervised learning that mixes supervised and unsupervised learning and transfer learning with models as an experiential training.

AI can improve patients' treatment results, ameliorate patients' treatment process and even mend medical management[7]. In view of the increasing application of AI in lung cancer treatment (Figure 1), this paper will review the AI applications being developed for NSCLC detection and treatment as well as the challenges facing clinical adaptability.

## APPLICATION OF AI IN SCREENING AND PRELIMINARY EVALUATION OF NSCLC

Pulmonary nodules are the early signs of lung cancer, which are of great significance for the diagnosis of early lung cancer. Early detection, early diagnosis and early treatment can improve the survival rate and prolong the survival time of patients. The national lung screening test showed that low-dose computed tomography (LDCT) screening was associated with a significant 20% reduction in overall mortality among current and previous high-risk smokers[8]. While conducting LDCT screening to detect patients with early-stage lung cancer, the number of health checkups, disease screenings and follow-up examinations is increasing. As a result, the workload of radiologists has multiplied. The increasing workload aggravates the fatigue of doctors, affects the quality of reading images and the accuracy of diagnosis results. The emergence of AI is just like a drop of sweet dew in a long drought for radiologists. AI can carry out self-learning and self-evolution under semi-supervision. At the same time as improving the accuracy of diagnosis, the time for doctors to read the images is greatly shortened, which solves the clinical needs well[9].

Most uncertain lung nodules were discovered by accident[10]. Every year, more than 1.5 million Americans are diagnosed with accidental detection of lung nodules[11]. Most of these nodules are benign granuloma and about 12% may be malignant[12]. Another potential hazard of lung cancer screening is the over diagnosis of slow-growing, inactive cancers. If left untreated, these cancers may not pose a threat. Therefore, over diagnosis must be identified and significantly reduced. Identifying the nature of pulmonary nodules by AI can effectively reduce the clinical work pressure as well as the long-term follow-up workload and ameliorate the psychological pressure of pulmonary nodule owners. In the field of cancer imaging, AI has found tremendous utility in three main clinical tasks: Detection, characterization and monitoring. In current clinical practice, imaging methods used to assess the presence of lung cancer include chest X-ray, computed tomography (CT) and positron emission tomography/computed tomography (PET/CT).

Chest X-ray is one of the most commonly used methods. The covering of the chest ribs on the lung field often affects the radiologists' reading of the film and increases the missed diagnosis rate of the lung nodule shadow. von Berg *et al*[13] used a dual energy subtraction technology based on ANN to reduce the bone density shadow in the X-ray film, expose the lung nodule covered by the bone structure and improve the sensitivity and specificity of the radiologist in the diagnosis of lung nodules. Nam *et al*[14] recently developed an algorithm for detecting malignant pulmonary nodules on chest X-ray films based on deep learning and compared its performance with that of physicians, half of whom were radiologists. They used 43292 cases of chest X-ray data. The ratio of normal to pathological changes was 3.67. Using external validation data sets, they found that the area under the curve (AUC) of the developed algorithm was higher than 17 of the 18 doctors. When all doctors used this algorithm as the second reader, they found the improvement of nodule detection.

For lung cancer screening, the sensitivity and specificity of LDCT are much higher than that of general chest X-ray[15]. More than 200 thin-layer images can be

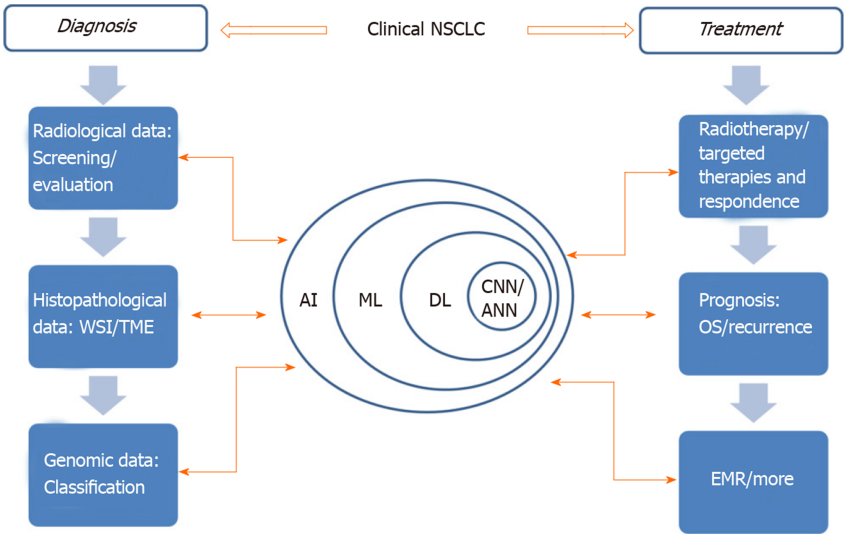


**Figure 1 The application of artificial intelligence involved in clinical non-small cell lung cancer.** Learning process and application of AI in different fields are indicated by those two-way arrows. AI: Artificial intelligence; ANN: Artificial neural network; CNN: Convolutional neural networks; DL: Deep learning; EMR: Electronic medical record; ML: Machine learning; NSCLC: Non-small cell lung cancer; OS: Overall survival time; TME: Tumor microenvironment; WSI: Whole slide image.

reconstructed after high-resolution CT scanning or spiral CT scanning, which results in excessive reading of radiologists. Pulmonary nodules < 3 mm are more time-consuming and laborious. This has caused a considerable workload for radiologists in the traditional mode. Pulmonary nodule AI detection software is most sensitive to pulmonary nodules of 3-6 mm followed by nodules above 6 mm. Nodules of 3-6 mm are the most easily missed diagnosis by human vision[16]. After the application of AI, the daily working time can be halved without changing the inspection amount, and there will be no missed diagnosis due to excessive fatigue[17,18]. Detection refers to the positioning of objects of interest in X-rays or CTs and is collectively referred to as computer-aided detection[19]. In the early 2000s, methods of computer-aided detection for automatically detecting lung nodules on CT were based on traditional ML methods, such as support vector machines[20]. Computer-aided detection is used as an assistant in LDCT screening to find missed cancers and to detect brain metastases on MRI to improve radiological interpretation time while maintaining high detection sensitivity[21]. The computer-aided detection x system has been used for the diagnosis of pulmonary nodules by thin-layer CT[22].

Due to the simplicity of clinical implementation, size-based measurements such as the longest tumor diameter are widely used for staging and response assessment. However, size-based features and disease stages have limitations such as imprecise diagnosis. A preliminary work shows that AI can automatically quantify the radiographic characteristics of tumor phenotype, which has a significant prognosis for many types of cancer, including lung cancer[23]. Liu *et al*[24] combined a model of four semantic features (minor axis diameter, contour, concavity and texture) of quantitative scores. The accuracy of distinguishing malignant and benign nodules in lung cancer screening environment was 74.3%. In a separate study[25], semantic features were identified from small lung nodules (less than 6 mm) to predict the incidence of lung cancer in the context of lung cancer screening. The AUC of the final model was 0.930 based on the total score of emphysema, vascular attachment, nodal location, border definition and concavity. Paul *et al*[26] used a kind of pre-trained CNN after large-scale data training to detect lung cancer by extracting the features of CT images. They combined the extracted deep neural network features with the traditional quantitative features and obtained 90% accuracy (AUC: 0.935) by using the five best corrected linear unit features and five best traditional features extracted by vgg-f pre-trained CNN.

In recent years, the number of pure ground glass nodules (pGGN) has increased significantly. Judging its nature and making the treatment plan is very important. Qi *et al*[27] retrospectively analyzed the clinical follow-up data of 573 CT scans belonging to 110 patients with pGGNs from January 2007 to October 2018. The Dr. Wise system based on CNN was used to segment the initial CT scan and all subsequent CT scans automatically. Then, the diameter, density, volume, mass, volume doubling time and mass doubling time of pGGNs were calculated. Kaplan-Meier analyses with the log-

rank test and Cox proportional hazards regression analysis were used to analyze the cumulative percentages of pGGN growth and identify risk factors for growth. It was found that persistent pGGNs showed a slow course. The 12-mo, 24.7-mo and 60.8-mo cumulative percentages of pGGN growth were 10%, 25.5% and 51.1%, respectively. Deep learning helps to clarify the natural history of pGGNs accurately. Those pGGNs with lobulated sign and larger initial diameter, volume and mass are more likely to grow up. Ardila *et al*[28] trained a deep learning algorithm on the NLST dataset, which came from 14851 patients and 578 of those patients developed lung cancer the following year. They tested the model on the first test data set of 6716 patients, and the AUC reached 94.4%. A part of 507 patients was compared with six radiologists. When a single CT is analyzed, the performance of the model was the same or higher than that of all radiologists.

The diagnosis of simultaneous or metachronous multiple pulmonary nodules is a new challenge for clinicians. In a retrospective study[29], a total of 53 patients with multiple pulmonary nodules, simultaneously or metachronously, were included. The coincidence rate of AI diagnosis and postoperative pathology to benign and malignant lesions was 88.8%. AI may represent a relevant diagnostic aid that can display more accurate and objective results when diagnosing multiple lung nodules. It may reduce the interpretation of results by displaying visual information directly to doctors and patients and the clinical status of multiple primary lung cancer patients. The time required and a reasonable follow-up and treatment plan may be more beneficial to the patient.

PET/CT using 18F-fluorodeoxyglucose (FDG) has been established as a great imaging method for the staging of patients with lung cancer[30]. Schwyzer *et al*[31] assessed whether machine learning would help detect lung cancer in FDG-PET imaging against the background of ultra-low-dose PET scans. The ANN was used to identify 3936 PET images, including images of lung tumors visible to the naked eye and image slices of patients without lung cancer. Based on clinical standard radiation dose PET images (PET 100%), 10% dose and 3.3% radiation dose (approximately 0.11 mSv), the diagnostic performance of the artificial neural network was evaluated. Their results indicated that even at very low effective radiation doses of 0.11 mSv, machine learning algorithms may contribute to fully automated lung cancer detection.

More and more new PET and single-photon emission computerized tomography tracers are used to explore various aspects of tumor biology, and hybrid multimodal imaging is increasingly used to provide multiparameter measurements. AI is needed to deal with the huge workload. According to reports[32], texture and color analysis of human FDG-PET images can be used to judge heterogeneity within tumors, thereby distinguishing NSCLC subtypes. Using support vector machine algorithm to extract texture and color features from FDG-PET images to differentiate histopathological tumor subtypes (squamous cell carcinoma and adenocarcinoma), the area under the receiver operating characteristic curve was 0.89. The use of the least absolute shrinkage and selection operator method[33] to derive radiographic descriptors of metastatic lymph nodes from FDG-PET images of patients with NSCLC has been found relate better with overall survival (OS) than the radiological data extracted from the primary tumor. Wang *et al*[34] made a comparison of ML methods for classifying NSCLC mediastinal lymph node metastasis from PET/CT images. A CNN and four ML methods (random forest, support vector machine, adaptive boosting and artificial neural networks) were used to classify mediastinal lymph node metastases of NSCLC. PET/CT images of 1397 lymph nodes were collected from 168 patients and were evaluated by the five methods with corresponding pathology analysis results as gold standard. The accuracy of CNN is 86%, which is not significantly different from the best ML method that uses standard diagnostic features or a combination of diagnostic features and texture features. CNN is more accurate than ML methods that simply use texture features.

## APPLICATION OF AI IN HISTOPATHOLOGY OF NSCLC

In the differential diagnosis of lung cancer, it is necessary to classify the types or subtypes accurately. Because the hematoxylin-eosin (HE) stained full-scale whole slide image (WSI) is usually at the megapixel level, the much smaller image blocks (about 300 × 300 pixels) extracted from it are often used as training input. For example, Wang *et al*[35] trained a CNN model; each 300 × 300 pixel image block of lung adenocarcinoma WSIs stained by HE was classified as malignant or nonmalignant. The overall classification accuracy (malignant and nonmalignant) of the test set was 89.8%. This

method can detect tumor rapidly when the tumor area is very small, which will greatly help pathologists in future clinical diagnoses. In the study reported by Teramoto *et al*[36], a deep CNN (DCNN) was developed for an automatic lung cancer classification scheme, which is a major deep learning technology. In the evaluation experiment, they used original database, including fine needle aspirate cytology images and HE stained WSIs and a graphics processing unit to train DCNN. First, the micro images were cropped and resampled to obtain the image with a resolution of 256 × 256 pixels. In order to prevent over fitting, the collected images were enhanced by rotation, flipping and filtering. The probability of three types of cancer was evaluated using the developed scheme, and its classification accuracy was evaluated using triple cross validation. In the results obtained, about 71% of the images were correctly classified, which is equivalent to the accuracy of cell technicians and pathologists.

The identification of early lung adenocarcinoma before operation, especially in the case of subcentimeter cancer, can provide important guidance for clinical decision making. Zhao *et al*[37] developed a 3D deep learning system based on 3D CNN and multitask learning. The deep learning system had better classification performance than radiologists. In terms of three-level weighted average F1 score, the model reached 63.3%, while the four radiologists reached 55.6%, 56.6%, 54.3% and 51.0%, respectively.

With tumor microenvironment increasingly considered as an important factor affecting tumor progression and immunotherapy response, tumor microenvironment for lung cancer has been studied in depth. Saltz *et al*[38] developed a CNN model to distinguish lymphocytes from necrotic or other tissues at the image spot level in multiple cancer types, including adenocarcinoma and small cell carcinoma of the lung. Then, by quantifying the spatial organization of lymphoid image plaques detected in WSIs, they reported the relationship between the distribution pattern, prognosis and lymphoid components of tumor infiltrated lymphocytes.

Lung cancer patients usually present with advanced, inoperable disease. Because the whole tumor specimen cannot be obtained, the size of the biopsy specimen obtained is usually very limited. It is difficult to distinguish squamous cell carcinoma and adenocarcinoma especially in poorly differentiated tumors because of their obscure histological features. ML in immunohistochemistry[39] was applied to establish a comprehensive and automatic diagnosis strategy for NSCLC biopsy specimen subtypes, which successfully solved this problem. Koh *et al*[40] described a comprehensive diagnostic strategy using a reliable and minimal immunohistochemistry team for histopathological subtype analysis of NSCLC biopsy specimens. The team used two ML methods: Decision tree and support vector machines to learn from 30 small NSCLC biopsies with fuzzy morphology. The decision tree model showed that the highest accuracy of the combination of two markers (such as p63 and CK5/6) was about 72% except for three other markers (*i.e.* TTF-1, Napsin A and P40).

Wang *et al*[41] explored the correlation between the morphological features of the WSIs stained with HE and the NSCLC epidermal growth factor receptor (EGFR) mutation to achieve the purpose of predicting the risk of gene mutation. The results showed that the AUC of the EGFR mutation risk prediction model proposed in this paper can reach 72.4% on the test set, and the accuracy rate was 70.8%, suggesting a close relationship between morphological characteristics and EGFR mutations of NSCLC. Coudray *et al*[42] trained a DCNN (inception V3) to accurately and automatically classify the WSIs obtained from The Cancer Genome Atlas. Its performance was comparable to that of the pathologist, and the average AUC was 0.97. They trained the network to predict the ten most common mutations in lung adenocarcinoma and found that six genes (*STK11*, *EGFR*, *FAT1*, *setbp1*, *KRAS* and *TP53*) could be predicted by pathological images. In the nonexperimental population, AUC was 0.733-0.856. It suggested that deep learning models could help pathologists detect cancer subtypes or gene mutations.

## APPLICATION OF AI IN GENOMIC CLASSIFICATION OF NSCLC

Various molecular abnormalities affecting oncogenes and tumor suppressor genes have been reported in NSCLC. It is so important to identify potential lung cancer genome subtypes that a specific targeted therapy was proposed. For example, mutations in EGFR or anaplastic lymphoma kinase (ALK) receptors are significant in NSCLC because they provide molecular targets for customized treatment regimens.

The gene expression profile of NSCLC subtype has been established by

microarray[43,44]. Microarray data used to identify NSCLC genetic subtypes can be used to train ML algorithms to better understand genomic pathways. Yamamoto *et al*[45] screened 24 CT image traits performed in a training set of 59 patients, followed by random forest variable selection incorporating 24 CT traits plus six clinical-pathologic covariates to identify a radiomic predictor of ALK+ status. This predictor was then validated in an independent cohort ($n$ = 113). Tests for accuracy and subset analyses were performed. It was found that ALK+ NSCLC had distinct characteristics at CT imaging that when combined with clinical covariate discriminated ALK+ from non-ALK tumors and could potentially identify patients with a shorter durable response to crizotinib.

With the commercialization of next generation sequencing technology and the improvement of the performance of these algorithms, clinicians will be able to better describe NSCLC based on genome data[46]. Duan *et al*[47] explored the application of the ANN model in the auxiliary diagnosis of lung cancer. They compared the effects of the back-propagation neural network with the Fisher discrimination model for lung cancer screening by combining the detection of four biomarkers, *p16*, *RASSF1A* and *FHIT* gene promoter methylation levels and the relative telomere length. The result of the back-propagation neural network AUC was higher than that of the Fisher discrimination analysis, which meant that the back-propagation neural network model for the prediction of lung cancer was better than Fisher discrimination analysis.

## APPLICATION OF AI IN THERAPY OF NSCLC

Systemic treatment is needed in most stages of NSCLC; for example, those in stage II often need adjuvant radiotherapy and chemotherapy. The contour of organs at risk is an important but time-consuming part of radiotherapy treatment planning. Lustberg *et al*[48] analyzed the CT scan data of 20 patients with stage I-III NSCLC and compared the user adjusted contour and manual contour based on atlas and deep learning contour. It was found that the median time of manual contour drawing was 20 minutes. When using atlas-based contour drawing, a total of 7.8 minutes was saved, while the deep learning contour drawing saved 10 minutes. It showed that it was a feasible strategy for users to adjust the contour generated by the software, which could reduce the contour time of organs at risk in lung radiotherapy. Compared with the existing programs, deep learning shows encouraging results.

At present, targeted therapies[49] such as EGFR tyrosine kinase inhibitors, ALK inhibitors or angiogenesis inhibitors are used depending on the patients' molecular status. The prediction of targeted therapy response is mainly accomplished by biopsy to analyze the status of the targeted mutation. AI prediction models can complement this by identifying the imaging phenotypes associated with mutation status. Support for this approach comes from quantitative imaging studies of patients with NSCLC treated with gefitinib. The results[50] showed that the mutation state of EGFR could be predicted by radiology. AI analysis of quantitative imaging data can also improve the assessment of response to targeted therapy. Bevacizumab (a monoclonal antibody against vascular endothelial growth factor)-treated NSCLC tumors had reduced FDG uptake and were found to have more patients responding to treatment (73% than 18%). In this study[51], both PET and CT were independent of OS (PET, $P$ = 0.833; CT, $P$ = 0.557).

The level of PD-L1 expression detected by immunohistochemistry is a key biomarker to identify whether NSCLC patients respond to the treatment of PD-1/PD-L1. The quantification of PD-L1 expression currently includes a pathologist's visual estimate of the percentage of PD-L1 staining (tumor proportion score or TPS) in tumor cells. Kapil *et al*[52] proposed a new deep learning solution that can automatically and objectively grade PD-L1 expression for the first time in advanced NSCLC biopsy. Using a semisupervised approach and a standard full supervised approach, they integrated manual annotation for training and visual tumor proportion scores for quantitative evaluation by multiple pathologists. It was believed to be the first proof of concept study that showed that deep learning could accurately and automatically estimate the PD-L1 expression level and PD-L1 status of small biopsy samples.

Researchers have studied the use of ML in predicting treatment failure or death. For example, Jochems *et al*[53] studied ML methods for predicting early death in NSCLC patients after receiving therapeutic chemical radiation. Similarly, Zhou *et al*[54] used ML to predict the failure of stereotactic body radiotherapy in early NSCLC patients. Both groups used ML methods to establish the prognosis model of early mortality or treatment failure, which could be used to inform patients of treatment plan and

optimize treatment. Kureshi *et al*[55] studied the role of multiple factors in predicting tumor response to EGFR-TKI therapy (erlotinib or gefitinib) in patients with advanced NSCLC.

## APPLICATION OF AI IN PROGNOSIS OF NSCLC

Accurate classification, clinical stage, molecular subtype and therapies of NSCLC are all important because prognosis is closely related to these factors. Hsia *et al*[56] incorporated the clinical detection indicators and gene polymorphism detection results and predicted the prognosis of 75 lung cancer patients without indications of surgical treatment through the ANN model and made treatment plans accordingly. The actual average survival time of the patients was 12.44 ± 7.95 mo, while the ANN prediction result was 13.16 ± 1.77 mo with an accuracy of 86.2%. Zhu *et al*[57] successfully used DCNN to directly predict the survival time of patients from lung cancer pathological images. Another lung cancer study[58] showed that the prognosis of OS can be improved by adding genomic and radiological information to clinical models, thereby increasing the 95% confidence index from 0.65 (Noether $P = 0.001$) to 0.73 ($P = 2 \times 10^{-9}$), and the inclusion of radiation data led to a significant improvement in performance ($P = 0.01$).

Wang *et al*[59] proposed a computational histomorphometric image classifier using nuclear direction, texture, shape and tumor structure to predict the recurrence of early NSCLC diseases from digital HE tissue microarray slides. The results showed that the combination of these four features could predict the early recurrence of NSCLC, but it had nothing to do with clinical parameters such as gender, cancer stage and histological subtype. Yu *et al*[60] reported that Zernike shape characteristics of the nucleus could predict the recurrence of NSCLC adenocarcinoma and stage I squamous cell carcinoma.

In an article published in 2018, Saltz *et al*[38] described the use of CNN combined with pathologist's feedback to automatically detect the spatial tissue of tumor infiltrating lymphocytes (TIL) in the tissue slide image of The Cancer Genome Atlas and found that this feature predicted the prognosis of 13 different cancer subtypes. In a related study, Corredor *et al*[61] showed the spatial arrangement of TIL clusters in early NSCLC, which was found by calculating the adjacent TILs and the prognosis of cancer cell nuclear recurrence risk compared with TIL density alone. The accuracy of the model in predicting recurrence was 82% and 75%, respectively, which proved to be an independent prognostic factor.

Blanc-Durand *et al*[62] trained a CNN in 189 NSCLC patients who received PET/CT examination. The subcutaneous adipose tissue, visceral adipose tissue and muscle weight were automatically segmented from the low-dose CT images. After a quintuple cross validation of a subset of 35 patients, body surface area was standardized as the anthropometric index extracted by deep learning. Cox risk regression analysis showed that body surface area normalized visceral adipose tissue/subcutaneous adipose tissue ratio was an independent predictor of progression free survival and OS in NSCLC patients.

Another study[63] evaluated the ability of CT radiomic features in patients with lung adenocarcinoma to predict distant metastasis. The phenotype of the primary tumor was quantified with 635 radiomic features in the pre-treatment CT scan. Univariate and multivariate analyses were performed using the consistency index to evaluate the efficacy of radiotherapy. Thirty-five radiomic features were used as prognostic indicators for distant metastasis (consistency index > 0.60, FDR < 5%) and 12 prognostic indicators. Notably, tumor volume was only a moderate prognostic indicator for distant metastasis in the discovery cohort (consistency index = 0.55, $P = 2.77 \times 10^{-5}$). This study suggested that radiomic features that capture the details of the tumor phenotype can be used as prognostic biomarkers for clinical factors such as distant metastasis.

## APPLICATION IN ELECTRONIC MEDICAL RECORDS OF NSCLC

Electronic medical records (EMR) can be used in clinical diagnosis and treatment, medical insurance and scientific research. EMR is rich in information that can provide evidence of clinical diagnosis, treatment and data source of clinical research phenotype. In Wang *et al*[64]'s study, multiobjective ensemble deep learning, a dynamic integrated deep learning and adaptive model selection method based on

multiobjective optimization, was developed. The information extracted from EMRs through analysis can better predict the treatment results than other conventional methods. According to accurate prognosis prediction, we can stratify the risk of treatment failure of lung cancer patients after radiotherapy. This method can help to design personalized treatment and follow-up plan and improve the survival rate of lung cancer patients after radiotherapy.

## FUTURE CHALLENGES

It is one of the key directions of medical research in the information age to build a big database by collecting and integrating various biomics, clinical detection indicators and nonbiological environmental background data of patients. Effective analysis and interpretation of these data will be the top priority, and the integration and analysis of the existing massive information is precisely the biggest advantage of AI.

At present, the investment in AI in lung cancer and the entire medical field is huge, but there is still a certain distance from the actual clinical application. The lack of a high-quality standardized lung cancer clinical database is an important factor restricting AI's use in lung cancer research. The deficiency of research sample size causes most prediction or diagnostic studies to not fully simulate the actual clinical environment, limiting the value of clinical applications. Studies[65] have pointed out that the current use of AI in the medical field, such as inadequacy of correct methods and evaluation criteria in ANN and the credibility of the results is questionable. In addition, in terms of social regulations, lack of common technical regulations on medical responsibility issues and information security issues exists.

In the future, major medical centers should take the lead to establish a multicenter standardized lung cancer clinical database as a world-class database in line with epidemiology and to develop an AI system that meets the clinical environment. Diagnosis, treatment and optimization of medical resources have positive significance. On the other hand, active promotion of AI-related system regulations, technical specification, audit systems to provide institutional support and corresponding constraints for the development of AI are needed. AI has promising prospects for lung cancer research in the future, but it is still full of challenges.

According to the accuracy stated, which is around 90%, misjudgment may happen in 10% of cases, which reflects a pitfall of AI. Therefore, in clinical work, AI must be placed in a subordinate position. It should exist as an assistant to clinicians and provide auxiliary information under the supervision of doctors to avoid mistakes as much as possible.

## CONCLUSION

AI has become an indispensable method to solve complex problems in modern life. In this review, I introduced various attempts and applications of AI in clinical work of NSCLC patients. According to a large number of imaging, histology, genomics, EMR system and other data, doctors can accurately diagnose and treat NSCLC patients. It has been shown that AI is gradually becoming a powerful assistant for doctors. Oncologists, radiologists and surgeons should continue to integrate AI into the clinical treatment of NSCLC in order to provide more patients with accurate and personalized therapy. Over time, both patients and doctors will benefit from the combination of AI and clinical practice.

## REFERENCES

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **Molina JR**, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc* 2008; **83**: 584-594 [PMID: 18452692 DOI: 10.4065/83.5.584]

3 **Travis WD**, Brambilla E, Riely GJ. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. *J Clin Oncol* 2013; **31**: 992-1001 [PMID: 23401443 DOI: 10.1200/JCO.2012.46.9270]

4 **Ganeshan B**, Panayiotou E, Burnand K, Dizdarevic S, Miles K. Tumour heterogeneity in non-small cell

lung carcinoma assessed by CT texture analysis: a potential marker of survival. *Eur Radiol* 2012; **22**: 796-802 [PMID: 22086561 DOI: 10.1007/s00330-011-2319-8]

5 **Hamet P**, Tremblay J. Artificial intelligence in medicine. *Metabolism* 2017; **69S**: S36-S40 [PMID: 28126242 DOI: 10.1016/j.metabol.2017.01.011]

6 **Sui J**, Liu M, Lee JH, Zhang J, Calhoun V. Deep learning methods and applications in neuroimaging. *J Neurosci Methods* 2020; **339**: 108718 [PMID: 32272117 DOI: 10.1016/j.jneumeth.2020.108718]

7 **Kononenko I**. Machine learning for medical diagnosis: history, state of the art and perspective. *Artif Intell Med* 2001; **23**: 89-109 [PMID: 11470218 DOI: 10.1016/s0933-3657(01)00077-x]

8 **National Lung Screening Trial Research Team,** Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; **365**: 395-409 [PMID: 21714641 DOI: 10.1056/NEJMoa1102873]

9 **Ciompi F**, Chung K, van Riel SJ, Setio AAA, Gerke PK, Jacobs C, Scholten ET, Schaefer-Prokop C, Wille MMW, Marchianò A, Pastorino U, Prokop M, van Ginneken B. Towards automatic pulmonary nodule management in lung cancer screening with deep learning. *Sci Rep* 2017; **7**: 46479 [PMID: 28422152 DOI: 10.1038/srep46479]

10 **Scholtz JE**, Lu MT, Hedgire S, Meyersohn NM, Oliveira GR, Prabhakar AM, Gupta R, Kalra MK, Shepard JO, Hoffmann U, Ghoshhajra BB. Incidental pulmonary nodules in emergent coronary CT angiography for suspected acute coronary syndrome: Impact of revised 2017 Fleischner Society Guidelines. *J Cardiovasc Comput Tomogr* 2018; **12**: 28-33 [PMID: 29195841 DOI: 10.1016/j.jcct.2017.11.005]

11 **Gould MK**, Tang T, Liu IL, Lee J, Zheng C, Danforth KN, Kosco AE, Di Fiore JL, Suh DE. Recent Trends in the Identification of Incidental Pulmonary Nodules. *Am J Respir Crit Care Med* 2015; **192**: 1208-1214 [PMID: 26214244 DOI: 10.1164/rccm.201505-0990OC]

12 **Furman AM**, Dit Yafawi JZ, Soubani AO. An update on the evaluation and management of small pulmonary nodules. *Future Oncol* 2013; **9**: 855-865 [PMID: 23718306 DOI: 10.2217/fon.13.17]

13 **von Berg J**, Young S, Carolus H, Wolz R, Saalbach A, Hidalgo A, Giménez A, Franquet T. A novel bone suppression method that improves lung nodule detection: Suppressing dedicated bone shadows in radiographs while preserving the remaining signal. *Int J Comput Assist Radiol Surg* 2016; **11**: 641-655 [PMID: 26337439 DOI: 10.1007/s11548-015-1278-y]

14 **Nam JG**, Park S, Hwang EJ, Lee JH, Jin KN, Lim KY, Vu TH, Sohn JH, Hwang S, Goo JM, Park CM. Development and Validation of Deep Learning-based Automatic Detection Algorithm for Malignant Pulmonary Nodules on Chest Radiographs. *Radiology* 2019; **290**: 218-228 [PMID: 30251934 DOI: 10.1148/radiol.2018180237]

15 **Horeweg N**, Nackaerts K, Oudkerk M, de Koning HJ. Low-dose computed tomography screening for lung cancer: results of the first screening round. *J Comp Eff Res* 2013; **2**: 433-436 [PMID: 24236740 DOI: 10.2217/cer.13.57]

16 **Liang M**, Tang W, Xu DM, Jirapatnakul AC, Reeves AP, Henschke CI, Yankelevitz D. Low-Dose CT Screening for Lung Cancer: Computer-aided Detection of Missed Lung Cancers. *Radiology* 2016; **281**: 279-288 [PMID: 27019363 DOI: 10.1148/radiol.2016150063]

17 **Jha S**, Topol EJ. Adapting to Artificial Intelligence: Radiologists and Pathologists as Information Specialists. *JAMA* 2016; **316**: 2353-2354 [PMID: 27898975 DOI: 10.1001/jama.2016.17438]

18 **Kermany DS**, Goldbaum M, Cai W, Valentim CCS, Liang H, Baxter SL, McKeown A, Yang G, Wu X, Yan F, Dong J, Prasadha MK, Pei J, Ting MYL, Zhu J, Li C, Hewett S, Dong J, Ziyar I, Shi A, Zhang R, Zheng L, Hou R, Shi W, Fu X, Duan Y, Huu VAN, Wen C, Zhang ED, Zhang CL, Li O, Wang X, Singer MA, Sun X, Xu J, Tafreshi A, Lewis MA, Xia H, Zhang K. Identifying Medical Diagnoses and Treatable Diseases by Image-Based Deep Learning. *Cell* 2018; **172**: 1122-1131.e9 [PMID: 29474911 DOI: 10.1016/j.cell.2018.02.010]

19 **Castellino RA**. Computer aided detection (CAD): an overview. *Cancer Imaging* 2005; **5**: 17-19 [PMID: 16154813 DOI: 10.1102/1470-7330.2005.0018]

20 **Chassagnon G**, Vakalopoulou M, Paragios N, Revel MP. Artificial intelligence applications for thoracic imaging. *Eur J Radiol* 2020; **123**: 108774 [PMID: 31841881 DOI: 10.1016/j.ejrad.2019.108774]

21 **Ambrosini RD**, Wang P, O'Dell WG. Computer-aided detection of metastatic brain tumors using automated three-dimensional template matching. *J Magn Reson Imaging* 2010; **31**: 85-93 [PMID: 20027576 DOI: 10.1002/jmri.22009]

22 **Chan HP**, Hadjiiski L, Zhou C, Sahiner B. Computer-aided diagnosis of lung cancer and pulmonary embolism in computed tomography-a review. *Acad Radiol* 2008; **15**: 535-555 [PMID: 18423310 DOI: 10.1016/j.acra.2008.01.014]

23 **Parmar C**, Grossmann P, Bussink J, Lambin P, Aerts HJWL. Machine Learning methods for Quantitative Radiomic Biomarkers. *Sci Rep* 2015; **5**: 13087 [PMID: 26278466 DOI: 10.1038/srep13087]

24 **Liu Y**, Balagurunathan Y, Atwater T, Antic S, Li Q, Walker RC, Smith GT, Massion PP, Schabath MB, Gillies RJ. Radiological Image Traits Predictive of Cancer Status in Pulmonary Nodules. *Clin Cancer Res* 2017; **23**: 1442-1449 [PMID: 27663588 DOI: 10.1158/1078-0432.CCR-15-3102]

25 **Liu Y**, Wang H, Li Q, McGettigan MJ, Balagurunathan Y, Garcia AL, Thompson ZJ, Heine JJ, Ye Z, Gillies RJ, Schabath MB. Radiologic Features of Small Pulmonary Nodules and Lung Cancer Risk in the National Lung Screening Trial: A Nested Case-Control Study. *Radiology* 2018; **286**: 298-306 [PMID: 28837413 DOI: 10.1148/radiol.2017161458]

26 **Paul R**, Hawkins SH, Balagurunathan Y, Schabath MB, Gillies RJ, Hall LO, Goldgof DB. Deep Feature Transfer Learning in Combination with Traditional Features Predicts Survival Among Patients with Lung Adenocarcinoma. *Tomography* 2016; **2**: 388-395 [PMID: 28066809 DOI: 10.18383/j.tom.2016.00211]

27 **Qi LL**, Wu BT, Tang W, Zhou LN, Huang Y, Zhao SJ, Liu L, Li M, Zhang L, Feng SC, Hou DH, Zhou Z, Li XL, Wang YZ, Wu N, Wang JW. Long-term follow-up of persistent pulmonary pure ground-glass nodules with deep learning-assisted nodule segmentation. *Eur Radiol* 2020; **30**: 744-755 [PMID: 31485837 DOI: 10.1007/s00330-019-06344-z]

28 **Ardila D**, Kiraly AP, Bharadwaj S, Choi B, Reicher JJ, Peng L, Tse D, Etemadi M, Ye W, Corrado G,

Naidich DP, Shetty S. End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. *Nat Med* 2019; **25**: 954-961 [PMID: 31110349 DOI: 10.1038/s41591-019-0447-x]

29 **Li X**, Hu B, Li H, You B. Application of artificial intelligence in the diagnosis of multiple primary lung cancer. *Thorac Cancer* 2019; **10**: 2168-2174 [PMID: 31529684 DOI: 10.1111/1759-7714.13185]

30 **Lardinois D**, Weder W, Hany TF, Kamel EM, Korom S, Seifert B, von Schulthess GK, Steinert HC. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. *N Engl J Med* 2003; **348**: 2500-2507 [PMID: 12815135 DOI: 10.1056/NEJMoa022136]

31 **Schwyzer M**, Ferraro DA, Muehlematter UJ, Curioni-Fontecedro A, Huellner MW, von Schulthess GK, Kaufmann PA, Burger IA, Messerli M. Automated detection of lung cancer at ultralow dose PET/CT by deep neural networks - Initial results. *Lung Cancer* 2018; **126**: 170-173 [PMID: 30527183 DOI: 10.1016/j.lungcan.2018.11.001]

32 **Ma Y**, Feng W, Wu Z, Liu M, Zhang F, Liang Z, Cui C, Huang J, Li X, Guo X. Intra-tumoural heterogeneity characterization through texture and colour analysis for differentiation of non-small cell lung carcinoma subtypes. *Phys Med Biol* 2018; **63**: 165018 [PMID: 30051884 DOI: 10.1088/1361-6560/aad648]

33 **Carvalho S**, Leijenaar RTH, Troost EGC, van Timmeren JE, Oberije C, van Elmpt W, de Geus-Oei LF, Bussink J, Lambin P. 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET)-Radiomics of metastatic lymph nodes and primary tumor in non-small cell lung cancer (NSCLC) - A prospective externally validated study. *PLoS One* 2018; **13**: e0192859 [PMID: 29494598 DOI: 10.1371/journal.pone.0192859]

34 **Wang H**, Zhou Z, Li Y, Chen Z, Lu P, Wang W, Liu W, Yu L. Comparison of machine learning methods for classifying mediastinal lymph node metastasis of non-small cell lung cancer from $^{18}$F-FDG PET/CT images. *EJNMMI Res* 2017; **7**: 11 [PMID: 28130689 DOI: 10.1186/s13550-017-0260-9]

35 **Wang S**, Chen A, Yang L, Cai L, Xie Y, Fujimoto J, Gazdar A, Xiao G. Comprehensive analysis of lung cancer pathology images to discover tumor shape and boundary features that predict survival outcome. *Sci Rep* 2018; **8**: 10393 [PMID: 29991684 DOI: 10.1038/s41598-018-27707-4]

36 **Teramoto A**, Tsukamoto T, Kiriyama Y, Fujita H. Automated Classification of Lung Cancer Types from Cytological Images Using Deep Convolutional Neural Networks. *Biomed Res Int* 2017; **2017**: 4067832 [PMID: 28884120 DOI: 10.1155/2017/4067832]

37 **Zhao W**, Yang J, Sun Y, Li C, Wu W, Jin L, Yang Z, Ni B, Gao P, Wang P, Hua Y, Li M. 3D Deep Learning from CT Scans Predicts Tumor Invasiveness of Subcentimeter Pulmonary Adenocarcinomas. *Cancer Res* 2018; **78**: 6881-6889 [PMID: 30279243 DOI: 10.1158/0008-5472.CAN-18-0696]

38 **Saltz J**, Gupta R, Hou L, Kurc T, Singh P, Nguyen V, Samaras D, Shroyer KR, Zhao T, Batiste R, Van Arnam J; Cancer Genome Atlas Research Network, Shmulevich I, Rao AUK, Lazar AJ, Sharma A, Thorsson V. Spatial Organization and Molecular Correlation of Tumor-Infiltrating Lymphocytes Using Deep Learning on Pathology Images. *Cell Rep* 2018; **23**: 181-193.e7 [PMID: 29617659 DOI: 10.1016/j.celrep.2018.03.086]

39 **Shulimzon TR**. Endomicroscopy, Not "Optical Biopsy" (Yet). *Am J Respir Crit Care Med* 2017; **195**: 962 [PMID: 28362205 DOI: 10.1164/rccm.201608-1616LE]

40 **Koh J**, Go H, Kim MY, Jeon YK, Chung JH, Chung DH. A comprehensive immunohistochemistry algorithm for the histological subtyping of small biopsies obtained from non-small cell lung cancers. *Histopathology* 2014; **65**: 868-878 [PMID: 25130792 DOI: 10.1111/his.12507]

41 **Wang Q**, Shen Q, Zhang Z, Cai C, Lu H, Zhou X, Xu J. [Prediction of gene mutation in lung cancer based on deep learning and histomorphology analysis]. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi* 2020; **37**: 10-18 [PMID: 32096372 DOI: 10.7507/1001-5515.201904018]

42 **Coudray N**, Ocampo PS, Sakellaropoulos T, Narula N, Snuderl M, Fenyö D, Moreira AL, Razavian N, Tsirigos A. Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning. *Nat Med* 2018; **24**: 1559-1567 [PMID: 30224757 DOI: 10.1038/s41591-018-0177-5]

43 **Ohashi K**, Sequist LV, Arcila ME, Moran T, Chmielecki J, Lin YL, Pan Y, Wang L, de Stanchina E, Shien K, Aoe K, Toyooka S, Kiura K, Fernandez-Cuesta L, Fidias P, Yang JC, Miller VA, Riely GJ, Kris MG, Engelman JA, Vnencak-Jones CL, Dias-Santagata D, Ladanyi M, Pao W. Lung cancers with acquired resistance to EGFR inhibitors occasionally harbor BRAF gene mutations but lack mutations in KRAS, NRAS, or MEK1. *Proc Natl Acad Sci USA* 2012; **109**: E2127-E2133 [PMID: 22773810 DOI: 10.1073/pnas.1203530109]

44 **Kikuchi T**, Daigo Y, Katagiri T, Tsunoda T, Okada K, Kakiuchi S, Zembutsu H, Furukawa Y, Kawamura M, Kobayashi K, Imai K, Nakamura Y. Expression profiles of non-small cell lung cancers on cDNA microarrays: identification of genes for prediction of lymph-node metastasis and sensitivity to anti-cancer drugs. *Oncogene* 2003; **22**: 2192-2205 [PMID: 12687021 DOI: 10.1038/sj.onc.1206288]

45 **Yamamoto S**, Korn RL, Oklu R, Migdal C, Gotway MB, Weiss GJ, Iafrate AJ, Kim DW, Kuo MD. ALK molecular phenotype in non-small cell lung cancer: CT radiogenomic characterization. *Radiology* 2014; **272**: 568-576 [PMID: 24885982 DOI: 10.1148/radiol.14140789]

46 **Podolsky MD**, Barchuk AA, Kuznetcov VI, Gusarova NF, Gaidukov VS, Tarakanov SA. Evaluation of Machine Learning Algorithm Utilization for Lung Cancer Classification Based on Gene Expression Levels. *Asian Pac J Cancer Prev* 2016; **17**: 835-838 [PMID: 26925688 DOI: 10.7314/apjcp.2016.17.2.835]

47 **Duan X**, Yang Y, Tan S, Wang S, Feng X, Cui L, Feng F, Yu S, Wang W, Wu Y. Application of artificial neural network model combined with four biomarkers in auxiliary diagnosis of lung cancer. *Med Biol Eng Comput* 2017; **55**: 1239-1248 [PMID: 27766520 DOI: 10.1007/s11517-016-1585-7]

48 **Lustberg T**, van Soest J, Gooding M, Peressutti D, Aljabar P, van der Stoep J, van Elmpt W, Dekker A. Clinical evaluation of atlas and deep learning based automatic contouring for lung cancer. *Radiother Oncol* 2018; **126**: 312-317 [PMID: 29208513 DOI: 10.1016/j.radonc.2017.11.012]

49 **Ellis PM**, Al-Saleh K. Multitargeted anti-angiogenic agents and NSCLC: clinical update and future directions. *Crit Rev Oncol Hematol* 2012; **84**: 47-58 [PMID: 22405734 DOI: 10.1016/j.critrevonc.2012.02.004]

50 **Aerts HJ**, Grossmann P, Tan Y, Oxnard GR, Rizvi N, Schwartz LH, Zhao B. Defining a Radiomic

Response Phenotype: A Pilot Study using targeted therapy in NSCLC. *Sci Rep* 2016; **6**: 33860 [PMID: 27645803 DOI: 10.1038/srep33860]

51 **de Jong EE**, van Elmpt W, Leijenaar RT, Hoekstra OS, Groen HJ, Smit EF, Boellaard R, van der Noort V, Troost EG, Lambin P, Dingemans AC. [18F]FDG PET/CT-based response assessment of stage IV non-small cell lung cancer treated with paclitaxel-carboplatin-bevacizumab with or without nitroglycerin patches. *Eur J Nucl Med Mol Imaging* 2017; **44**: 8-16 [PMID: 27600280 DOI: 10.1007/s00259-016-3498-y]

52 **Kapil A**, Meier A, Zuraw A, Steele KE, Rebelatto MC, Schmidt G, Brieu N. Deep Semi Supervised Generative Learning for Automated Tumor Proportion Scoring on NSCLC Tissue Needle Biopsies. *Sci Rep* 2018; **8**: 17343 [PMID: 30478349 DOI: 10.1038/s41598-018-35501-5]

53 **Jochems A**, El-Naqa I, Kessler M, Mayo CS, Jolly S, Matuszak M, Faivre-Finn C, Price G, Holloway L, Vinod S, Field M, Barakat MS, Thwaites D, de Ruysscher D, Dekker A, Lambin P. A prediction model for early death in non-small cell lung cancer patients following curative-intent chemoradiotherapy. *Acta Oncol* 2018; **57**: 226-230 [PMID: 29034756 DOI: 10.1080/0284186X.2017.1385842]

54 **Zhou Z**, Folkert M, Cannon N, Iyengar P, Westover K, Zhang Y, Choy H, Timmerman R, Yan J, Xie XJ, Jiang S, Wang J. Predicting distant failure in early stage NSCLC treated with SBRT using clinical parameters. *Radiother Oncol* 2016; **119**: 501-504 [PMID: 27156652 DOI: 10.1016/j.radonc.2016.04.029]

55 **Kureshi N**, Abidi SS, Blouin C. A Predictive Model for Personalized Therapeutic Interventions in Non-small Cell Lung Cancer. *IEEE J Biomed Health Inform* 2016; **20**: 424-431 [PMID: 25494516 DOI: 10.1109/JBHI.2014.2377517]

56 **Hsia TC**, Chiang HC, Chiang D, Hang LW, Tsai FJ, Chen WC. Prediction of survival in surgical unresectable lung cancer by artificial neural networks including genetic polymorphisms and clinical parameters. *J Clin Lab Anal* 2003; **17**: 229-234 [PMID: 14614746 DOI: 10.1002/jcla.10102]

57 **Zhu X**, Yao J, Huang J, editors. Deep convolutional neural network for survival analysis with pathological images. 2016 IEEE International Conference on Bioinformatics and Biomedicine (BIBM); 2016 Dec 15-18; Shenzhen, China. IEEE, 2017: 544-547 [DOI: 10.1109/BIBM.2016.7822579]

58 **Grossmann P**, Stringfield O, El-Hachem N, Bui MM, Rios Velazquez E, Parmar C, Leijenaar RT, Haibe-Kains B, Lambin P, Gillies RJ, Aerts HJ. Defining the biological basis of radiomic phenotypes in lung cancer. *Elife* 2017; **6** [PMID: 28731408 DOI: 10.7554/eLife.23421]

59 **Wang X**, Janowczyk A, Zhou Y, Thawani R, Fu P, Schalper K, Velcheti V, Madabhushi A. Prediction of recurrence in early stage non-small cell lung cancer using computer extracted nuclear features from digital H&E images. *Sci Rep* 2017; **7**: 13543 [PMID: 29051570 DOI: 10.1038/s41598-017-13773-7]

60 **Yu KH**, Zhang C, Berry GJ, Altman RB, Ré C, Rubin DL, Snyder M. Predicting non-small cell lung cancer prognosis by fully automated microscopic pathology image features. *Nat Commun* 2016; **7**: 12474 [PMID: 27527408 DOI: 10.1038/ncomms12474]

61 **Corredor G**, Wang X, Zhou Y, Lu C, Fu P, Syrigos K, Rimm DL, Yang M, Romero E, Schalper KA, Velcheti V, Madabhushi A. Spatial Architecture and Arrangement of Tumor-Infiltrating Lymphocytes for Predicting Likelihood of Recurrence in Early-Stage Non-Small Cell Lung Cancer. *Clin Cancer Res* 2019; **25**: 1526-1534 [PMID: 30201760 DOI: 10.1158/1078-0432.CCR-18-2013]

62 **Blanc-Durand P**, Campedel L, Mule S, Jegou S, Luciani A, Pigneur F, Itti E. Prognostic value of anthropometric measures extracted from whole-body CT using deep learning in patients with non-small-cell lung cancer. *Eur Radiol* 2020; **30**: 3528-3537 [PMID: 32055950 DOI: 10.1007/s00330-019-06630-w]

63 **Coroller TP**, Grossmann P, Hou Y, Rios Velazquez E, Leijenaar RT, Hermann G, Lambin P, Haibe-Kains B, Mak RH, Aerts HJ. CT-based radiomic signature predicts distant metastasis in lung adenocarcinoma. *Radiother Oncol* 2015; **114**: 345-350 [PMID: 25746350 DOI: 10.1016/j.radonc.2015.02.015]

64 **Wang R**, Weng Y, Zhou Z, Chen L, Hao H, Wang J. Multi-objective ensemble deep learning using electronic health records to predict outcomes after lung cancer radiotherapy. *Phys Med Biol* 2019; **64**: 245005 [PMID: 31698346 DOI: 10.1088/1361-6560/ab555e]

65 **Bertolaccini L**, Solli P, Pardolesi A, Pasini A. An overview of the use of artificial neural networks in lung cancer research. *J Thorac Dis* 2017; **9**: 924-931 [PMID: 28523139 DOI: 10.21037/jtd.2017.03.157]

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ORIGINAL ARTICLE

Basic Study

# Impact of blurs on machine-learning aided digital pathology image analysis

Maki Ogura, Tomoharu Kiyuna, Hiroshi Yoshida

**ORCID number:** Maki Ogura 0000-0002-0380-9396; Tomoharu Kiyuna 0000-0003-3050-6718; Hiroshi Yoshida 0000-0002-7569-7813.

**Author contributions:** Ogura M, Kiyuna T, and Yoshida H drafted and revised the manuscript and prepared the figures; Ogura M collected the pathological data; Kiyuna T performed all the image analysis; all the authors have read and approved the final manuscript.

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**Maki Ogura, Tomoharu Kiyuna,** Digital Healthcare Business Development Office, NEC Corporation, Tokyo 108-8001, Japan

**Hiroshi Yoshida,** Department of Diagnostic Pathology, National Cancer Center Hospital, Tokyo 104-0045, Japan

**Corresponding author:** Hiroshi Yoshida, MD, PhD, Staff Physician, Department of Diagnostic Pathology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. hiroyosh@ncc.go.jp

## Abstract

*BACKGROUND*

Digital pathology image (DPI) analysis has been developed by machine learning (ML) techniques. However, little attention has been paid to the reproducibility of ML-based histological classification in heterochronously obtained DPIs of the same hematoxylin and eosin (HE) slide.

*AIM*

To elucidate the frequency and preventable causes of discordant classification results of DPI analysis using ML for the heterochronously obtained DPIs.

*METHODS*

We created paired DPIs by scanning 298 HE stained slides containing 584 tissues twice with a virtual slide scanner. The paired DPIs were analyzed by our ML-aided classification model. We defined non-flipped and flipped groups as the paired DPIs with concordant and discordant classification results, respectively. We compared differences in color and blur between the non-flipped and flipped groups by L1-norm and a blur index, respectively.

*RESULTS*

We observed discordant classification results in 23.1% of the paired DPIs obtained by two independent scans of the same microscope slide. We detected no significant difference in the L1-norm of each color channel between the two groups; however, the flipped group showed a significantly higher blur index than the non-flipped group.

*CONCLUSION*

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Our results suggest that differences in the blur - not the color - of the paired DPIs may cause discordant classification results. An ML-aided classification model for DPI should be tested for this potential cause of the reduced reproducibility of the model. In a future study, a slide scanner and/or a preprocessing method of minimizing DPI blur should be developed.

**Key words:** Machine learning; Digital pathology image; Automated image analysis; Blur; Color; Reproducibility



**Core tip**: Little attention has been paid to the reproducibility of machine learning (ML)-based histological classification in heterochronously obtained Digital pathology images (DPIs) of the same hematoxylin and eosin slide. This study elucidated the frequency and preventable causes of discordant classification results of DPI analysis using ML for the heterochronously obtained DPIs. We observed discordant classification results in 23.1% of the paired DPIs obtained by two independent scans of the same microscope slide. The group with discordant classification results showed a significantly higher blur index than the other group. Our results suggest that differences in the blur of the paired DPIs may cause discordant classification results.

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## INTRODUCTION

Recent developments in medical image analysis empowered by machine learning (ML) have expanded to digital pathology image (DPI) analysis[1-3]. For over ten years, NEC Corporation has researched and developed image analysis software that can detect carcinomas in tissue in the digital images of hematoxylin and eosin (HE) stained slides. DPI analysis is generally performed for digital images obtained with special devices such as microscopic cameras or slide scanners. These devices cannot make completely identical digital images or data matrices even when the same microscope slide is repeatedly shot with the same camera or scanned by the same scanner.

In general, image analysis by ML can provide different classification results if an object has multiple images showing different features. Therefore, slight differences in a DPI made by imaging devices can also cause different classification results. Each digital image will have different characteristics even when the same microscope slide of a patient is repeatedly digitized by the same slide scanner. Similarly, the same microscope slide of a patient can be digitized at a local hospital and then at a referral hospital. The resulting differences in image features of the same microscope slide can provide discordant classification results of DPI analysis, confusing both patients and medical professionals. However, only a few reports have mentioned this issue.

The aim of this study is to elucidate the frequency and preventable cause of discordant classification results of DPI analysis using ML in the aforementioned situation. We compared the classification results between paired DPIs of the same microscope slide obtained from two independent scans using the same slide scanner (Figure 1).

## MATERIALS AND METHODS

### *Tissue sample*

We conducted the study in accordance with the Declaration of Helsinki and with the approval of the Institutional Review Board of the National Cancer Center, Tokyo, Japan. We consecutively collected 3062 gastric biopsy specimens between January 19-April 30, 2015 at the National Cancer Center (Tsukiji and Kashiwa campuses). The

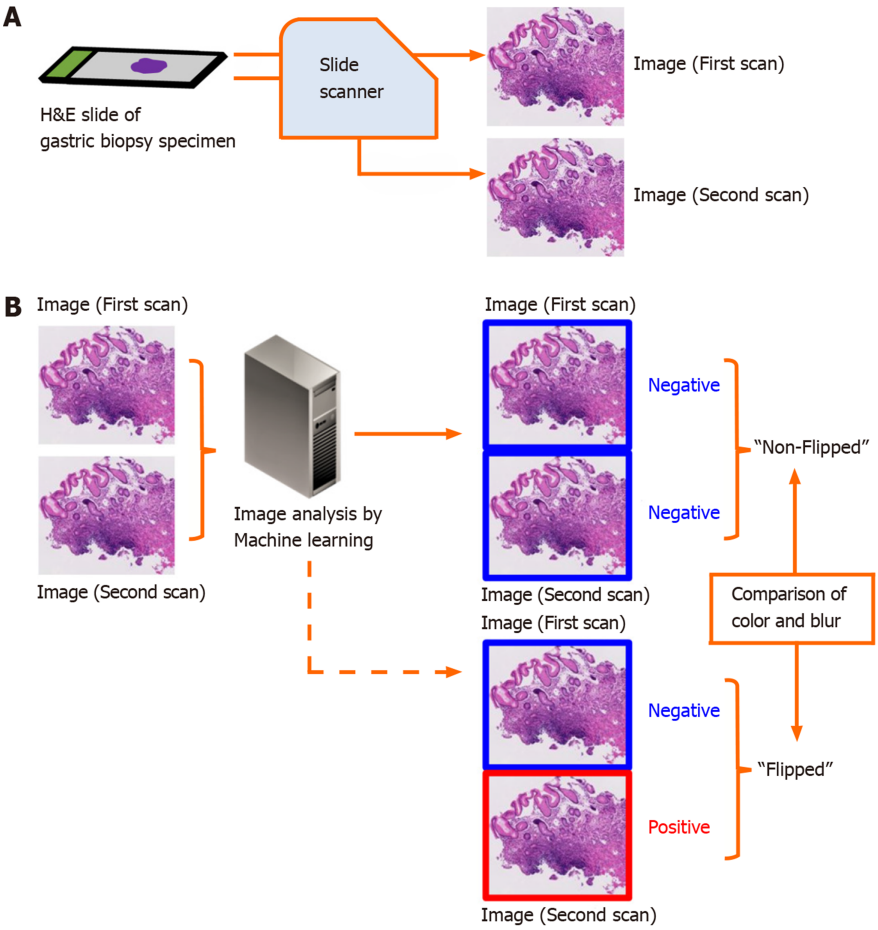


**Figure 1 The schema of this study.** A: Hematoxylin and eosin stained slides of gastric biopsy specimens were scanned twice by the same slide scanner, then the paired digital images were created; B: The paired images were independently analyzed and classified by our machine-learning model. If concordant classification results were obtained, the case is "Non-flipped"; if discordant classification results were obtained, the case is "Flipped." Then, color and blur differences were compared between the "Non-flipped" and "Flipped" groups.

specimens were placed in 10% buffered formalin and embedded in paraffin. Each block was sliced into 4-μm thick sections. Routine HE staining was performed for each slide using an automated staining system.

### *Digital image acquisition and automated image analysis*

During the image collection and analysis procedure, the researchers were blind to all of the diagnoses of the human pathologists. We developed an ML model to analyze the DPIs using a multi-instance learning framework[4]. The results of the concordance between pathological diagnosis by human pathologists and classification by an ML model was previously reported[5]. In our study, we randomly selected 584 images of the 3062 specimens to use for the present analysis.

We scanned 298 HE stained slides containing 584 tissues twice using the NanoZoomer (Hamamatsu Photonics K. K., Shizuoka, Japan) virtual slide scanner, creating the paired DPIs. The paired DPIs were analyzed by our ML-aided classification model[4]. Our ML-aided classification model classified the results of each tissue as "Positive" or "Negative". "Positive" denoted neoplastic lesions or suspicion of neoplastic lesions and "Negative" denoted the absence of neoplastic lesions. The procedure for classification of a cancerous areas in a given whole-slide image is as follows: (1) Identify the tissue regions at 1.25 ×; (2) The tissue area was then divided into several rectangular regions of interest (ROIs); (3) From each ROI, the structural and nuclear features are extracted at different magnification (10 × and 20 ×); (4) After the feature extraction, all ROIs were classified as positive or negative using a pre-trained classifier (support vector machine, SVM); and (5) The SVM-based classifier assigns a real number $t$ to each ROI, where $t$ takes value in the range (-1.0, 1.0). A value of 1.0 indicates a positive ROI and a value of -1.0 indicates a negative ROI[5]. In this experiment, we interpreted the value of $t \geq 0.4$ indicates a positive ROI.

We defined the group without discordant classification results between the paired

DPIs as the "non-flipped group" and the group with discordant classification results as the "flipped group".

For reference, we repeated analysis of the identical DPIs that had identical data matrices twice, then compared their results.

### Color analysis

We separated tissue images into tissue regions and non-tissue regions. To examine the differences in tissue color in the first and second scanned images, we measured the L1-norm distance between color distributions of images in each color channel; *i.e.*, red (R), green (G), and blue (B). The L1-norm distance between normalized histograms $p$ and $q$ were defined as Formula 1:

Where $p_i$ and $q_i$ are the normalized frequencies at the $i$-th bin of histograms $p$ and $q$, respectively.

### Quantification of the degree of image blurring

We quantified the degree of image blurring using the variance of wavelet coefficients of an image[6]. The degree of image blurring is calculated and normalized as follows: (1) 2D convolution by neighboring fileter; (2) Local variance of a 5 × 5 area; and (3) Captures local phase variations after convolution with wavelet filters, normalized by a sigmoid function to (0, 1) range. The degree of blurring was then normalized to between 0 and 255 and we calculated its distribution (normalized histogram). We defined the blur index using the 98$^{th}$ percentile of the above distribution of the variance of wavelet coefficients.

### Statistical analysis

We used the Mann-Whitney test to evaluate the significant differences in the blur index between the non-flipped and flipped groups.

## RESULTS

### Classification results of the paired DPIs

The analysis results did not change in 449 tissues; however, the results changed in 135 tissues (23.1%), either from positive to negative or from negative to positive (Table 1). Therefore, 135 tissues were in the flipped group.

On the other hand, 100% (584/584) of the concordance rate was observed between the classification results of the first analysis and the second analysis of the identical DPIs by our ML-aided classification model.

### Comparison of the DPI color

We compared the medians of the L1-norm in the non-flipped and flipped groups and found no significant difference (Table 2).

### Comparison of the blur index of the DPIs

Next, we calculated the blur index of the paired DPIs and compared it between the non-flipped group and the flipped group. The flipped group showed a significantly higher blur index than the non-flipped group (Figure 2). Figure 3 shows a representative case of the flipped group's results.

## DISCUSSION

We observed 23.1% of discordant classification results between the paired DPIs obtained from two independent scans of the same microscope slide. Furthermore, we detected differences in blur (not color) of the paired DPIs as a potential cause of different classification results.

Differences in the colors of DPIs did not correlate with discordant classification results in this study. Since differences in the colors of digitized images reportedly result in different features of digitized images and different data matrices[7], we expected the difference in color to reduce reproducibility in our ML-aided classification model. However, the distribution of RGB value did not differ significantly between the paired DPIs and did not seem to cause discordant classification results. Nevertheless, color differences should be a concern because the

**Table 1 Concordance of classification results between the paired digital pathology images**

| | | The second scan | | |
|---|---|---|---|---|
| | | Positive | Negative | Unclassifiable |
| The first scan | Positive | 248 | 66 | 0 |
| | Negative | 69 | 197 | 2 |
| | Unclassifiable | 1 | 0 | 4 |

**Table 2 Comparison of pair-wise L1-norm between non-flipped and flipped groups**

| Color channel | Median of the non-flipped group | Median of the flipped group | *P* value |
|---|---|---|---|
| R | 0.0350 ± 0.0220 | 0.0347 ± 0.0217 | 0.900 |
| G | 0.0319 ± 0.0197 | 0.0313 ± 0.0205 | 0.931 |
| B | 0.0266 ± 0.0148 | 0.0250 ± 0.0190 | 0.255 |

$$D_{L1}(p,q) = \sum_{i=1}^{255} |p_i - q_i|$$

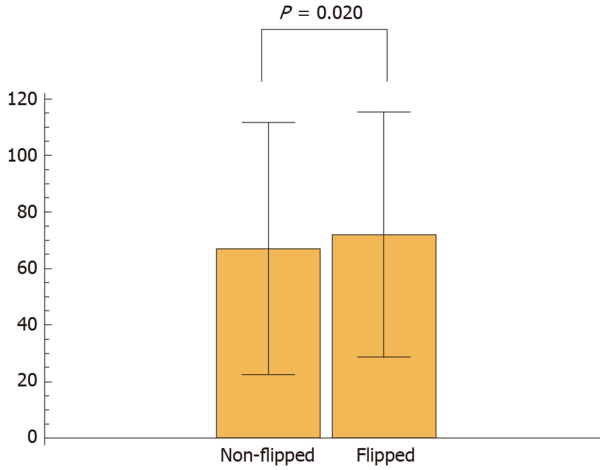


**Figure 2 Differences in the blur index between the "Non-flipped" and "Flipped" groups.**

color of HE stained slides obviously differed between different pathological laboratories. In such cases, a discordant classification result was observed in the same specimen with an identical pathological diagnosis (unpublished data). Therefore, even DPIs taken from the same microscope slide might show discordant classification results from obvious color changes due to the miscalibration of an imaging device.

Although qualitative changes in the blurs of the paired DPIs were macroscopically recognizable, their qualitative assessment was difficult. However, we developed a blur index that provided a quantitative comparison and detected the significant differences in blurs between the DPIs of the non-flipped group and those of the flipped group. Reportedly, blur can potentially influence the stability of features of a digitized image[7]; so, first, our study demonstrated that quantifying blurs revealed their impact on classification results.

A significant portion of cases showed discordant classification results; however, our ML-aided classification model worked efficiently for our intended purpose. 80.7% of all the flipped cases was non-tumor tissue, and 6.5% was carcinoma tissue. Our ML-aided classification model set a lower threshold than the best one (*i.e.*, the threshold that yields a minimum error rate) because we made our model minimize false negative results, classifying carcinoma as non-tumor tissue. This lower threshold caused more frequent flipped cases in non-tumor tissue. In other words, the larger the percentage of

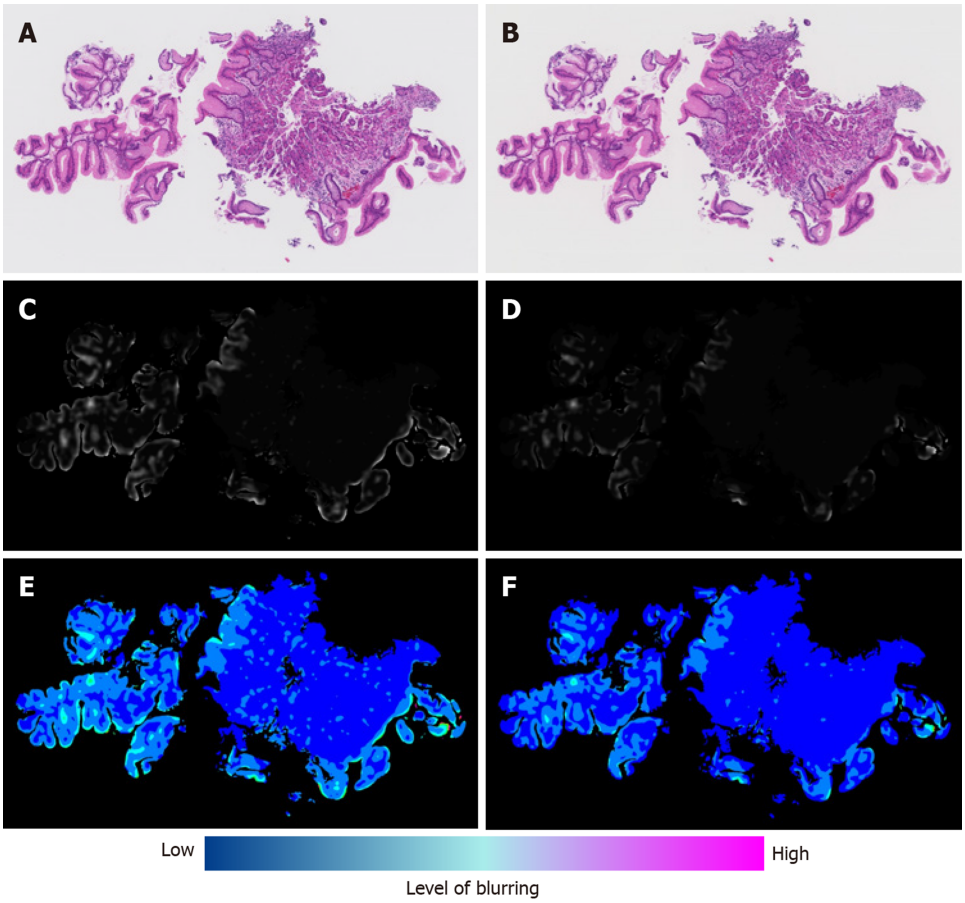


**Figure 3 Typical examples of differences in the blurring level.** A: Whole-slide image at the first scan; B: Whole-slide image at the second scan; C: The blurring level at the first scan (blur index = 115); D: The blurring level at the second scan (blur index = 78); E: A heat map representation of the blurring level at the first scan; F: A heat map representation of the blurring level at the second scan.

non-tumor tissue included in the dataset, the greater the total number of flipped cases. Our dataset contained non-tumor tissue images 4.4 times more than cancerous tissue images, so the total number of flipped cases increased. Slide scanners have been broadly used to obtain DPIs for ML-aided image analysis, so the issue of blurring should be mentioned more in the implementation of DPI analysis and in the development of more robust ML-aided classification models.

This study had some limitations. First, the robustness of a classification model for DPIs differs depending on the objects being analyzed, the method of machine-learning, and the quality and quantity of the dataset for learning. Therefore, the issue mentioned above should not be overgeneralized. However, a classification model for medical images (including DPI) should be tested to find if image blur might reduce reproducibility of the classification model. Second, we only investigated differences in color and blur in this study, while there may be another potential cause of discordant classification.

In conclusion, our findings suggest that differences in the blur in paired DPIs from the same microscope slide could cause different classification results by an ML-aided classification model. If an ML model has sufficient robustness, these slight differences in DPI might not cause a different classification result. However, an ML-aided classification model for DPI should be tested for this potential cause of the reduced reproducibility of the model. Since our method provides a quantitative measure for the degree of blurring, it is possible to avoid discordance through excluding these disqualified slides using this measure. However, further experiments are required to establish more reliable measure together with other factors, for instance, such as tissue area size and nuclear densities. In a future study, we will develop a slide scanner and/or a preprocessing method that will minimize DPI blur.

## ARTICLE HIGHLIGHTS

### *Research background*

Little attention has been paid to the frequency and preventable causes of discordant classification results of digital pathological image (DPI) analysis using machine learning (ML) for the heterochronously obtained DPIs.

### *Research motivation*

Authors compared the classification results between paired DPIs of the same microscope slide obtained from two independent scans using the same slide scanner.

### *Research objectives*

In this study, the authors elucidated the frequency and preventable causes of discordant classification results of DPI analysis using ML for the heterochronously obtained DPIs.

### *Research methods*

Authors created paired DPIs by scanning 298 hematoxylin and eosin stained slides containing 584 tissues twice with a virtual slide scanner. The paired DPIs were analyzed by our ML-aided classification model. Differences in color and blur between the non-flipped and flipped groups were compared by L1-norm and a blur index.

### *Research results*

Discordant classification results in 23.1% of the paired DPIs obtained by two independent scans of the same microscope slide were observed. No significant difference in the L1-norm of each color channel between the two groups; however, the flipped group showed a significantly higher blur index than the non-flipped group.

### *Research conclusions*

The results suggest that differences in the blur - not the color - of the paired DPIs may cause discordant classification results.

### *Research perspectives*

An ML-aided classification model for DPI should be tested for this potential cause of the reduced reproducibility of the model. In a future study, a slide scanner and/or a preprocessing method of minimizing DPI blur should be developed.

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## REFERENCES

1 **Al-Janabi S**, Huisman A, Van Diest PJ. Digital pathology: current status and future perspectives. *Histopathology* 2012; **61**: 1-9 [PMID: 21477260 DOI: 10.1111/j.1365-2559.2011.03814.x]

2 **Park S**, Parwani AV, Aller RD, Banach L, Becich MJ, Borkenfeld S, Carter AB, Friedman BA, Rojo MG, Georgiou A, Kayser G, Kayser K, Legg M, Naugler C, Sawai T, Weiner H, Winsten D, Pantanowitz L. The history of pathology informatics: A global perspective. *J Pathol Inform* 2013; **4**: 7 [PMID: 23869286 DOI: 10.4103/2153-3539.112689]

3 **Coudray N**, Ocampo PS, Sakellaropoulos T, Narula N, Snuderl M, Fenyö D, Moreira AL, Razavian N, Tsirigos A. Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning. *Nat Med* 2018; **24**: 1559-1567 [PMID: 30224757 DOI: 10.1038/s41591-018-0177-5]

4 **Cosatto E**, Laquerre PF, Malon C, Graf HP, Saito A, Kiyuna T, Marugame A, Kamijo K. Automated gastric cancer diagnosis on H&E-stained sections; ltraining a classifier on a large scale with multiple instance machine learning. Proceedings of SPIE 8676, Medical Imaging 2013: Digital Pathology, 867605; 2013 Mar 29; Florida, USA [DOI: 10.1117/12.2007047]

5 **Yoshida H**, Shimazu T, Kiyuna T, Marugame A, Yamashita Y, Cosatto E, Taniguchi H, Sekine S, Ochiai A. Automated histological classification of whole-slide images of gastric biopsy specimens. *Gastric Cancer* 2018; **21**: 249-257 [PMID: 28577229 DOI: 10.1007/s10120-017-0731-8]

6 **Yang G**, Nelson BJ. Wavelet-based autofocusing and unsupervised segmentation of microscopic images. Proceedings. Proceedings 2003 IEEE/RSJ International Conference on Intelligent Robots and Systems

(IROS 2003) (Cat. No.03CH37453); 2003 Oct 27-31; Las Vegas, USA. IEEE, 2003: 2143-2148 [DOI: 10.1109/IROS.2003.1249188]

7 **Aziz MA**, Nakamura T, Yamaguchi M, Kiyuna T, Yamashita Y, Abe T, Hashiguchi A, Sakamoto M. Effectiveness of color correction on the quantitative analysis of histopathological images acquired by different whole-slide scanners. *Artif Life Robotics* 2019; **24**: 28-37 [DOI: 10.1007/s10015-018-0451-0]

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Artificial Intelligence in Cancer

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## EVIDENCE REVIEW

*Artificial Intelligence in Cancer*

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## ABOUT COVER

Editor-in-Chief of *Artificial Intelligence in Cancer*, Dr. Mujib Ullah is an expert in the field of regenerative medicine and a United States trained investigator in artificial intelligence (AI) and in cancer. Dr. Ullah conducts preclinical and clinical studies to determine how turning off oncogenes (cancer genes) can cause tumor regression. His work is based upon a learned appreciation of AI techniques and deep learning, and their potential to develop predictive models for personalized treatments with engineered stem cells, immune cells and regenerative tissue. He is currently expanding his translational research to include early diagnostics, therapeutic monitoring, and prediction of response to therapeutics in solid tumors, such as kidney cancer and lung cancer, helping to make personalized medicine possible. The ultimate goal of this research is to achieve accurate diagnoses of aggressive cancers as well as to provide new insights about metastatic spread and the development of resistance against therapies. (L-Editor: Filipodia)

## AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Cancer* (*AIC*, *Artif Intell Cancer*) is to provide scholars and readers from various fields of artificial intelligence in cancer with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*AIC* mainly publishes articles reporting research results obtained in the field of artificial intelligence in cancer and covering a wide range of topics, including artificial intelligence in bone oncology, breast cancer, gastrointestinal cancer, genitourinary cancer, gynecological cancer, head and neck cancer, hematologic malignancy, lung cancer, lymphoma and myeloma, pediatric oncology, and urologic oncology.

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EVIDENCE REVIEW

# Applications of artificial intelligence in, early detection of cancer, clinical diagnosis and personalized medicine

Mujib Ullah, Asma Akbar, Gustavo Yannarelli

**ORCID number:** Mujib Ullah 0000-0003-0168-8700; Asma Akbar 0000-0002-4139-112X; Gustavo Yannarelli 0000-0003-1450-5483.

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**Mujib Ullah, Asma Akbar,** Institute for Immunity, Transplantation, Stem Cell Biology and Regenerative Medicine, School of Medicine, Stanford University, Palo Alto, CA 94304, United States

**Mujib Ullah, Asma Akbar,** Molecular Medicine, Department of Radiology, School of Medicine, Stanford University, Palo Alto, CA 94304, United States

**Gustavo Yannarelli,** Laboratorio de Regulación Génica y Células Madre, Instituto de Medicina Traslacional, Trasplante y Bioingeniería, Universidad Favaloro-CONICET, Buenos Aires 1078, Argentina

**Corresponding author:** Mujib Ullah, MD, PhD, Assistant Professor, Senior Scientist, Institute for Immunity, Transplantation, Stem Cell Biology and Regenerative Medicine, School of Medicine, Stanford University, 3145 Porter Dr, Palo Alto, CA 94304, United States. ullah@stanford.edu

## Abstract

Artificial intelligence (AI) refers to the simulation of human intelligence in machines programmed to convert raw input data into decision-making actions, like humans. AI programs are designed to make decisions, often using deep learning and computer-guided programs that analyze and process raw data into clinical decision making for effective treatment. New techniques for predicting cancer at an early stage are needed as conventional methods have poor accuracy and are not applicable to personalized medicine. AI has the potential to use smart, intelligent computer systems for image interpretation and early diagnosis of cancer. AI has been changing almost all the areas of the medical field by integrating with new emerging technologies. AI has revolutionized the entire health care system through innovative digital diagnostics with greater precision and accuracy. AI is capable of detecting cancer at an early stage with accurate diagnosis and improved survival outcomes. AI is an innovative technology of the future that can be used for early prediction, diagnosis and treatment of cancer.

**Key Words:** Artificial intelligence; Cancer; Clinical tumor prediction; Early detection of cancer; Clinical diagnosis; Personalized medicine

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**Core Tip:** Early detection of cancer potentially enhances the chances for successful treatment and patient survival outcome. Artificial intelligence (AI), a field of computer science, aims to develop algorithms or computer programs with advanced analytical or predictive capabilities. The development of highly accurate AI algorithms for the early recognition of the disease is crucial not only for the rapid identification and diagnosis of cancer patients, but also for the treatment. Many AI platforms are being developed and approved by the US Food and Drug Administration for use in some areas of cancer, such as identifying suspicious lesions in cancer and interpretation of magnetic resonance imaging or computed tomography. Similarly, the Big Data to Knowledge initiative was launched by National Institute of Health to support the research and development of tools to integrate big data and data science into biomedical research. AI-guided clinical care has the potential to play an essential role in the screening, diagnosis and treatment of cancer.

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## INTRODUCTION

Cancer is a major public health problem and remains the second leading cause of death in the United States[1,2]. Early detection of cancer potentially enhances the chances for successful treatment and patient survival outcomes[1-3]. Prediction of early cancer and treatment response is a crucial issue in personalized treatment for cancer patients[4]. Artificial intelligence (AI), a field of computer science, aims to develop algorithms or computer programs with advanced analytical or predictive capabilities (Figure 1)[1,3,5]. Integration of AI technology into early detection of cancer could improve precision diagnosis, improve the clinical decision-making process, and lead to revolutionize the future of diagnostics and treatment[5,6].

AI innovation has the potential to affect several parameters of cancer therapy[5,6]. These include prediction, screening, analysis and interpretation of huge data sets, decoding tumor-imaging data, drug discovery and drug validation in a clinical setting[6,7]. Screening of tumor targets in both healthy and high-risk populations offers the opportunity to detect cancer early and with an improved recovery chance for treatment and cure (Figure 2)[7-9]. Advances in AI with machine learning and deep learning are rapidly evolving, and will soon change the science of cancer screening and detection[8,10]. There is a need to train cutting-edge AI technologies to predict early cancer in patients[5]. Although AI applications are still limited, the potential role of AI for early detection of cancer is huge to extract information on diagnosis, prognosis, and therapy responsiveness[5,11,12].

## AI IN EARLY DETECTION OF CANCER

The precision algorithms of AI can be used to improve precision medicine to target the right patient for the right therapy at the right time[5,12,13]. The scoring of proliferation marker Ki-67 is highly relevant for early-stage breast cancer diagnosis, classification, prognosis, and treatment[2,4,7]. Automated brain tumor segmentation methods are computational algorithms that yield tumor delineation and have become an important diagnostic tool in planning precision medicine[4,7,14]. Accurate identification and detection of lymph node metastasis are critical for planning treatments for colon cancer[2,4,15]. Given the complexities and heterogeneity within the cancer data, AI-based algorithms can be used for digitalized identification of histopathologic tumor specimens and image analysis (Figure 1)[4,10]. Gene mutation prediction and validation using raw input digitized histopathology give promising results for six different genetic mutations (STK11, EGFR, FAT1, SETBP1, KRAS, and TP53) in lung cancer[2,4,7,10]. Mutations in KRAS, tumor protein P53 and predictive accuracy of these markers can be used for early diagnosis of cancer[1,2,4]. Clinicians have utilized AI to establish an early signature (Programmed death-ligand 1), which could predict the

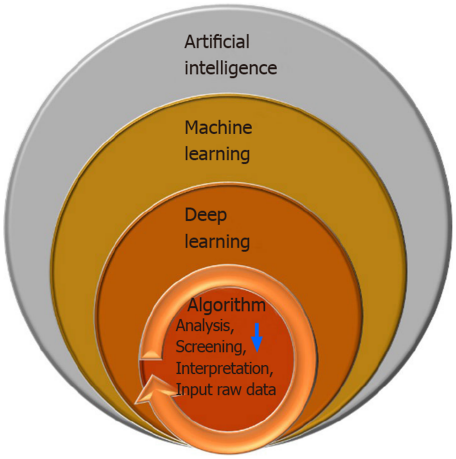


**Figure 1 Artificial intelligence (vehicle with innovative technology), machine learning (the engine that drives artificial intelligence) deep learning (the wave comes to healthcare), and raw data (feeding materials of the artificial intelligence engine).**

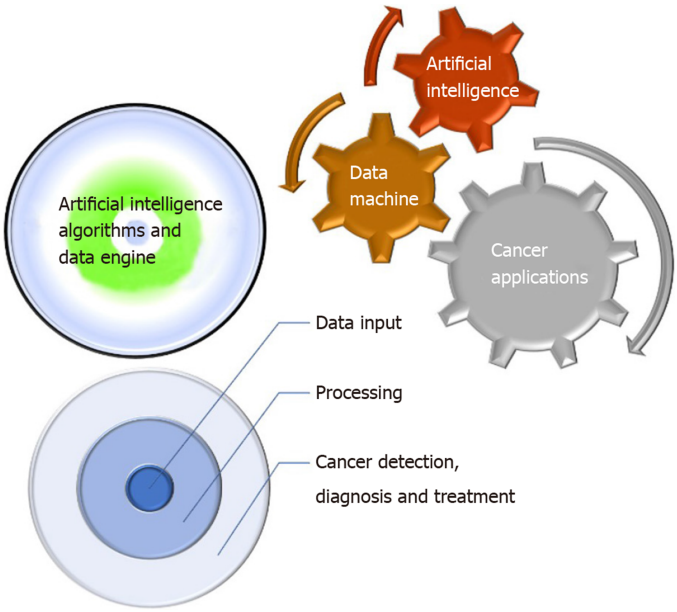


**Figure 2 Applications of artificial intelligence in tumor detection, diagnosis and treatment.**

effectiveness of cancer immunotherapy[1,13].

Data analytics capabilities of AI have made a leap forward in recent years to predict cancer at its starting point[5,16,17]. Screening algorithms for cancer targets and processing data via AI will allow increased early detection and intervention[5,13,18]. Conventional cancer detection and treatment methods are expensive, time-consuming and often result in poor treatment outcomes[1,5,19]. To tackle this issue, the development of machine learning techniques is central to discovering novel biomarkers for early diagnostics[1,2,19]. Precise and early cancer diagnosis is fundamental for clinical management of cancer[2]. AI can accelerate drug discovery, harness biomarkers to accurately match patients to clinical trials, and truly personalize cancer therapy using only a patient's own data[2,5,20]. These advances are indicators that practice-changing cancer therapy empowered by AI may be on the horizon.

## AI IN CLINICAL DIAGNOSTICS

The development of highly accurate AI algorithms for the early recognition of the disease is crucial not only for the rapid identification and diagnosis of cancer patients, but also for the treatment[6,21]. AI can be helpful in clinical diagnostics to ensure

adequate patient care[6]. Useful screening tools to precisely diagnose cancer, such as mammography, radiology and image processing would improve the efficacy of clinical diagnostics[22]. The AI algorithms are already developed with large data sets that show improved diagnostics than clinicians[22]. AI-aided diagnostics for detecting cancer at heterogeneous and complex stage, showed effectiveness in various clinical datasets[22].

Many AI platforms are being developed and approved by the US Food and Drug Administration for use in some areas of cancer, such as for the identification of suspicious lesions in cancer and interpretation of magnetic resonance imaging or computed tomography[23,24]. There are several AI algorithms for the screening of cancer, for the identification of flagged areas in tumors, or treatment trends, and for the evaluation of big data sets[23]. For instance, there is an AI algorithm to visualize lung nodules in lung cancer patients and another AI algorithm to detect breast abnormalities[25-27].

## AI AND NEW EMERGING TECHNOLOGIES

Cutting-edge technologies such as AI are diffusing throughout the health-care system and reshaping patient care[15,28]. The volume of available data has grown exponentially, which can be used for early diagnosis and clinical decision-making process[5,15,28]. The revolution of AI in biomedical science is crucial to develop the concept of precision medicine[7,15]. Concurrent with the development of the field of precision medicine is an even larger revolution in understanding the events of early detection of cancer using digital technology[5,7]. AI in cancer has focused on risk prediction in the hopes of using risk information to influence health behaviors and treatment outcomes[4,7,15]. Understanding the science of early perdition in cancer offers tools and insights to help how to translate AI information into effective treatment (Figure 2)[4,18]. To date, AI has been used in many examples of clinical medicine[12,14]. For example, a smartphone app called DiagnosUs developed by AI technology for analyzing and annotating medical images and videos based on tight linkages between cancer prediction and patient treatment response[12,14,28].

AI could fuel everything from drug development to innovative design to new, better therapies[3,5,28]. Advanced analysis of big data with AI can make predictive modeling of biological processes transform research into development, and increase the accuracy to choose the right medication and dosage for complex diseases[5,28]. For example, the Google-backed company DeepMind has built a device that can diagnose different diseases in real-time[11,28]. It can be used for quick scan, diagnosis, and can detect early conditions such as diabetic retinopathy, age-related degeneration and cancer[11,28]. Similarly, the Big Data to Knowledge initiative was launched by National Institute of Health to support the research and development of tools to integrate big data and data science into biomedical research[11,29].

AI-guided clinical care has the potential to play an important role in screening, diagnosis and treatment of cancer[5,28]. The integration of AI technology into cancer care could further improve the accuracy and speed of diagnosis for better health outcomes[7,11,29]. Scientists trained computer algorithms to analyze patient images of prostate, breast and brain tumors[1,5,7,29]. It can be used at clinics as a tool to help with diagnosis, clinical decision-making and for the prediction of patient outcomes[1,29]. AI can predict commonly mutated genes, identify biomarkers, interpret complex images, and diagnose solutions for challenging types of cancer (Figure 2)[2].

## CONCLUSION

AI has improved diagnosis and treatment outcomes in cancer patients[15]. AI can recognize patterns that can easily be missed by clinicians[10,15]. Cancer is an aggressive disease with a low survival rate, and the treatment process is lengthy and very costly[10]. Furthermore, the lack of large publicly available data sets, concerns over interpretation, lack of well-annotated databases, reproducibility and validation-issues have been significant barriers for AI practice and algorithm development[7]. There is a need to establish a central platform for sharing standardized cancer datasets to drive AI innovation[7]. In the near future AI can be integrated into a multitude of innovative emerging mobile health interfaces, such as digital technologies, smartphone apps and wearable devices, to develop real-time trackers for digital biomarkers that can explain, influence, and predict clinical outcomes[10,15,28].

## REFERENCES


1 **Bi WL**, Hosny A, Schabath MB, Giger ML, Birkbak NJ, Mehrtash A, Allison T, Arnaout O, Abbosh C, Dunn IF, Mak RH, Tamimi RM, Tempany CM, Swanton C, Hoffmann U, Schwartz LH, Gillies RJ, Huang RY, Aerts HJWL. Artificial intelligence in cancer imaging: Clinical challenges and applications. *CA Cancer J Clin* 2019; **69**: 127-157 [PMID: 30720861 DOI: 10.3322/caac.21552]

2 **Coudray N**, Ocampo PS, Sakellaropoulos T, Narula N, Snuderl M, Fenyö D, Moreira AL, Razavian N, Tsirigos A. Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning. *Nat Med* 2018; **24**: 1559-1567 [PMID: 30224757 DOI: 10.1038/s41591-018-0177-5]

3 **Hirasawa T**, Aoyama K, Tanimoto T, Ishihara S, Shichijo S, Ozawa T, Ohnishi T, Fujishiro M, Matsuo K, Fujisaki J, Tada T. Application of artificial intelligence using a convolutional neural network for detecting gastric cancer in endoscopic images. *Gastric Cancer* 2018; **21**: 653-660 [PMID: 29335825 DOI: 10.1007/s10120-018-0793-2]

4 **Mojarad S**, Venturini B, Fulgenzi P, Papaleo R, Brisigotti M, Monti F, Canuti D, Ravaioli A, Woo L, Dlay S, Sherbet GV. Prediction of nodal metastasis and prognosis of breast cancer by ANN-based assessment of tumour size and p53, Ki-67 and steroid receptor expression. *Anticancer Res* 2013; **33**: 3925-3933 [PMID: 24023330]

5 **Topol EJ**. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med* 2019; **25**: 44-56 [PMID: 30617339 DOI: 10.1038/s41591-018-0300-7]

6 **Houssami N**, Kirkpatrick-Jones G, Noguchi N, Lee CI. Artificial Intelligence (AI) for the early detection of breast cancer: a scoping review to assess AI's potential in breast screening practice. *Expert Rev Med Devices* 2019; **16**: 351-362 [PMID: 30999781 DOI: 10.1080/17434440.2019.1610387]

7 **Liang Y**, Kelemen A. Big Data Science and Its Applications in Health and Medical Research: Challenges and Opportunities. *J Biom Biostat* 2016; **7**: 307 [DOI: 10.4172/2155-6180.1000307]

8 **Sadoughi F**, Kazemy Z, Hamedan F, Owji L, Rahmanikatigari M, Azadboni TT. Artificial intelligence methods for the diagnosis of breast cancer by image processing: a review. *Breast Cancer (Dove Med Press)* 2018; **10**: 219-230 [PMID: 30555254 DOI: 10.2147/BCTT.S175311]

9 **Ullah M**. Need For Specialized Therapeutic Stem Cells Banks Equipped With Tumor Regression Enzymes And Anti-Tumor Genes. *J Biomed Allied Res* 2020; **2**: 1-6 [DOI: 10.37191/Mapsci-2582-4937-2(1)-013]

10 **Robertson S**, Azizpour H, Smith K, Hartman J. Digital image analysis in breast pathology-from image processing techniques to artificial intelligence. *Transl Res* 2018; **194**: 19-35 [PMID: 29175265 DOI: 10.1016/j.trsl.2017.10.010]

11 **Krumholz HM**. Big data and new knowledge in medicine: the thinking, training, and tools needed for a learning health system. *Health Aff (Millwood)* 2014; **33**: 1163-1170 [PMID: 25006142 DOI: 10.1377/hlthaff.2014.0053]

12 **Divya S**, Indumathi V, Ishwarya S, Priyasankari M, Devi SK. A self-diagnosis medical chatbot using artificial intelligence. *J Web Development Web Designing* 2018; **3**

13 **Acs B**, Rantalainen M, Hartman J. Artificial intelligence as the next step towards precision pathology. *J Intern Med* 2020; **288**: 62-81 [PMID: 32128929 DOI: 10.1111/joim.13030]

14 **Pearce G**, Wong J, Mirtskhulava L, Al-Majeed S, Bakuria K, Gulua N, editors. Artificial Neural Network and Mobile Applications in Medical diagnosis. 2015 17th UKSim-AMSS International Conference on Modelling and Simulation (UKSim); 2015 Mar 25-27; Cambridge, UK. IEEE, 2016 [DOI: 10.1109/UKSim.2015.34]

15 **Jiang Y**, Yang M, Wang S, Li X, Sun Y. Emerging role of deep learning-based artificial intelligence in tumor pathology. *Cancer Commun (Lond)* 2020; **40**: 154-166 [PMID: 32277744 DOI: 10.1002/cac2.12012]

16 **Ullah M**, Qiao Y, Concepcion W, Thakor AS. Stem cell-derived extracellular vesicles: role in oncogenic processes, bioengineering potential, and technical challenges. *Stem Cell Res Ther* 2019; **10**: 347 [PMID: 31771657 DOI: 10.1186/s13287-019-1468-6]

17 **Ullah M**, Ng NN, Concepcion W, Thakor AS. Emerging role of stem cell-derived extracellular microRNAs in age-associated human diseases and in different therapies of longevity. *Ageing Res Rev* 2020; **57**: 100979 [PMID: 31704472 DOI: 10.1016/j.arr.2019.100979]

18 **Ullah M**, Akbar A. Clinical Relevance of RNA Editing to Early Detection of Cancer in Human. *Int J Stem Cell Res Ther* 2020 [DOI: 10.23937/2469-570X/1410066]

19 **Ullah M**, Akbar A, Thakor AS. An emerging role of CD9 in stemness and chemoresistance. *Oncotarget* 2019; **10**: 4000-4001 [PMID: 31258843 DOI: 10.18632/oncotarget.27021]

20 **Ullah M**. The Pandemic of Novel Coronavirus Disease 2019 (COVID-19): Need for an Immediate Action. *J Biomed Sci* 2020 [DOI: 10.38125/oajbs.000168]

21 **Bhatia A**, Mago VK, Singh R. Use of soft computing techniques in medical decision making: A survey. 2014 International Conference on Advances in Computing, Communications and Informatics (ICACCI); 2014 Sep 24-27; New Delhi, India. IEEE, 2014: 1131 [DOI: 10.1109/ICACCI.2014.6968460]

22 **McKinney SM**, Sieniek M, Godbole V, Godwin J, Antropova N, Ashrafian H, Back T, Chesus M, Corrado GC, Darzi A, Etemadi M, Garcia-Vicente F, Gilbert FJ, Halling-Brown M, Hassabis D, Jansen S, Karthikesalingam A, Kelly CJ, King D, Ledsam JR, Melnick D, Mostofi H, Peng L, Reicher JJ, Romera-Paredes B, Sidebottom R, Suleyman M, Tse D, Young KC, De Fauw J, Shetty S. International evaluation of an AI system for breast cancer screening. *Nature* 2020; **577**: 89-94 [PMID: 31894144 DOI: 10.1038/s41586-019-1799-6]

23 **Weisberg EM**, Chu LC, Fishman EK. The first use of artificial intelligence (AI) in the ER: triage not diagnosis. *Emerg Radiol* 2020; **27**: 361-366 [PMID: 32643069 DOI: 10.1007/s10140-020-01773-6]

24 **Ratner M**. FDA backs clinician-free AI imaging diagnostic tools. *Nat Biotechnol* 2018; **36**: 673-674 [DOI: 10.1038/nbt0818-673a]

25 **Yu KH**, Beam AL, Kohane IS. Artificial intelligence in healthcare. *Nat Biomed Eng* 2018; **2**: 719-731 [PMID: 31015651 DOI: 10.1038/s41551-018-0305-z]

26 **Liu Y**. Application of artificial intelligence in clinical non-small cell lung cancer. *Artif Intell Cancer* 2020; **1**: 19-30 [DOI: 10.35713/aic.v1.i1.19]

27 **Alcantud JCR**, Varela G, Santos-Buitrago B, Santos-García G, Jiménez MF. Analysis of survival for lung cancer resections cases with fuzzy and soft set theory in surgical decision making. *PLoS One* 2019; **14**: e0218283 [PMID: 31216304 DOI: 10.1371/journal.pone.0218283]
28 **Powles J**, Hodson H. Google DeepMind and healthcare in an age of algorithms. *Health Technol (Berl)* 2017; **7**: 351-367 [PMID: 29308344 DOI: 10.1007/s12553-017-0179-1]
29 **Balthazar P**, Harri P, Prater A, Safdar NM. Protecting Your Patients' Interests in the Era of Big Data, Artificial Intelligence, and Predictive Analytics. *J Am Coll Radiol* 2018; **15**: 580-586 [PMID: 29402532 DOI: 10.1016/j.jacr.2017.11.035]

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## EDITORIAL

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## ABOUT COVER

Editor-in-Chief of *Artificial Intelligence in Cancer*, Massoud Mirshahi, MD, PhD is Professor in the Department of Oncology, Université de Paris (France). He previously served as Co-Head of Regenerative Medicine in Avicenna University (Tajikistan), from 2009-2015. His career research has yielded several patents as well as awards of distinction, ranging from Immunopathology of the Eye (Japan, 1986) and American College of Toxicology (USA, 2002) to the "Institute de France" prize (Prix Dalloz, 2006) and Korean Cancer Institute (2016). He has published over 200 international scientific papers and 280 congress communications. He currently serves as reviewer for many international journals in oncology, immunology and ophthalmology, and as a member of several International Academic Associations. His ongoing research interests include cancerology, thrombosis and coagulation, immunopathology, and health and microenvironment pollution. (L-Editor: Filipodia)

## AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Cancer* (*AIC, Artif Intell Cancer*) is to provide scholars and readers from various fields of artificial intelligence in cancer with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*AIC* mainly publishes articles reporting research results obtained in the field of artificial intelligence in cancer and covering a wide range of topics, including artificial intelligence in bone oncology, breast cancer, gastrointestinal cancer, genitourinary cancer, gynecological cancer, head and neck cancer, hematologic malignancy, lung cancer, lymphoma and myeloma, pediatric oncology, and urologic oncology.

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EDITORIAL

# How can artificial intelligence and humans work together to fight against cancer?

Shihori Tanabe

**ORCID number:** Shihori Tanabe 0000-0003-3706-0616.

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**Shihori Tanabe,** Division of Risk Assessment, Center for Biological Safety and Research, National Institute of Health Sciences, Kawasaki 210-9501, Kanagawa, Japan

**Corresponding author:** Shihori Tanabe, PhD, Senior Research Fellow, Division of Risk Assessment, Center for Biological Safety and Research, National Institute of Health Sciences, 3-25-26, Tonomachi, Kawasaki-ku, Kawasaki 210-9501, Kanagawa, Japan. stanabe@nihs.go.jp

## Abstract

This editorial will focus on and discuss growing artificial intelligence (AI) and the utilization of AI in human cancer therapy. The databases and big data related to genomes, genes, proteins and molecular networks are rapidly increasing all worldwide where information on human diseases, including cancer and infection resides. To overcome diseases, prevention and therapeutics are being developed with the abundant data analyzed by AI. AI has so much potential for handling considerable data, which requires some orientation and ambition. Appropriate interpretation of AI is essential for understanding disease mechanisms and finding targets for prevention and therapeutics. Collaboration with AI to extract the essence of cancer data and model intelligent networks will be explored. The utilization of AI can provide humans with a predictive future in disease mechanisms and treatment as well as prevention.

**Key Words:** Artificial intelligence; Cancer; Cancer therapy; Database; Molecular network; Network data analysis



**Core Tip:** The utilization of artificial intelligence (AI) is important for analyzing abundant data on diseases in the big data era. The genomic and molecular data in cancer have been accumulated in databases worldwide. Collaboration with AI in human cancer research is explored in this editorial.

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## INTRODUCTION

Artificial intelligence (AI) has been emphasized since the application of AI expanded into the analysis and prediction of cancer data. The abundant digital cancer data have been accumulated in open-sourced databases worldwide. It is anticipated that new breakthroughs in AI-oriented analysis for utilizing crowd space for big data will predict the treatment of diseases. To explore the coordination in AI and humans, the evolution of AI and the history of supercomputers is summarized, and AI in data analysis and the utilization of AI in the interpretation of cancer data and the predictive role of AI in cancer therapy are overviewed[1]. Many studies related to AI have been conducted for identifying cancer, which are emerging to produce another data field to be interpreted. Machine learning-based models are being actively applied for predicting the toxic outcome of radiotherapy[2]. It is clear that AI can be utilized in data analysis, but they require orientation toward the desired goal. The future perspective of AI applications in cancer will also be discussed.

Recent advances in AI have enabled AI-based clinical prediction in medicine[3-5]. In many cases, machine learning techniques are utilized to learn from data related to diagnosis, prognosis or treatment to predict and support medical decisions[5,6]. Additionally, there is a growing demand for targeting cancer with novel technology such as nanomedicines[7]. Deep-learning methods for image recognition can predict and classify cancer[8]. The utilization of AI is greatly in need in this "big data" era to bridge new technologies and cancer treatment.

## EVOLUTION OF AI

The modern history of AI begins in the 1950s[1,9,10]. Turing[1] proposed thinking about whether machines think to compute machinery and intelligence. New languages have been created to communicate with AI[10]. To think deeply about AI, three key words may exist: Machine learning, deep neural networks and supercomputers. Machine learning can be considered as an in silico method that includes databases, quantitative structure-activity relationships, pharmacophores, homology models and other molecular modeling approaches, and data analysis that uses a computer such as network analysis[11]. Deep neural networks have been developed by mimicking "networks of neurons" in the human brain. In 2006, further evolution in AI occurred, where data were translated into codes[12]. The data translation and coding in neural networks conferred AI to image recognition and interruption[12]. Deep learning with newly developed functions such as rectified linear units (ReLUs) has also produced computational speech translation[13]. AI is utilized in image recognition based on deep neural networks[14]. Deep learning of cancer tissue can predict individual risk, such as the probability of 5-year disease-specific survival[15]. Outstanding advances in the neural network field have achieved a multimodel neural network approach for emotion recognition[16].

Supercomputing has been developed worldwide in multiple fields from black hole exploration to biology research[17]. The development of supercomputers is rapid, and the top supercomputer in performance changes every year in the TOP500 (https://top500.org/Lists/top500/2020/06/). Supercomputer Fugaku, which is named from the Japanese traditional name of Mt. Fuji, the highest mountain in Japan, achieved a calculation speed of 415.5 petaflops/sec, followed by Summit, Sierra, Sunway TaihuLight, and Tianhe, as of June 2020 (https://top500.org/Lists/top500/2020/06/). New supercomputers will be developed in the near future, which will be accompanied by AI as well.

## AI IN DATA ANALYSIS

Recent advances in AI have promoted digital approaches in which pathological images are analyzed in deep learning, and machine learning is utilized for diagnosis[18]. AI is also utilized in human genetics and genomics data, such as nucleic sequence differences in medical applications[19]. AI is utilized for big data analysis for precision medicine[20]. Genome medicine data are analyzed with AI to explore new therapeutic targets[21]. AI might be utilized to diagnose nanomaterial engineering with image recognition[22]. A deep neural network is utilized for data in games to create a specialized AI such as AlphaGo[23]. Deep-learning technology has enabled live-cell superresolution imaging[24]. AI is applied in clinical radiology, such as thoracic

imaging, abdominal and pelvic imaging, colonoscopy, mammography, brain imaging, and radiation oncology[25]. AI, including machine learning and natural language processing, has been optimized for decision-making in health intelligence and precision medicine[26]. Abundant machine learning algorithms have been developed to build prediction models in digital medicine fields, which allows us to predict and proactively intervene in healthcare with AI companions[26-28]. Digital therapeutics where symptoms, disease progression and medication adherence are monitored need AI integration in controlling data and appropriate feedback[29]. AI has been utilized in digital pathology in a wide variety of fields[30]. Careful consideration for AI utilization is also essential for the safe contribution of AI in digital health[31] (Figure 1).

## UTILIZATION OF AI IN THE INTERPRETATION OF CANCER DATA

AI, which includes machine learning and deep learning, has been utilized in cancer data analysis, such as The Cancer Genome Atlas and the Catalogue of Somatic Mutations in Cancer[21,32-34]. In the 2000s, the AI concept became popular for classifying cancer stages with abundant data[35]. The increasing data in the oncology field will be suitable for machine learning to predict cancer prognosis[34]. AI utilization in cancer variants and mutation data for cancer drug discovery has been developed in integration with computational biology[36]. Currently, AI is applied in quantitative imaging to predict the future risk of cancer development[37]. Genomics data obtained from next-generation sequencing can be analyzed by AI for precision medicine[38]. Molecular mechanisms and digital biomarkers can be analyzed with AI to build a disease knowledge network[39]. Deep-learning methods with convolutional neural networks successfully classified liver tumors in magnetic resonance imaging (MRI) images[40]. Machine learning of MRI image data showed significant performance in the detection of prostate cancer[41].

## PREDICTIVE ROLE OF AI IN CANCER THERAPY

Since the 1990s, cancer therapy has been assisted by computational methods[42-44]. The analysis of genomic features and quantitative radiomic phenotypes through gene-set enrichment analysis has revealed integrated relationships between cancer-related genetic pathways and radiomic phenotypes in cancer diagnosis[45]. The in silico profiling of microRNA networks enabled the classification of cancer phenotypes[46]. The relationships between complex molecular pathways and cancer phenotypes may be predicted by AI. In fact, deep-learning methods and modeling with manually defined features are combined in the radiomics pipeline for application in cancer diagnosis, prognosis and treatment evaluation[47]. Furthermore, the morphology of cancer stem cells can be predicted by AI with a conditional generative adversarial network[48]. Cancer image data are deep-learned by AI with convolutional neuronal networks to predict lung cancer subtypes[49]. Prediction of immunotherapy targets in lung cancer by AI was successful in some models, while the need for further validation has also been noted[50] (Table 1).

## CONCLUSION

AI application in cancer therapy is rapidly increasing. The expanding computational technology has conferred AI with the capacity to interpret and predict cancer data. As image recognition by AI is becoming precise and accurate, digital cancer captures will advance in more predictably. There remain challenges for AI to overcome, where human knowledge and ambitiously mining data maximize AI performance.

**Table 1 The various roles of artificial intelligence in cancer therapy**

| Role of AI | Prediction object | Application in cancer therapy |
|---|---|---|
| Deep learning of cancer images | Cancer subtypes | Diagnosis |
| Conditional generative adversarial network | Morphology of cancer stem cells | Prediction of cancer drug resistance |
| Modeling of cancer immunology | Immunotherapy targets | Prediction of therapeutic targets |
| In silico profiling of microRNA networks | Cancer phenotypes | Classification of cancer and identification of therapeutic targets |

AI: Artificial intelligence.

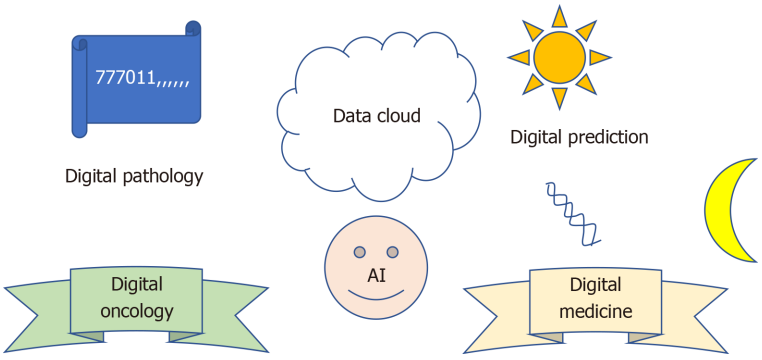


**Figure 1 Artificial intelligence in medicinal data analysis.** Artificial intelligence is utilized for big data analysis in the digital era. AI: Artificial intelligence.

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## REFERENCES

1 **Turing AM**. I. - Computing machinery and intelligence. *Mind* 1950; **LIX**: 433-460 [DOI: 10.1093/mind/LIX.236.433]
2 **Isaksson LJ**, Pepa M, Zaffaroni M, Marvaso G, Alterio D, Volpe S, Corrao G, Augugliaro M, Starzyńska A, Leonardi MC, Orecchia R, Jereczek-Fossa BA. Machine Learning-Based Models for Prediction of Toxicity Outcomes in Radiotherapy. *Front Oncol* 2020; **10**: 790 [PMID: 32582539 DOI: 10.3389/fonc.2020.00790]
3 **Thongprayoon C**, Hansrivijit P, Bathini T, Vallabhajosyula S, Mekraksakit P, Kaewput W, Cheungpasitporn W. Predicting Acute Kidney Injury after Cardiac Surgery by Machine Learning Approaches. *J Clin Med* 2020; **9** [PMID: 32517295 DOI: 10.3390/jcm9061767]
4 **Rajkomar A**, Dean J, Kohane I. Machine Learning in Medicine. *N Engl J Med* 2019; **380**: 1347-1358 [PMID: 30943338 DOI: 10.1056/NEJMra1814259]
5 **Schaefer J**, Lehne M, Schepers J, Prasser F, Thun S. The use of machine learning in rare diseases: a scoping review. *Orphanet J Rare Dis* 2020; **15**: 145 [PMID: 32517778 DOI: 10.1186/s13023-020-01424-6]
6 **Huemer F**, Leisch M, Geisberger R, Melchardt T, Rinnerthaler G, Zaborsky N, Greil R. Combination Strategies for Immune-Checkpoint Blockade and Response Prediction by Artificial Intelligence. *Int J Mol Sci* 2020; **21** [PMID: 32325898 DOI: 10.3390/ijms21082856]
7 **Garcia-Chica J**, D Paraiso WK, Tanabe S, Serra D, Herrero L, Casals N, Garcia J, Ariza X, Quader S, Rodriguez-Rodriguez R. An overview of nanomedicines for neuron targeting. *Nanomedicine (Lond)* 2020; **15**: 1617-1636 [PMID: 32618490 DOI: 10.2217/nnm-2020-0088]
8 **Kanavati F**, Toyokawa G, Momosaki S, Rambeau M, Kozuma Y, Shoji F, Yamazaki K, Takeo S, Iizuka O, Tsuneki M. Weakly-supervised learning for lung carcinoma classification using deep learning. *Sci Rep* 2020; **10**: 9297 [PMID: 32518413 DOI: 10.1038/s41598-020-66333-x]
9 **Kaul V**, Enslin S, Gross SA. History of artificial intelligence in medicine. *Gastrointest Endosc* 2020 [PMID: 32565184 DOI: 10.1016/j.gie.2020.06.040]
10 **McCarthy JJ**, Minsky ML, Rochester N. Artificial intelligence. Massachusetts: Research Laboratory of Electronics (RLE) at the Massachusetts Institute of Technology (MIT), 1959. Available from: http://hdl.handle.net/1721.1/52263
11 **Ekins S**, Mestres J, Testa B. In silico pharmacology for drug discovery: methods for virtual ligand screening and profiling. *Br J Pharmacol* 2007; **152**: 9-20 [PMID: 17549047 DOI: 10.1038/sj.bjp.0707305]
12 **Hinton GE**, Salakhutdinov RR. Reducing the dimensionality of data with neural networks. *Science* 2006; **313**: 504-507 [PMID: 16873662 DOI: 10.1126/science.1127647]
13 **LeCun Y**, Bengio Y, Hinton G. Deep learning. *Nature* 2015; **521**: 436-444 [PMID: 26017442 DOI: 10.1038/nature14539]

14 **Chen R**, Wang M, Lai Y. Analysis of the role and robustness of artificial intelligence in commodity image recognition under deep learning neural network. *PLoS One* 2020; **15**: e0235783 [PMID: 32634167 DOI: 10.1371/journal.pone.0235783]

15 **Bychkov D**, Linder N, Turkki R, Nordling S, Kovanen PE, Verrill C, Walliander M, Lundin M, Haglund C, Lundin J. Deep learning based tissue analysis predicts outcome in colorectal cancer. *Sci Rep* 2018; **8**: 3395 [PMID: 29467373 DOI: 10.1038/s41598-018-21758-3]

16 **Asghar MA**, Khan MJ, Rizwan M, Mehmood RM, Kim SH. An Innovative Multi-Model Neural Network Approach for Feature Selection in Emotion Recognition Using Deep Feature Clustering. *Sensors (Basel)* 2020; **20** [PMID: 32635609 DOI: 10.3390/s20133765]

17 **Butler D**. Computing 2010: from black holes to biology. *Nature* 1999; **402**: C67-C70 [PMID: 10591228 DOI: 10.1038/35011561]

18 **Bera K**, Schalper KA, Rimm DL, Velcheti V, Madabhushi A. Artificial intelligence in digital pathology - new tools for diagnosis and precision oncology. *Nat Rev Clin Oncol* 2019; **16**: 703-715 [PMID: 31399699 DOI: 10.1038/s41571-019-0252-y]

19 **Dias R**, Torkamani A. Artificial intelligence in clinical and genomic diagnostics. *Genome Med* 2019; **11**: 70 [PMID: 31744524 DOI: 10.1186/s13073-019-0689-8]

20 **Williams AM**, Liu Y, Regner KR, Jotterand F, Liu P, Liang M. Artificial intelligence, physiological genomics, and precision medicine. *Physiol Genomics* 2018; **50**: 237-243 [PMID: 29373082 DOI: 10.1152/physiolgenomics.00119.2017]

21 **Fujiwara T**, Kamada M, Okuno Y. [Artificial Intelligence in Drug Discovery]. *Gan To Kagaku Ryoho* 2018; **45**: 593-596 [PMID: 29650810]

22 **Ho D**, Fung AO, Montemagno CD. Engineering novel diagnostic modalities and implantable cytomimetic nanomaterials for next-generation medicine. *Biol Blood Marrow Transplant* 2006; **12**: 92-99 [PMID: 16399592 DOI: 10.1016/j.bbmt.2005.09.013]

23 **Silver D**, Huang A, Maddison CJ, Guez A, Sifre L, van den Driessche G, Schrittwieser J, Antonoglou I, Panneershelvam V, Lanctot M, Dieleman S, Grewe D, Nham J, Kalchbrenner N, Sutskever I, Lillicrap T, Leach M, Kavukcuoglu K, Graepel T, Hassabis D. Mastering the game of Go with deep neural networks and tree search. *Nature* 2016; **529**: 484-489 [PMID: 26819042 DOI: 10.1038/nature16961]

24 **Ouyang W**, Aristov A, Lelek M, Hao X, Zimmer C. Deep learning massively accelerates super-resolution localization microscopy. *Nat Biotechnol* 2018; **36**: 460-468 [PMID: 29658943 DOI: 10.1038/nbt.4106]

25 **Hosny A**, Parmar C, Quackenbush J, Schwartz LH, Aerts HJWL. Artificial intelligence in radiology. *Nat Rev Cancer* 2018; **18**: 500-510 [PMID: 29777175 DOI: 10.1038/s41568-018-0016-5]

26 **Ahmed Z**, Mohamed K, Zeeshan S, Dong X. Artificial intelligence with multi-functional machine learning platform development for better healthcare and precision medicine. *Database (Oxford)* 2020; **2020** [PMID: 32185396 DOI: 10.1093/database/baaa010]

27 **Sitapati A**, Kim H, Berkovich B, Marmor R, Singh S, El-Kareh R, Clay B, Ohno-Machado L. Integrated precision medicine: the role of electronic health records in delivering personalized treatment. *Wiley Interdiscip Rev Syst Biol Med* 2017; **9** [PMID: 28207198 DOI: 10.1002/wsbm.1378]

28 **Jiang F**, Jiang Y, Zhi H, Dong Y, Li H, Ma S, Wang Y, Dong Q, Shen H, Wang Y. Artificial intelligence in healthcare: past, present and future. *Stroke Vasc Neurol* 2017; **2**: 230-243 [PMID: 29507784 DOI: 10.1136/svn-2017-000101]

29 **Palanica A**, Docktor MJ, Lieberman M, Fossat Y. The Need for Artificial Intelligence in Digital Therapeutics. *Digit Biomark* 2020; **4**: 21-25 [PMID: 32399513 DOI: 10.1159/000506861]

30 **Browning L**, Colling R, Rakha E, Rajpoot N, Rittscher J, James JA, Salto-Tellez M, Snead DRJ, Verrill C. Digital pathology and artificial intelligence will be key to supporting clinical and academic cellular pathology through COVID-19 and future crises: the PathLAKE consortium perspective. *J Clin Pathol* 2020 [PMID: 32620678 DOI: 10.1136/jclinpath-2020-206854]

31 **Kelly CJ**, Karthikesalingam A, Suleyman M, Corrado G, King D. Key challenges for delivering clinical impact with artificial intelligence. *BMC Med* 2019; **17**: 195 [PMID: 31665002 DOI: 10.1186/s12916-019-1426-2]

32 **Saltz J**, Gupta R, Hou L, Kurc T, Singh P, Nguyen V, Samaras D, Shroyer KR, Zhao T, Batiste R, Van Arnam J; Cancer Genome Atlas Research Network, Shmulevich I, Rao AUK, Lazar AJ, Sharma A, Thorsson V. Spatial Organization and Molecular Correlation of Tumor-Infiltrating Lymphocytes Using Deep Learning on Pathology Images. *Cell Rep* 2018; **23**: 181-193.e7 [PMID: 29617659 DOI: 10.1016/j.celrep.2018.03.086]

33 **Forbes SA**, Beare D, Boutselakis H, Bamford S, Bindal N, Tate J, Cole CG, Ward S, Dawson E, Ponting L, Stefancsik R, Harsha B, Kok CY, Jia M, Jubb H, Sondka Z, Thompson S, De T, Campbell PJ. COSMIC: somatic cancer genetics at high-resolution. *Nucleic Acids Res* 2017; **45**: D777-D783 [PMID: 27899578 DOI: 10.1093/nar/gkw1121]

34 **Shimizu H**, Nakayama KI. Artificial intelligence in oncology. *Cancer Sci* 2020; **111**: 1452-1460 [PMID: 32133724 DOI: 10.1111/cas.14377]

35 **Montie JE**, Wei JT. Artificial neural networks for prostate carcinoma risk assessment. An overview. *Cancer* 2001; **91**: 1647-1652 [PMID: 11309763 DOI: 10.1002/1097-0142(20010415)91:8+<1647::aid-cncr1178>3.0.co;2-3]

36 **Nagarajan N**, Yapp EKY, Le NQK, Kamaraj B, Al-Subaie AM, Yeh HY. Application of Computational Biology and Artificial Intelligence Technologies in Cancer Precision Drug Discovery. *Biomed Res Int* 2019; **2019**: 8427042 [PMID: 31886259 DOI: 10.1155/2019/8427042]

37 **Bi WL**, Hosny A, Schabath MB, Giger ML, Birkbak NJ, Mehrtash A, Allison T, Arnaout O, Abbosh C, Dunn IF, Mak RH, Tamimi RM, Tempany CM, Swanton C, Hoffmann U, Schwartz LH, Gillies RJ, Huang RY, Aerts HJWL. Artificial intelligence in cancer imaging: Clinical challenges and applications. *CA Cancer J Clin* 2019; **69**: 127-157 [PMID: 30720861 DOI: 10.3322/caac.21552]

38 **Xu J**, Yang P, Xue S, Sharma B, Sanchez-Martin M, Wang F, Beaty KA, Dehan E, Parikh B. Translating cancer genomics into precision medicine with artificial intelligence: applications, challenges and future perspectives. *Hum Genet* 2019; **138**: 109-124 [PMID: 30671672 DOI: 10.1007/s00439-019-01970-5]

39 **Seyhan AA**, Carini C. Are innovation and new technologies in precision medicine paving a new era in patients centric care? *J Transl Med* 2019; **17**: 114 [PMID: 30953518 DOI: 10.1186/s12967-019-1864-9]

40 **Zhen SH**, Cheng M, Tao YB, Wang YF, Juengpanich S, Jiang ZY, Jiang YK, Yan YY, Lu W, Lue JM, Qian JH, Wu ZY, Sun JH, Lin H, Cai XJ. Deep Learning for Accurate Diagnosis of Liver Tumor Based on Magnetic Resonance Imaging and Clinical Data. *Front Oncol* 2020; **10**: 680 [PMID: 32547939 DOI: 10.3389/fonc.2020.00680]

41 **Woźnicki P**, Westhoff N, Huber T, Riffel P, Froelich MF, Gresser E, von Hardenberg J, Mühlberg A, Michel MS, Schoenberg SO, Nörenberg D. Multiparametric MRI for Prostate Cancer Characterization: Combined Use of Radiomics Model with PI-RADS and Clinical Parameters. *Cancers (Basel)* 2020; **12** [PMID: 32630787 DOI: 10.3390/cancers12071767]

42 **Musen MA**, Tu SW, Das AK, Shahar Y. EON: a component-based approach to automation of protocol-directed therapy. *J Am Med Inform Assoc* 1996; **3**: 367-388 [PMID: 8930854 DOI: 10.1136/jamia.1996.97084511]

43 **El-Deredy W**, Ashmore SM, Branston NM, Darling JL, Williams SR, Thomas DG. Pretreatment prediction of the chemotherapeutic response of human glioma cell cultures using nuclear magnetic resonance spectroscopy and artificial neural networks. *Cancer Res* 1997; **57**: 4196-4199 [PMID: 9331074]

44 **Naguib RN**, Robinson MC, Neal DE, Hamdy FC. Neural network analysis of combined conventional and experimental prognostic markers in prostate cancer: a pilot study. *Br J Cancer* 1998; **78**: 246-250 [PMID: 9683301 DOI: 10.1038/bjc.1998.472]

45 **Zhu Y**, Li H, Guo W, Drukker K, Lan L, Giger ML, Ji Y. Deciphering Genomic Underpinnings of Quantitative MRI-based Radiomic Phenotypes of Invasive Breast Carcinoma. *Sci Rep* 2015; **5**: 17787 [PMID: 26639025 DOI: 10.1038/srep17787]

46 **Gallivanone F**, Cava C, Corsi F, Bertoli G, Castiglioni I. *In Silico* Approach for the Definition of radiomiRNomic Signatures for Breast Cancer Differential Diagnosis. *Int J Mol Sci* 2019; **20** [PMID: 31756987 DOI: 10.3390/ijms20235825]

47 **Liu Z**, Wang S, Dong D, Wei J, Fang C, Zhou X, Sun K, Li L, Li B, Wang M, Tian J. The Applications of Radiomics in Precision Diagnosis and Treatment of Oncology: Opportunities and Challenges. *Theranostics* 2019; **9**: 1303-1322 [PMID: 30867832 DOI: 10.7150/thno.30309]

48 **Aida S**, Okugawa J, Fujisaka S, Kasai T, Kameda H, Sugiyama T. Deep Learning of Cancer Stem Cell Morphology Using Conditional Generative Adversarial Networks. *Biomolecules* 2020; **10** [PMID: 32575396 DOI: 10.3390/biom10060931]

49 **Kriegsmann M**, Haag C, Weis CA, Steinbuss G, Warth A, Zgorzelski C, Muley T, Winter H, Eichhorn ME, Eichhorn F, Kriegsmann J, Christopoulos P, Thomas M, Witzens-Harig M, Sinn P, von Winterfeld M, Heussel CP, Herth FJF, Klauschen F, Stenzinger A, Kriegsmann K. Deep Learning for the Classification of Small-Cell and Non-Small-Cell Lung Cancer. *Cancers (Basel)* 2020; **12** [PMID: 32560475 DOI: 10.3390/cancers12061604]

50 **Ninatti G**, Kirienko M, Neri E, Sollini M, Chiti A. Imaging-Based Prediction of Molecular Therapy Targets in NSCLC by Radiogenomics and AI Approaches: A Systematic Review. *Diagnostics (Basel)* 2020; **10** [PMID: 32486314 DOI: 10.3390/diagnostics10060359]

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## ABOUT COVER

Editorial Board Member of *Artificial Intelligence in Cancer*, Dr. Salvatore Perrotti is an expert in oncological, especially colorectal, and emergency surgery. Dr. Perrotti carried out his training in Catania and Rome, Italy. Today, he works in the Oncological Surgery Unit at the University of Catania, performing laparoscopic and robotic colorectal resections with the application of "enhanced recovery after surgery" protocols. Dr. Perrotti is very active in scientific research activities, focusing on pancreatic, gastrointestinal, colorectal and hepatobiliary diseases and surgeries. (L-Editor: Filipodia)

## AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Cancer* (*AIC, Artif Intell Cancer*) is to provide scholars and readers from various fields of artificial intelligence in cancer with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*AIC* mainly publishes articles reporting research results obtained in the field of artificial intelligence in cancer and covering a wide range of topics, including artificial intelligence in bone oncology, breast cancer, gastrointestinal cancer, genitourinary cancer, gynecological cancer, head and neck cancer, hematologic malignancy, lung cancer, lymphoma and myeloma, pediatric oncology, and urologic oncology.

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*MINIREVIEWS*

# Artificial intelligence for modeling uveal melanoma

Beatriz Santos-Buitrago, Gustavo Santos-García, Emiliano Hernández-Galilea

**ORCID number:** Beatriz Santos-Buitrago 0000-0001-6609-5494; Gustavo Santos-García 0000-0001-6609-5493; Emiliano Hernández-Galilea 0000-0001-6609-5495.

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**Beatriz Santos-Buitrago,** Bio and Health Informatics Lab, Seoul National University, Seoul 151-742, South Korea

**Gustavo Santos-García,** IME, University of Salamanca, Salamanca 37007, Spain

**Gustavo Santos-García,** FADoSS Research Unit, Universidad Complutense de Madrid, Madrid 28040, Spain

**Emiliano Hernández-Galilea,** Department of Ophthalmology, Institute of Biomedicine Investigation of Salamanca (IBSAL), University Hospital of Salamanca, University of Salamanca, Salamanca 37007, Spain

**Corresponding author:** Gustavo Santos-García, PhD, Professor, IME, University of Salamanca, FES Building, Campus Miguel de Unamuno, Salamanca 37007, Spain. santos@usal.es

## Abstract

Understanding of the cellular signaling pathways involved in cancer disease is of great importance. These complex biological mechanisms can be thoroughly revealed by their structure, dynamics, and control methods. Artificial intelligence offers rule-based models that favor the research of human signaling processes. In this paper, we give an overview of the advantages of the formalism of symbolic models in medical biology and cell biology of the uveal melanoma. A language is described that allows us: (1) To define the system states and elements with their alterations; (2) To model the dynamics of the cellular system; and (3) To perform inference-based analysis with the logical tools of the language.

**Key Words:** Uveal melanoma; Signal transduction; Pathway Logic; Symbolic systems biology; Artificial intelligence



**Core Tip:** Artificial intelligence offers rule-based models that favor the understanding of cell biology (signaling pathways) involved in the uveal melanoma.

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## INTRODUCTION

Regarding the eye anatomy, the uvea is the middle layer of the eyeball, also known as the vascular tunic, uveal layer, uveal coat, or uveal tract. It consists of three parts: the iris, the ciliary body, and the choroid (Figure 1). These parts in turn divide the uvea into anterior (iris), intermediate (ciliary leather), and posterior (choroid).

The anatomy of the eye is schematized in Figure 2, where the inside of the eye is represented. The drawing exhibits the interior of the eye including the lens, cornea, ciliary body, retina, choroid, vitreous humor, and optic nerve.

An ocular melanoma is a melanoma located in the eye or near the eye. This type of cancer develops in the cells that produce the pigment. The pigment is the substance that gives color to the eyes, skin, and hair. The melanoma develops in the skin, but it can also develop in the conjunctiva or in the eye.

The number of cancer deaths worldwide recorded by the World Health Organization is approximately 9.6 million in 2018. Therefore, cancer is the second leading cause of death globally. This data means that about one-sixth of all deaths are a result of cancer. Lung, prostate, colorectal, stomach and liver cancer are the most common cancers in the case of men. However, the most frequent types for women are breast, colorectal, lung, cervical and thyroid cancer.

Melanoma represents a small percentage among skin cancers, but it is responsible for the vast number of skin cancer deaths. Approximately half of patients with uveal melanoma develop metastases and die from the disease[1-4]. The most common site for metastatic spread is the liver. In most cases, liver metastases are due to a poor prognosis; and life expectancy is 4 to 15 mo if no treatment is performed[5,6]. The incidence of melanoma is increasing worldwide. It is estimated that in 2030 there will be a total of 23.6 million new cases[7].

Melanoma of the uvea is a rare kind of cancer, accounting for 5% of all melanomas[3,5,8,9]. Uveal melanoma represents the most widespread primary eye malignancy in adults, being exceptional in children, with an incidence of about 7 annual cases per million in Europe[10] and 5.3 to 10.9 annual cases per million in the United States[11]. In the case of Europe, incidence rates increase from South to North, being less than two cases per million in Southern Italy and Spain and more than 8 cases per million in Denmark and Norway[10]. In the United States, the difference in incidence among different ethnic groups is large, with the annual age-adjusted incidence being 0.38 for Asians, 0.31 for African Americans, 1.67 for Hispanics, and 6.02 for non-Hispanic whites[11]. However, the prognosis does not differ between ethnic groups[12].

The incidence increases with age, the maximum peak is reached between 60 and 70 years. It is slightly more frequent in men than in women and in people with iris and light skin. Normally, the affectation is unilateral and rarely bilateral. Solar exposure has been considered a possible contributing factor to the development of this tumor. It usually appears sporadically, although it is described as an increased factor in certain diseases: Uveal nevus, xeroderma pigmentosum, oculodermal melanocytosis (nevus of Ota), dysplastic nevus syndrome, and neurofibromatosis type I[13].

The incidence is variable depending on your location. Melanomas are more frequent in the choroid and less in the ciliary body and in the iris (90%, 7%, and 2% of uveal melanomas, respectively)[14]. The clinical and histopathological characteristics of conjunctival and uveal melanomas are distinct: The conjunctival is similar to cutaneous melanoma, and the uveal presents molecular similarities with melanocytic tumors of the central nervous system[15,16].

Mortality rates in five years are variable, between 6% and 53%, regardless of the first line treatment used for local control of the disease. It is known that approximately 50% of patients will develop distant metastasis, mainly in the liver, lung, bone, and skin[17,18]. The average survival period after diagnosis is about seven months.

At the present, there is no treatment for metastatic uveal melanoma. The survival rates have remained stable since the 1970s despite advances in treatment and knowledge of tumor biology. In this sense, it is essential to deepen the knowledge of the molecular actors involved in the initiation and progression of the tumor.

Despite the complexity of the mechanisms of cell biology, we can analyze them in depth by means of their structure, dynamics and control procedures. Predictive models can provide a great benefit for the knowledge of signaling pathways processes in humans. Basically, these molecular pathways carry out the detection of cells, transformation/modification of their components, and transmission of information from their environment to intracellular targets[19,20].

There are numerous perspectives for computational analysis of cellular signaling networks, such as statecharts[21], ordinary differential equations[22], Petri nets[23,24], live

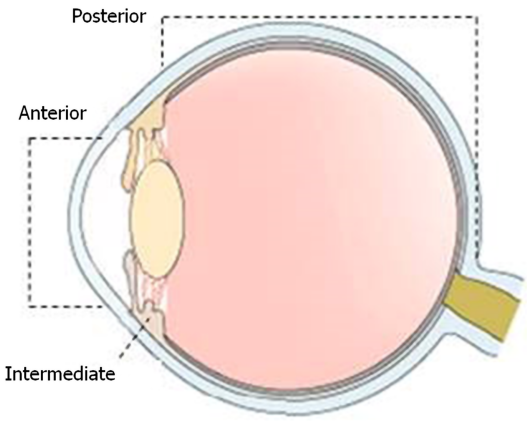


**Figure 1 Diagram of sagittal section of the eye.** Portions of the uvea: Anterior (iris), intermediate (ciliary body), and posterior (choroid).

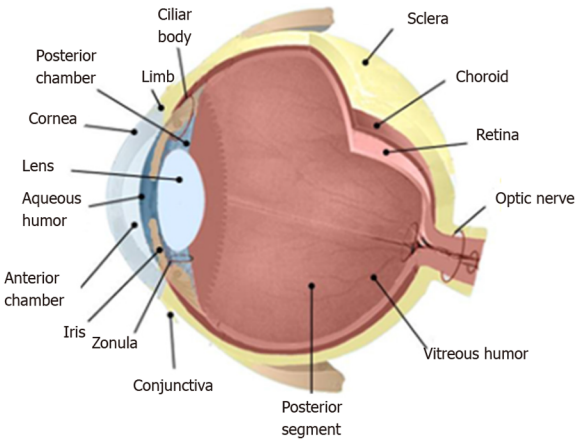


**Figure 2 Anatomy of the eye: Eyeball, tunics and layers of the eye, and intraocular structures.**

sequence charts[25], and ambient/membrane calculi[26], and rule-based[27,28]. Quantitative analyses require the use of a large number of molecules per species. However, in the case of huge numbers, the complexity increases enormously. Qualitative modeling supplies alternative approaches when quantitative methods do not give efficient solutions.

Computational analysis with qualitative approaches have provided a breakthrough in research cell biology and medical biology[29-32]. Symbolic models allow us to model, compute, analyze, and reason about networks of molecular interactions at multiple levels of detail[33,34]. Such models can suggest new knowledge and understanding of complex biological processes. This formalism provides a language for representing system states (different elements, with their locations that are present in the cell at a given time) and mechanisms of change (such as reactions), as well as analysis tools based on logical inference. In this way, behavior of a system can be simulated by symbolic models. The goal is to achieve formal models that are closer to the mindset of biologists[35].

Rule-based models allow managing biological interactions in a natural manner[36-38]. Highly complex cellular processes are successfully and efficiently handled due to the competence of rule-based systems which deal with complex systems[28,39-43].

The rest of the paper reviews the main features of uveal melanoma in Section 2. A description of signaling pathways involved in uveal melanoma is presented in Section 3. The application of artificial intelligence (AI) in modeling and analysis of signaling pathways involved in uveal melanoma with rule-based symbolic systems is presented in Section 4. Finally, we draw our discussion in Section 5.

## UVEAL MELANOMA

### *Etiology of uveal melanoma*

The etiology of uveal melanoma is not yet clear[44]. Ultraviolet radiation (UV radiation) is established as the main risk factor for cutaneous melanoma, although the role of UV radiation in the development of uveal melanoma remains controversial[45,46]. On the other hand, we also comment on the possible influence of genetic factors and somatic mutations.

**Ultraviolet radiation:** Population pigmentation and geographical parameters, such as latitude and altitude, influence the incidence of melanoma. This indicates that UV radiation has a causal role in the development of melanoma[47,48]. The solar radiation that reaches the earth's surface is a range of electromagnetic radiation that is composed of two ranges of ultraviolet wave bands: 95% ultraviolet A (with range between 320 and 400 nm) and 5% ultraviolet B (with range between 280 and 230 nm). The role of these two types of waves is different in the ability to initiate DNA damage, cell signaling pathways and immune alterations[7,49].

Ultraviolet B is considered the main carcinogen of melanoma[50]. The predominant photo-lesions induced by ultraviolet B are: the DNA cyclobutane pyrimidine dimers, pyrimidine-6, 4-pyrimidone photoproducts, and Dewar photoproducts. These DNA lesions are only repaired by a nucleotide excision repair system. If unrepaired, these mutations at dipyrimidine sites induce the characteristic ultraviolet-signature mutation[7]. On the other hand, ultraviolet A wavelengths interact with cellular photosensitizers to produce reactive oxygen species and oxidative damage to DNA. Although rare, ultraviolet radiation also has the capacity to induce other types of DNA alterations, such as protein-DNA crosslinks, single-strand breaks, oxidative base damage, epigenetic changes, and chromosomal aberrations[7].

Exposure to ultraviolet radiation produces numerous cellular reactions, such as epidermal hyperplasia, cutaneous inflammation, and migration of melanocyte stem cells to the interfollicular epidermis. It has been observed that melanoma occurs commonly after intermittent sun exposure and in people with frequent sunburns, especially during childhood[51]. Risk of melanoma has also been associated with high-dose use of indoor artificial tanning devices[52]. However, chronic or low-grade exposures to ultraviolet radiation induce DNA protection due to increased skin thickness and melanin production resulting from chronic ultraviolet exposure[51,53].

**Genetic factors:** A common characteristic of melanoma patients is a pale-skinned complexion, red or blond hair, blue eyes and a high number of large and irregular nevi. The presence of nevi has a high correlation with exposure to ultraviolet radiation. Familial melanomas constitute 8%–12% of all melanoma cases and allow identification of the melanoma susceptibility genes involved in the familial disease, even in sporadic cases[7,54].

**Somatic mutations:** The interruption of the precise control of the transduction of cell signaling pathways is linked to many oncogenes and tumor suppressors. Signal transduction is the complex communication system that coordinates the actions of cells and governs cellular activities[55]. Poor regulation of this network can induce the acquisition of cancer phenotypes. In this way, cell signaling pathways allow us to understand the processes that are also closely involved in cancer: Cell growth and death, migration, metabolism, angiogenesis, and so on.

### *Diagnosis and treatment*

Uveal melanoma can develop without any symptoms and is diagnosed by a routine eye examination. It often causes painless distortion of vision and other nonspecific visual symptoms[56].

The diagnosis of uveal melanoma consists of clinical examination and ocular ultrasonography. The high levels of accuracy and detection rates at the first visit of an experienced eye oncologist make it possible to avoid an invasive diagnostic biopsy[57,58]. Delayed operating time may affect prognosis, especially in older patients with smaller tumors.

For melanoma of the anterior uvea (iris), the best diagnostic criteria are evidence that the lesion is growing. Figure 3 shows an iris melanoma that extends to the ciliary body.

For the diagnosis of posterior uvea melanoma (ciliary body and choroids), transillumination and fundoscopic examination through pupil dilation (indirect ophthalmoscopy) remain the first steps in the diagnostic process[59]. A choroidal nevus

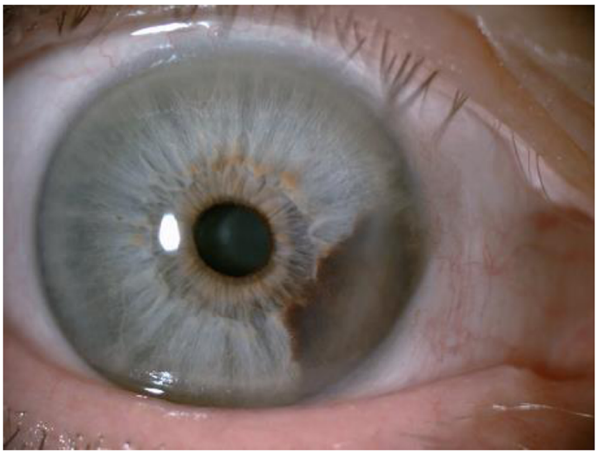

**Figure 3 Iris melanoma.** Iris melanic neoformation that extends to the ciliary body.

in a patient with choroidal melanoma of the contralateral eye is shown in Figure 4.

A shortcoming is the diagnosis of small tumors since it is not possible to distinguish whether they are melanomas or nevi. For this purpose, specialized ocular imaging techniques are useful in order to detect clinical signs that can help in the differential diagnosis, such as: thickness > 2 mm, subretinal fluid, symptoms related to alteration of vision, orange pigmentation, tumor very close to the optic nerve, absence of dorsum, absence of acoustic halo in the US, absence of pattern with pigmented halo, which favor the diagnosis of malignancy[60,61].

For the extension study, in order to assess metastatic lesions, the techniques used are: Computerized tomography of the chest and abdomen, positron emission tomography PET-CT, ultrasonography, and abdominal magnetic resonance imaging (liver)[61]. The usefulness of detecting circulating tumor cells in the bloodstream in order to discover patients at risk of metastasis is questioned[62]. In oncology, the treatment of malignant tumors usually requires histological confirmation of the clinical diagnosis. For intraocular melanoma, therapeutic decisions are mostly based on clinical diagnosis[63].

There are different ways of treatment: (1) Surgery (local resection, endoresection, or enucleation); and (2) Local radiotherapy (106-ruthenium or 125-iodine brachytherapy, proton beam therapy, or stereotactic radiosurgery)[58]. To minimize the side effects of brachytherapy, the neoadjuvant phototherapy is proposed[64].

Currently, the management of posterior uveal melanoma depends on several factors such as: size of the tumor, extension, age of the patient, general health status, condition of the opposite eye, patient's desire and psychological status.

After proton beam therapy, local control of the disease is achieved in 96.4%[65], however local recurrence can take place up to almost ten years after primary therapy and poses a higher risk of metastasis[66].

### *Prognostic factors for the development of melanoma*

The malignant potential of tumors has been a great concern for years. Therefore, it is important to understand why some patients evolve more torpidly and quickly than others despite having the same type of neoplasm. For this reason, we need to be able to recognize factors intrinsic to the tumor or to the patient himself, that allow classifying and/or predicting the evolution of the course of the disease (prognostic factors) in order to be able to offer effective and/or preventive treatments. In uveal melanoma, several clinical, histopathological, cytogenetic and molecular factors have been described which allow the identification of those patients who present a higher risk of developing distant metastasis and who could probably benefit from an adequate prophylactic and/or adjuvant treatment[59,67].

Some features increase the likelihood of developing uveal melanoma. Age, sex, and ethnicity are related to different incidence rates of the disease. The risk of uveal melanoma increases with age (the peak value is reached at age 70), men develop it more often than women and Caucasians are more likely to develop it compared to populations with a darker skin type. In the development of uveal melanoma, there are some other risk factors such as fair skin, inability to tan, light eye color, and blond hair. Other clinical features associated with an increased risk of uveal melanoma are oculodermal melanocytosis and cutaneous, iris and choroidal nevi[5,68].

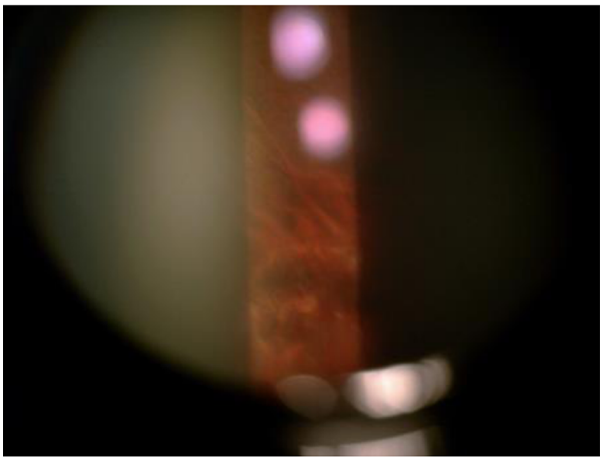

**Figure 4 Choroidal nevus in a patient with choroidal melanoma of the contralateral eye.**

According to the literature[59], the prognostic factors that have been described in uveal melanoma are: (1) Clinical: Age and sex, location and configuration of the tumor, tumor size and staging [American Joint Committee on Cancer develops a classification system for describing the extent of disease progression in cancer patients ( https://cancerstaging.org/)], association with ocular or oculodermal melanocytosis; (2) Histological: Cellular type and nuclear size, mytotic activity, vascular pattern and density, inflammatory infiltrate, necrosis and pigmentation; and (3) Cytogenetic and molecular: cytogenetic alterations and molecular alterations.

## SIGNALING PATHWAYS IN UVEAL MELANOMA

The interruption of the precise control of the transduction of the cell signaling pathways is related to several oncogenes and tumor suppressors. Management of cellular activities and coordination of the actions of the cells constitute a complex system of communication known as signal transduction. A poor regulation of this network can lead to the acquisition of cancer phenotypes. Cellular signaling pathways are also fundamental to understanding processes that are also closely related to cancer: cell growth and death, migration, metabolism, and angiogenesis.

From the genetic point of view, melanoma is a complex disease[69]. Its genetic alterations affect genes in key signaling pathways that govern: (1) Proliferation ( *NRAS*, *BRAF*, and *NF1*); (2) Growth and metabolism (*STK11*, *PTEN*, and *KIT*); (3) Replicative response (*TERT*); (4) Cell cycle control (*CDKN2A*); and (5) Resistance to apoptosis (*TP53*).

Knowledge of the molecular system of uveal melanoma has improved in recent decades and is constantly being updated. Unlike cutaneous melanoma, in uveal melanoma, *NRAS*, *BRAF*, *NF1*, and *c-KIT* mutations are rarely produced. However, some other mutations have been detected: *BAP1*, *EIF1AX*, *CYSLTR2*, *GNA11*, *GNAQ*, *PLCβ4*, and *SF3B1*. These genetic changes allow us to better categorize patients according to the individual risk of distant metastasis[70]. The most common mutations identified in primary uveal melanoma are *GNAQ/11* mutations. *GNAQ* mutations are present in up to half of the cases[71,72].

*GNAQ/11* mutations that occur in uveal melanomas cause *PI3K/Akt/mTOR* signaling to be regulated upwards. The activation of the *PI3K* pathway triggers antiapoptotic signals that complement the proliferative effects of the overactive *MAPK* signaling that contributes to uveal melanomagenesis[5,73]. Figure 5 shows an outline of the signaling pathways involved in the development of uveal melanoma, as well as the specific inhibitors used in preclinical studies (based on Álvarez-Rodríguez *et al*[5]).

The activation of GPCR, a type of receptor on the cell surface, can be caused by various stimuli. This type of activation triggers the exchange of GDP to GTP in the Gα subunit of the heterotrimeric G-protein leading to the dissociation of the Gα subunit from the other two Gβγ subunits. Some mutations can produce activation of G-proteins, such as those that occur in *GNAQ* or *GNA11* in 75% of uveal melanomas. After activation, the subunit Gα causes the cleavage of PIP2 into IP3, and DAG by *PLCβ*. The activation of the *MAPK* pathway is followed by the activation of PKC

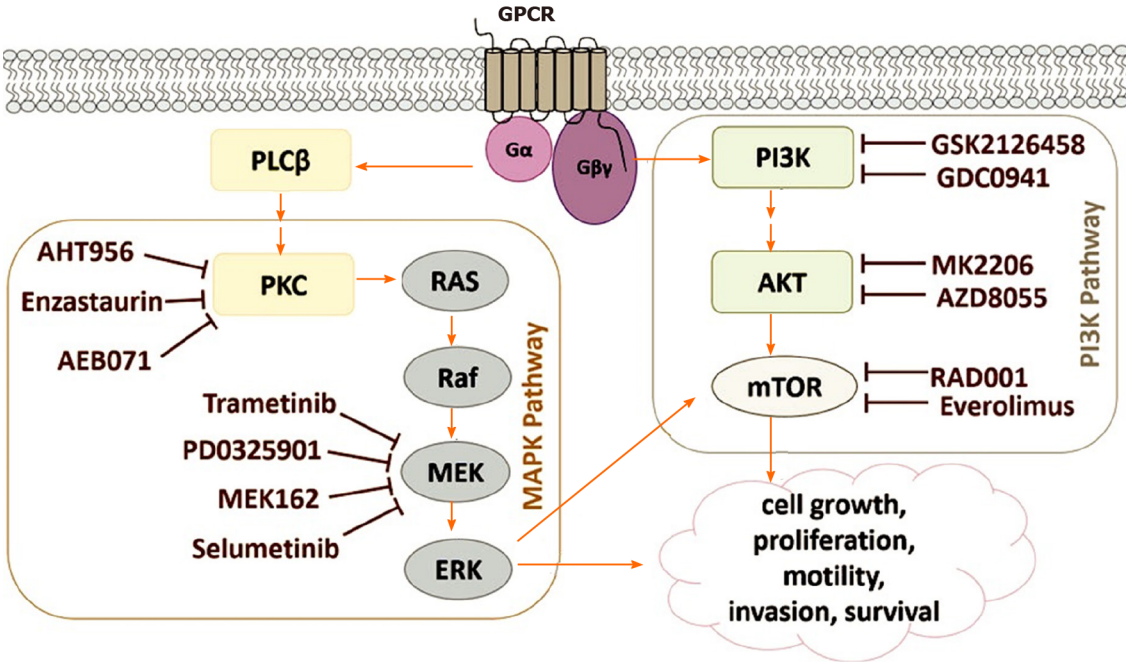


**Figure 5 Signaling pathways involved in the development of uveal melanoma.**

(protein kinase C) by DAG. In addition, Gβγ activates the *PI3K* route. These two pathways are involved in cell survival, mobility, growth, invasion, and proliferation[5].

## RULE-BASED SIGNALING PATHWAYS IN UVEAL MELANOMA

Complex biological mechanisms can be thoroughly revealed by their structure, dynamics, and control methods. AI helps the research of human signaling processes[74,75]. Molecular pathways detect cells, transform components, and internally transmit information from their environment to intracellular targets, such as the genome[20,76].

Symbolic models can be used to model, compute with, analyze, and reason on nets of molecular interactions at different levels of detail, depending on the information available and the aspects to be investigated. These models facilitate a deep knowledge of biological processes and new relationships between their elements. This formalism includes a language to model the states of the system and the dynamics of change (such as reactions), as well as computational inference or logic tools that allow us to analyze the processes[75,77]. In this manner, system behavior can be mimicked with symbolic models. The objective is to establish formal models close to the mentality of biologists[35]. Rule-based models can handle molecular interactions in a natural way. The skills of rule-based systems allow to deal with schemes of a large underlying complexity. In this way, complex cellular processes are managed adequately and efficiently[28].

We define a rule-based system which allows us to carry out an analysis of the change of different initial states, and of the study of the states that can be reached at the initial states in the signaling pathways involved in uveal melanoma. This task is carried out thanks to rewriting logic and Pathway Logic, which we briefly describe below.

**Rewriting logic and Pathway Logic:** Rewriting logic constitutes a logic of change or becoming[78]. It allows you to easily set the specification of the dynamic features of systems and naturally deals with highly nondeterministic concurrent computations. Rewriting logic provides a flexible and general semantic framework to confer semantics to a wide range of languages and concurrency models[79]. Rewriting logic is efficiently implemented in the Maude language[80].

On the one hand, the rewriting logic consists of an equational theory that define sorts, constructors, function symbols, and equality between terms. On the other hand, the rewriting logic extends the equational theory with rewrite rules that allows

expressing the dynamics between the states of the system. Rewrite rules lay down local and parallel changes in a dynamic concurrent system. In this manner, these deduction rules establish a sound reasoning. From a purely logical point of view, we will say that each rewrite rule is a logical entailment in a formal model.

Based on rewriting logic, Pathway Logic[27] is a platform for modeling and analyzing molecular and cellular processes. The resulting formal models can be executed and analyzed using the Maude system[81]. Many models have been developed with Pathway Logic because of the naturalness of rewriting logic to model and experiment with mathematical and biological problems[82,83]. Pathway Logic is presently being used to curate several models of signal transduction and metabolic networks[31].

A rule knowledge base in Pathway Logic consists of rewrite rules and supporting data type specifications[27]. The model of melanoma signaling system consists of: (1) A specification of the starting cell components with their locations, the so-called initial state; and (2) A collection of rewrite rules derived from the global knowledge base by a symbolic reasoning process that recruits all rewrite rules that are potentially executable from the initial state. These executable models collect the possible paths in which a system can progress. Logical inference of Pathway Logic can: (1) Simulate possible ways in which a system could evolve; (2) Build pathways in response to queries; and (3) Think logically about dynamic assembly of complexes and cascade transmission of signals[19,84].

**Modeling of signaling pathways in uveal melanoma:** Through the language Maude and pathway logic, the various elements found in a cell (proteins, genes, chemicals, *etc.*) are defined as a Soup (*i.e.* a set or an associative and commutative list with a neutral element). Such elements constitute a location and are identified by a location name (LocName): op {_|_}: LocName Soup -> Location [ctor].

Some of the various parts or locations of the cell can be: In the nucleus (NUc), in the cytoplasm (CLc), in/across the cell membrane (CLm), outside the cell (XOut), or attached to the inside of the cell membrane (CLi).

In the following code fragment, the nucleus location (NUc) is defined with some elements, such as genes and proteins (*e.g.*, *Maz*, *Myc*, and *Rb1*), some of which are modified (*e.g.*, a high mRNA expression level of *Tp53* gene is presented: [*Tp53*-gene - on]): {NUc | Maz Myc Rb1 NProteasome Chek2 Chek1 Tp53 [Tp53-gene - on]}.

In turn, we can have a set or Soup of the different locations of the cell with their corresponding contents. At last, all location sets (Soups) are collected in wrappers called dishes, through the PD operator.

For the purpose of better understanding the modeling of a state, a small dummy cell is represented in Maude with the following dish:

op DummyDish: -> Dish.

eq DummyDish = PD({CLm | Erbb2 Igf1R [Cbl - Yphos]} {XOut | Igf1 } {CLi | [Gnai1 - act] [Hras - GDP]} {NUc | Elk1 Msk1 Maz} {CLc | Mek1 Akts [Csnk1a1 - act] [Gsk3s - act]}).

Several proteins are included in the dish, such as receptor tyrosine-protein kinase erbB-2 (written as Erbb2 according to Pathway Logic notation), insulin-like growth factor I (Igf1), and Myc-associated zinc finger protein (Maz). Some of these components have modifications, such as phosphorylation on tyrosine (Yphos), binding to GDP, or activation (act). On the other hand, the ligand/receiver bond between cell components can be defined in Maude with the operator (_:_). As an example, a bond between Egf and EgfR is written in Maude as (Egf : EgfR). A pictorial and informal representation of this dummy cell is shown in Figure 6. In this figure, unmodified proteins are shown in green. Proteins with modifications are exhibited with different colors: red for activated proteins, blue for phosphorylated proteins, and yellow for those bound to GDP.

Below, we model a complete dish MELANOMADish for a melanoma case study. This cellular dish is composed of several locations, such as CLc or NUc. The contents of each cell location, such as CLc or NUc, are defined as a soup of elements. Each of the elements or components, such as Akts, may include some modifications (*e.g.*, [Rheb - GTP], [Gsk3s - act], *etc.*). Here is a rough version of Maude's module containing this dish:

mod MELANOMA is inc ALLOPS.

op MELANOMADish : -> Dish.

eq MELANOMADish = PD(

{CLc | [Csnk1a1 - act] [Gsk3s - act] [Ilk - act] Akts Igf1R Axin1 BrafV600E Btrc Rnf6 Trim28 Bim Ctnnb1 Cul7 Eif4ebp1 Pkca Erks Cdc42 Fbxw8 Irs1 Cdkn2a Mek1 Mlst8 Mtor Pdpk1 Erbb2 Ep300 Proteasome Rac1 Rad54b Rbbp6 Raptor Rbx1 Rps6 Rictor Mdm4 Ube2d2 Ube2d1 Rsk1 S6k1 Sin1 Skp1 Ybx1 Ywhas Akt1 Ang Dzip3 Baiap2 L1

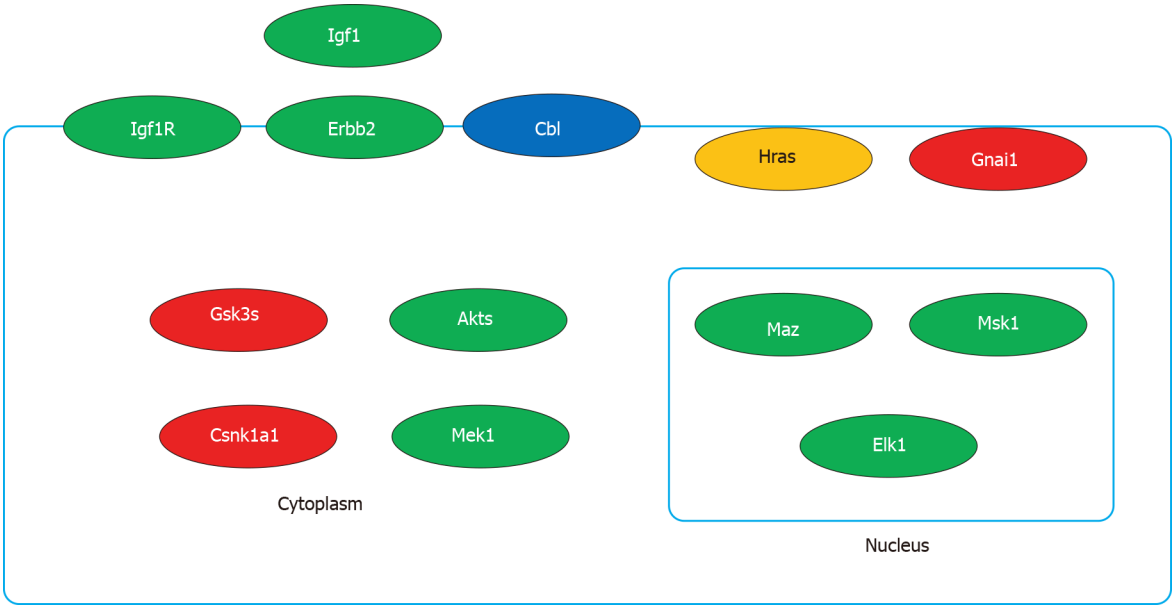


**Figure 6 Schematic representation of a dummy cell.**

C10orf90 Cdk5rap3 Cbp Cul5 G3bp1 Rchy1 Rnf31 Syvn1 Magea3 Erk5 Mdm2 Mkrn1 NgfR Nr0b2 Nus1 Pax3 Pcmt1 Pdlim7 Pkch Ppm1d Psme3 Ube4b Rnf43 Stub1 Tax1bp3 Huwe1 Gli1 Tpt1 Trim24 Ube2d3 Ubc13 Ube3a}
{NUc | [Tp53-gene - on] Maz Myc Rb1 Chek1 NProteasome Chek2 Tp53}
{CVc | [Rheb - GTP] (Tsc1 : Tsc2)} {Sig | empty})
{CLm | PIP2} {XOut | empty} {CLi | Pld1 Pi3k Parva} {CLo | empty}.
endm

**Rule-based dynamics in uveal melanoma:** According to the literature, the *PI3K*, *MAPK*, *IGF-1R*, and *mTOR* pathways are actively involved in uveal melanoma[85-87]. Based on Krantz *et al*[85], Figure 7 illustrates the main signaling pathways that influence uveal melanoma.

Maude's rewriting rules establish the dynamics of our biological system. Concurrent cellular reactions can be defined with these rules. To illustrate this, the 3820c rule states that Pi3k the inside of the cell membrane mediates phosphorylation of PIP2 into PIP3 in the cell membrane [The variables clm and cli indicate that they can be replaced by any soup of elements in/across the cell membrane and attached to the inside of the cell membrane, respectively (Figure 8)]: rl[3820c.PIP3.from.PIP2]: {CLi | cli Pi3k} {CLm | clm PIP2} => {CLi | cli Pi3k} {CLm | clm PIP3}.

Each of these rules is extracted from scientific knowledge. In the case of rule 3820c, the evidence was obtained from KEGG and HumanCyc curated databases containing metabolic reactions [HumanCyc reaction 2.7.1.153 (http://humancyc.org/HUMAN/NEW-IMAGE?type=NIL&object=2.7.1.153-RXN), and KEGG reaction R04545 (http://www.kegg.jp/dbget-bin/www_bget?rn:R04545)].

Once the biological system has been modeled with the elements involved (proteins, genes, *etc*.) and with the rewriting rules that define the dynamics of the model, we can now express the potential of rewriting logic and the environment of Pathway Logic to analyze our biological system from different points of view and draw inferences.

For example, the rewrite command allows to apply rewrite rules and obtain a reachable dish from our initial dish. That is, starting from the cell that we have defined with MELANOMADish, we obtain the final state of the cell only after five of the possible reactions have taken place. The result of applying five rewrite steps to our initial dish is shown in the following example:

Maude > rewrite [5] MELANOMADish.
result Dish: PD({CLm | PIP3} {CLo | empty} {CLi | Pld1 Pi3k Parva}
{NUc | NProteasome Rb1 Tp53 Maz Chek1 Myc Chek2 [Tp53-gene - on]}
{CVc | [Rheb - GTP] (Tsc1 : Tsc2)} {XOut | empty} {Sig | empty}
{CLc | Ube2d3 Erks Fbxw8 Ybx1 G3bp1 Ang Ywhas Ctnnb1 Cul7 Cul5 Axin1 Bim Btrc Mdm4 BrafV600E NgfR Mtor Cdkn2a C10orf90 Pdlim7 Pkch Eif4ebp1 S6k1 Sin1 Syvn1 Tax1bp3 Pkca Proteasome Ppm1d Dzip3 Rictor Rnf6 Rnf31 Rnf43 Erbb2 Ep300 Erk5 Gli1 Trim28 Baiap2 L1 Ubc13 Huwe1 Ube2d2 Mdm2 Magea3 Mek1 Stub1 Mlst8

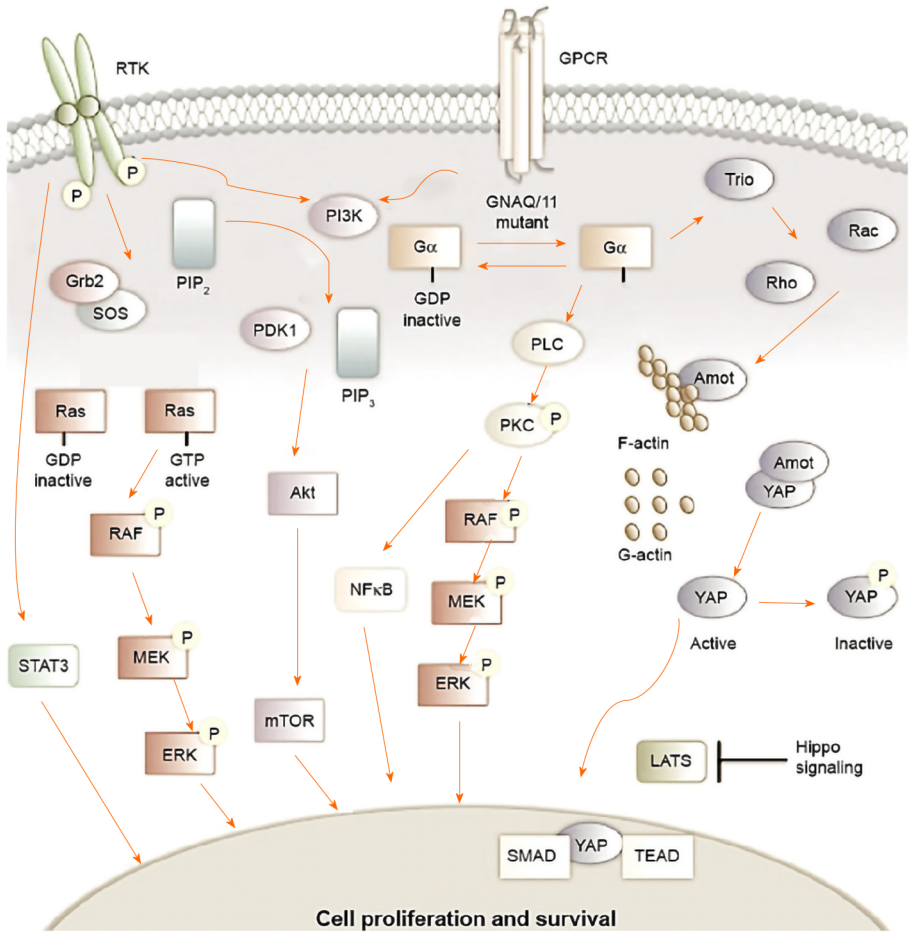


**Figure 7 Signaling pathways in uveal melanoma.**

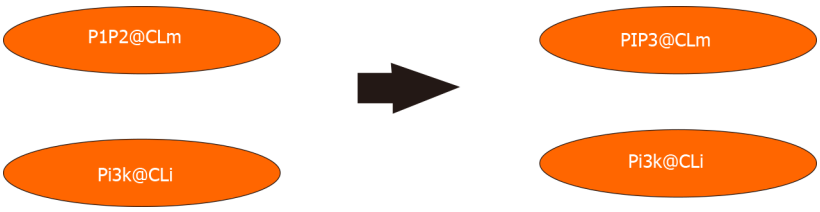


**Figure 8 Outline of the 3820c.PIP3.from.PIP2 rewrite rule.**

Pax3 Pcmt1 Psme3 Rac1 Igf1R Irs1 Rbbp6 Rad54b Raptor Ube3a Cbp Cdc42 Mkrn1 Ube4b Cdk5rap3 Rbx1 Nus1 Nr0b2 Rchy1 Rps6 Rsk1 Skp1 Tpt1 Trim24 Akts Akt1 [Gsk3s - act] [Ilk - act] [Csnk1a1 - act] [Pdpk1 - act] Ube2d1 })

In this first possible solution, some activated proteins are observed in the cytoplasm, such as Gsk3s, Csnk1a1, and Ilk. However, the possible results of rewriting a term may be different, depending on the rules and the order in which they are applied.

Moreover, we can also carry out a breadth-first search with a given pattern using the search instruction. In the following example, we are looking for two states of a cell that satisfy the following conditions: (1) An Erks protein is activated in the nucleus or cytoplasm; (2) A Pi3k protein is attached to the inside of the plasma membrane; and (3) Each of the cell states is reached in a maximum of five steps.

search [2,5] MELANOMADish =>* PD(S:Soup {NUc | nuc:Things}
{CLi | cli:Things Pi3k} {CLm | clm:Things PIP3}
{loc:LocName | things:Things [Erks - erksmodset:ModSet act]})
such that (loc:LocName == NUc) or (loc:LocName == CLc).

In this example, we use the search option =>*, which means that the search must be performed in zero or more steps. Moreover, the variable S:Soup in the search pattern indicates the rest of elements. Maude achieves two possible solutions which fulfill

these conditions and displays the terms that show matching/adjustment in the solutions.

Solution 1 (state 186)

S:Soup --> {CLo | empty} {CVc | [Rheb - GTP] (Tsc1 : Tsc2)} {Sig | empty} {XOut | empty}

nuc:Things --> Maz Myc Chek1 NProteasome Rb1 [Tp53-gene - on] Chek2 Tp53

clm:Things --> empty cli:Things --> Parva Pld1

loc:LocName --> CLc erksmodset:ModSet --> phos(TEY)

things : Things --> C10orf90 Cdk5rap3 Rnf43 Rsk1 Cdkn2a Cul7 Dzip3 Erbb2 Magea3 Huwe1 Stub1 Syvn1 Mkrn1 Mtor Cdc42 NgfR Nr0b2 Pcmt1 Ube2d1 Ube2d2 Pdpk1 Pkca Eif4ebp1 Rps6 Ep300 Pkch Ppm1d G3bp1 Gli1 Psme3 Fbxw8 Proteasome Rac1 Mdm2 Mlst8 Rad54b Cbp Raptor Rbbp6 Nus1 Pax3 Rbx1 Rchy1 Akts Ube2d3 Ube3a Pdlim7 Akt1 Ang Axin1 Baiap2 L1 Bim [ Csnk1a1 - act] [Gsk3s - act] Btrc Rictor [Mek1 - act phos(SMANS)] Rnf6 Rnf31S6k1 Igf1R Sin1 Mdm4 Skp1 Tax1bp3 Tpt1 Ybx1 Trim24 Erk5 Irs1 Trim28 Ubc13 Ube4b Ctnnb1 Cul5 Ywhas [Braf - act] [Ilk - act]

The set of modifications erksmodset:ModSet of this solution contains the protein Erks which is activated and phosphorylated in TEY domain.

In addition, the rules that have been applied to reach state 186 can be obtained by using the instruction show path labels:

Maude > show path labels 186.

3820c.PIP3.from.PIP2

3808c.BrafV600E.act

431c.Mek1.by.Braf

014c.ErkS.by.Mek1

The output of the previous command indicates that 3820c, 3808c, 431c, and 014c rules have been applied to the initial state (MELANOMADish).

## DISCUSSION

In 2018 the World Health Organization recorded approximately 9.6 million cancer deaths worldwide. Therefore, cancer is the second leading cause of death. This data means that about one-sixth of all deaths are the result of cancer. Melanoma represents only about 1% of skin cancer, but it is responsible for the vast majority of skin cancer deaths. Uveal melanoma is a rare type of cancer and represents up to 5% of all melanomas[3,5,8,9]. Approximately half of patients with uveal melanoma develop metastases and die from the disease[1-3].

Symbolic systems biology can explore and analyze biochemical reactions that occur concurrently in a cell. The use of rewriting rules of AI models allows the modeling of biological processes in the cell[74,77]. Our final goal is to provide models that encloses the reasoning and intuitions of biologists.

The computational analyses with qualitative approaches have brought about a breakthrough in research in medical biology and cell biology[19,20]. Symbolic models allow us to model, compute, analyze and reason on networks of molecular interactions at multiple levels of detail[33,34]. Such models can suggest new knowledge and understanding of challenging cellular processes. This formalism provides us with a language that can to be able to represent system states and mechanisms of change and with tools to perform logical inferences and other meta-analyses[32,81].

## CONCLUSION

This paper gives an overview of the computational analysis of signaling pathways based on rewriting logic paradigm. Pathway Logic's SKMELL33 model provides a specific symbolic logic system that browses the complex and dynamic cellular signaling processes that lead to cell survival and proliferation in uveal melanoma[27,84]. The understanding of the signaling pathways involved in melanoma will offer new strategies for effective treatments.

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## REFERENCES


1 **Carvajal RD**, Schwartz GK, Tezel T, Marr B, Francis JH, Nathan PD. Metastatic disease from uveal melanoma: treatment options and future prospects. *Br J Ophthalmol* 2017; **101**: 38-44 [PMID: 27574175 DOI: 10.1136/bjophthalmol-2016-309034]

2 **Char DH**. Metastatic choroidal melanoma. *Am J Ophthalmol* 1978; **86**: 76-80 [PMID: 677236 DOI: 10.1016/0002-9394(78)90018-1]

3 **Chattopadhyay C**, Kim DW, Gombos DS, Oba J, Qin Y, Williams MD, Esmaeli B, Grimm EA, Wargo JA, Woodman SE, Patel SP. Uveal melanoma: From diagnosis to treatment and the science in between. *Cancer* 2016; **122**: 2299-2312 [PMID: 26991400 DOI: 10.1002/cncr.29727]

4 **Karlsson J**, Nilsson LM, Mitra S, Alsén S, Shelke GV, Sah VR, Forsberg EMV, Stierner U, All-Eriksson C, Einarsdottir B, Jespersen H, Ny L, Lindnér P, Larsson E, Olofsson Bagge R, Nilsson JA. Molecular profiling of driver events in metastatic uveal melanoma. *Nat Commun* 2020; **11**: 1894 [PMID: 32313009 DOI: 10.1038/s41467-020-15606-0]

5 **Álvarez-Rodríguez B**, Latorre A, Posch C, Somoza Á. Recent advances in uveal melanoma treatment. *Med Res Rev* 2017; **37**: 1350-1372 [PMID: 28759124 DOI: 10.1002/med.21460]

6 **Dogrusöz M**, Jager MJ, Damato B. Uveal Melanoma Treatment and Prognostication. *Asia Pac J Ophthalmol (Phila)* 2017; **6**: 186-196 [PMID: 28399342 DOI: 10.22608/APO.201734]

7 **González Sánchez E**. Study of the cooperative effect of UVR, BRAF and LKB1 in melanoma. PhD thesis, Autonomous University of Barcelona. 2019. Available from: https://hdl.handle.net/10803/667375

8 **Egan KM**, Seddon JM, Glynn RJ, Gragoudas ES, Albert DM. Epidemiologic aspects of uveal melanoma. *Surv Ophthalmol* 1988; **32**: 239-251 [PMID: 3279559 DOI: 10.1016/0039-6257(88)90173-7]

9 **Kaliki S**, Shields CL. Uveal melanoma: relatively rare but deadly cancer. *Eye (Lond)* 2017; **31**: 241-257 [PMID: 27911450 DOI: 10.1038/eye.2016.275]

10 **Virgili G**, Gatta G, Ciccolallo L, Capocaccia R, Biggeri A, Crocetti E, Lutz JM, Paci E; EUROCARE Working Group. Incidence of uveal melanoma in Europe. *Ophthalmology* 2007; **114**: 2309-2315 [PMID: 17498805 DOI: 10.1016/j.ophtha.2007.01.032]

11 **Singh AD**, Topham A. Incidence of uveal melanoma in the United States: 1973-1997. *Ophthalmology* 2003; **110**: 956-961 [PMID: 12750097 DOI: 10.1016/S0161-6420(03)00078-2]

12 **Shields CL**, Kaliki S, Cohen MN, Shields PW, Furuta M, Shields JA. Prognosis of uveal melanoma based on race in 8100 patients: The 2015 Doyne Lecture. *Eye (Lond)* 2015; **29**: 1027-1035 [PMID: 26248525 DOI: 10.1038/eye.2015.51]

13 **Laver NV**, McLaughlin ME, Duker JS. Ocular melanoma. *Arch Pathol Lab Med* 2010; **134**: 1778-1784 [PMID: 21128775 DOI: 10.1043/2009-0441-RAR.1]

14 **Shields CL**, Manalac J, Das C, Ferguson K, Shields JA. Choroidal melanoma: clinical features, classification, and top 10 pseudomelanomas. *Curr Opin Ophthalmol* 2014; **25**: 177-185 [PMID: 24614143 DOI: 10.1097/ICU.0000000000000041]

15 **Amaro A**, Gangemi R, Piaggio F, Angelini G, Barisione G, Ferrini S, Pfeffer U. The biology of uveal melanoma. *Cancer Metastasis Rev* 2017; **36**: 109-140 [PMID: 28229253 DOI: 10.1007/s10555-017-9663-3]

16 **Smit KN**, Jager MJ, de Klein A, Kiliç E. Uveal melanoma: Towards a molecular understanding. *Prog Retin Eye Res* 2020; **75**: 100800 [PMID: 31563544 DOI: 10.1016/j.preteyeres.2019.100800]

17 **Gragoudas ES**, Egan KM, Seddon JM, Glynn RJ, Walsh SM, Finn SM, Munzenrider JE, Spar MD. Survival of patients with metastases from uveal melanoma. *Ophthalmology* 1991; **98**: 383-9; discussion 390 [PMID: 2023760 DOI: 10.1016/s0161-6420(91)32285-1]

18 **Woodman SE**. Metastatic uveal melanoma: biology and emerging treatments. *Cancer J* 2012; **18**: 148-152 [PMID: 22453016 DOI: 10.1097/PPO.0b013e31824bd256]

19 **Santos-Buitrago B**, Riesco A, Knapp M, Santos-García G, Talcott CL. Reverse inference in symbolic systems biology. In: Fdez-Riverola F, Mohamad MS, Rocha MP, De Paz JF, Pinto T, editors. Volume 616 of Advances in Intelligent Systems and Computing. 11th International Conference on Practical Applications of Computational Biology & Bioinformatics, PACBB 2017; 2017 June 21-23; Porto, Portugal. Springer, 2017: 101-109 [DOI: 10.1007/978-3-319-60816-7_13]

20 **Weng G**, Bhalla US, Iyengar R. Complexity in biological signaling systems. *Science* 1999; **284**: 92-96 [PMID: 10102825 DOI: 10.1126/science.284.5411.92]

21 **Efroni S**, Harel D, Cohen IR. Toward rigorous comprehension of biological complexity: modeling, execution, and visualization of thymic T-cell maturation. *Genome Res* 2003; **13**: 2485-2497 [PMID: 14597657 DOI: 10.1101/gr.1215303]

22 **Stei MM**, Loeffler KU, Holz FG, Herwig MC. Animal Models of Uveal Melanoma: Methods, Applicability, and Limitations. *Biomed Res Int* 2016; **2016**: 4521807 [PMID: 27366747 DOI: 10.1155/2016/4521807]

23 **Hardy S**, Robillard PN. Petri net-based method for the analysis of the dynamics of signal propagation in signaling pathways. *Bioinformatics* 2008; **24**: 209-217 [PMID: 18033796 DOI: 10.1093/bioinformatics/btm560]

24 **Li C**, Ge QW, Nakata M, Matsuno H, Miyano S. Modelling and simulation of signal transductions in an apoptosis pathway by using timed Petri nets. *J Biosci* 2007; **32**: 113-127 [PMID: 17426385 DOI: 10.1007/s12038-007-0011-6]

25 **Sadot A**, Fisher J, Barak D, Admanit Y, Stern MJ, Hubbard EJ, Harel D. Toward verified biological models. *IEEE/ACM Trans Comput Biol Bioinform* 2008; **5**: 223-234 [PMID: 18451431 DOI: 10.1109/TCBB.2007.1076]

26 **Regev A**, Panina EM, Silverman W, Cardelli L, Shapiro E. BioAmbients: An abstraction for biological compartments. *Theor Comput Sci* 2004; **325**: 141–167 [DOI: 10.1016/j.tcs.2004.03.061]

27 **Talcott CL**. Pathway Logic. In: Bernardo M, Degano P, Zavattaro G, editors. Advanced Lectures, volume 5016 of Lecture Notes in Computer Science. Formal Methods for Computational Systems Biology 8th International School on Formal Methods for the Design of Computer, Communication, and Software Systems, SFM 2008; 2008 Jun 2-7; Bertinoro, Italy. Springer, 2008: 21-53 [DOI:

10.1007/978-3-540-68894-5_2]
28 **Hwang W**, Hwang Y, Lee S, Lee D. Rule-based multi-scale simulation for drug effect pathway analysis. *BMC Med Inform Decis Mak* 2013; **13** Suppl 1: S4 [PMID: 23566173 DOI: 10.1186/1472-6947-13-S1-S4]
29 **Burnier JV**, Mastromonaco C, Lasiste JM, Burnier MN. Animal models in uveal melanoma. In: Uveal Tumors, Clinical Ophthalmic Oncology. Cham: Springer, 2019: 135-154 [DOI: 10.1007/978-3-030-17879-6_9]
30 **Metzcar J**, Wang Y, Heiland R, Macklin P. A Review of Cell-Based Computational Modeling in Cancer Biology. *JCO Clin Cancer Inform* 2019; **3**: 1-13 [PMID: 30715927 DOI: 10.1200/CCI.18.00069]
31 **Riesco A**, Santos-Buitrago B, De Las Rivas J, Knapp M, Santos-García G, Talcott C. Epidermal Growth Factor Signaling towards Proliferation: Modeling and Logic Inference Using Forward and Backward Search. *Biomed Res Int* 2017; **2017**: 1809513 [PMID: 28191459 DOI: 10.1155/2017/1809513]
32 **Santos-García G**, Talcott CL, De Las Rivas J. Analysis of cellular proliferation and survival signaling by using two ligand/receptor systems modeled by Pathway Logic. In: Abate A, Safránek D, editors. Revised Selected Papers, volume 9271 of Lecture Notes in Computer Science. Hybrid Systems Biology - Fourth International Workshop, HSB 2015; 2015 Sep 4-5; Madrid, Spain. Springer, 2015: 226-245 [DOI: 10.1007/978-3-319-26916-0_13]
33 **Knapp M**, Briesemeister L, Eker S, Lincoln P, Poggio A, Talcott CL, Laderoute K. Pathway Logic helping biologists understand and organize pathway information. In: Markstein P, Xu Y, editors. Proceedings of the Fourth International IEEE Computer Society Computational Systems Bioinformatics Conference Workshops & Poster Abstracts (CSB 2005 Workshops); 2005 Aug 8-11; Stanford, United States. IEEE Computer Society, 2005: 155-156 [DOI: 10.1109/CSBW.2005.103]
34 **Talcott CL**, Dill DL. Multiple representations of biological processes. In: Corrado Priami C, Plotkin GD, editors. Transactions on Computational Systems Biology VI, volume 4220 of Lecture Notes in Computer Science. Springer, 2006: 221-245 [DOI: 10.1007/11880646_10]
35 **Tenazinha N**, Vinga S. A survey on methods for modeling and analyzing integrated biological networks. *IEEE/ACM Trans Comput Biol Bioinform* 2011; **8**: 943-958 [PMID: 21116043 DOI: 10.1109/TCBB.2010.117]
36 **Chylek LA**, Harris LA, Faeder JR, Hlavacek WS. Modeling for (physical) biologists: an introduction to the rule-based approach. *Phys Biol* 2015; **12**: 045007 [PMID: 26178138 DOI: 10.1088/1478-3975/12/4/045007]
37 **Chylek LA**, Harris LA, Tung CS, Faeder JR, Lopez CF, Hlavacek WS. Rule-based modeling: a computational approach for studying biomolecular site dynamics in cell signaling systems. *Wiley Interdiscip Rev Syst Biol Med* 2014; **6**: 13-36 [PMID: 24123887 DOI: 10.1002/wsbm.1245]
38 **Chylek LA**, Stites EC, Posner RG, Hlavacek WS. Innovations of the rule-based modeling approach. In: Prokop A, Csukás B, editors. Systems Biology, Integrative Biology and Simulation Tools. Dordrecht: Springer, 2013: 273-300 [DOI: 10.1007/978-94-007-6803-1_9]
39 **Harmer R**, Le Cornec YS, Legare S, Oshurko E. Bio-Curation for Cellular Signalling: The KAMI Project. *IEEE/ACM Trans Comput Biol Bioinform* 2019; **16**: 1562-1573 [PMID: 30908261 DOI: 10.1109/TCBB.2019.2906164]
40 **Harris LA**, Hogg JS, Tapia JJ, Sekar JA, Gupta S, Korsunsky I, Arora A, Barua D, Sheehan RP, Faeder JR. BioNetGen 2.2: advances in rule-based modeling. *Bioinformatics* 2016; **32**: 3366-3368 [PMID: 27402907 DOI: 10.1093/bioinformatics/btw469]
41 **Hogg JS**. Advances in rule-based modeling: Compartments, energy, and hybrid simulation, with application to sepsis and cell signaling. PhD thesis, University of Pittsburgh. 2013. Available from: http://d-scholarship.pitt.edu/id/eprint/19621
42 **Schaff JC**, Vasilescu D, Moraru II, Loew LM, Blinov ML. Rule-based modeling with Virtual Cell. *Bioinformatics* 2016; **32**: 2880-2882 [PMID: 27497444 DOI: 10.1093/bioinformatics/btw353]
43 **Smith AM**, Xu W, Sun Y, Faeder JR, Marai GE. RuleBender: integrated modeling, simulation and visualization for rule-based intracellular biochemistry. *BMC Bioinformatics* 2012; **13** Suppl 8: S3 [PMID: 22607382 DOI: 10.1186/1471-2105-13-S8-S3]
44 **Khan S**, Carvajal RD. Novel Approaches to the Systemic Management of Uveal Melanoma. *Curr Oncol Rep* 2020; **22**: 104 [PMID: 32725406 DOI: 10.1007/s11912-020-00965-0]
45 **Gandini S**, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, Melchi CF. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer* 2005; **41**: 45-60 [PMID: 15617990 DOI: 10.1016/j.ejca.2004.10.016]
46 **Mallet JD**, Gendron SP, Drigeard Desgarnier MC, Rochette PJ. Implication of ultraviolet light in the etiology of uveal melanoma: A review. *Photochem Photobiol* 2014; **90**: 15-21 [PMID: 23981010 DOI: 10.1111/php.12161]
47 **Schadendorf D**, van Akkooi ACJ, Berking C, Griewank KG, Gutzmer R, Hauschild A, Stang A, Roesch A, Ugurel S. Melanoma. *Lancet* 2018; **392**: 971-984 [PMID: 30238891 DOI: 10.1016/S0140-6736(18)31559-9]
48 **Singh AD**, Bergman L, Seregard S. Uveal melanoma: epidemiologic aspects. *Ophthalmol Clin North Am* 2005; **18**: 75-84, viii [PMID: 15763193 DOI: 10.1016/j.ohc.2004.07.002]
49 **Johansson PA**, Brooks K, Newell F, Palmer JM, Wilmott JS, Pritchard AL, Broit N, Wood S, Carlino MS, Leonard C, Koufariotis LT, Nathan V, Beasley AB, Howlie M, Dawson R, Rizos H, Schmidt CW, Long GV, Hamilton H, Kiilgaard JF, Isaacs T, Gray ES, Rolfe OJ, Park JJ, Stark A, Mann GJ, Scolyer RA, Pearson JV, van Baren N, Waddell N, Wadt KW, McGrath LA, Warrier SK, Glasson W, Hayward NK. Whole genome landscapes of uveal melanoma show an ultraviolet radiation signature in iris tumours. *Nat Commun* 2020; **11**: 2408 [PMID: 32415113 DOI: 10.1038/s41467-020-16276-8]
50 **De Fabo EC**, Noonan FP, Fears T, Merlino G. Ultraviolet B but not ultraviolet A radiation initiates melanoma. *Cancer Res* 2004; **64**: 6372-6376 [PMID: 15374941 DOI: 10.1158/0008-5472.CAN-04-1454]
51 **Shain AH**, Bagger MM, Yu R, Chang D, Liu S, Vemula S, Weier JF, Wadt K, Heegaard S, Bastian BC, Kiilgaard JF. The genetic evolution of metastatic uveal melanoma. *Nat Genet* 2019; **51**: 1123-1130 [PMID: 31253977 DOI: 10.1038/s41588-019-0440-9]
52 **Lo JA**, Fisher DE. The melanoma revolution: from UV carcinogenesis to a new era in therapeutics. *Science*

2014; **346**: 945-949 [PMID: 25414302 DOI: 10.1126/science.1253735]
53 **Pho L**, Grossman D, Leachman SA. Melanoma genetics: a review of genetic factors and clinical phenotypes in familial melanoma. *Curr Opin Oncol* 2006; **18**: 173-179 [PMID: 16462187 DOI: 10.1097/01.cco.0000208791.22442.09]
54 **Greene MH**, Clark WH Jr, Tucker MA, Kraemer KH, Elder DE, Fraser MC. High risk of malignant melanoma in melanoma-prone families with dysplastic nevi. *Ann Intern Med* 1985; **102**: 458-465 [PMID: 3977193 DOI: 10.7326/0003-4819-102-4-458]
55 **Rouse WB**. Understanding the complexity of health. *Syst Res Behav Sci* 2020 [DOI: 10.1002/sres.2723]
56 **Singh AD**, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology* 2011; **118**: 1881-1885 [PMID: 21704381 DOI: 10.1016/j.ophtha.2011.01.040]
57 **Damato B**. Detection of uveal melanoma by optometrists in the United Kingdom. *Ophthalmic Physiol Opt* 2001; **21**: 268-271 [PMID: 11430620 DOI: 10.1046/j.1475-1313.2001.00595.x]
58 **Nathan P**, Cohen V, Coupland S, Curtis K, Damato B, Evans J, Fenwick S, Kirkpatrick L, Li O, Marshall E, McGuirk K, Ottensmeier C, Pearce N, Salvi S, Stedman B, Szlosarek P, Turnbull N; United Kingdom Uveal Melanoma Guideline Development Working Group. Uveal Melanoma UK National Guidelines. *Eur J Cancer* 2015; **51**: 2404-2412 [PMID: 26278648 DOI: 10.1016/j.ejca.2015.07.013]
59 **Dinarès Fernández CM**. Estudio de la vía de señalización de 4E-BP1. Implicaciones pronósticas y terapéuticas en el melanoma uveal. PhD thesis, Autonomous University of Barcelona. 2017. Available from: https://hdl.handle.net/10803/405446
60 **Aughton K**, Shahidipour H, Djirackor L, Coupland SE, Kalirai H. Characterization of Uveal Melanoma Cell Lines and Primary Tumor Samples in 3D Culture. *Transl Vis Sci Technol* 2020; **9**: 39 [PMID: 32832244 DOI: 10.1167/tvst.9.7.39]
61 **Weis E**, Salopek TG, McKinnon JG, Larocque MP, Temple-Oberle C, Cheng T, McWhae J, Sloboda R, Shea-Budgell M. Management of uveal melanoma: a consensus-based provincial clinical practice guideline. *Curr Oncol* 2016; **23**: e57-e64 [PMID: 26966414 DOI: 10.3747/co.23.2859]
62 **Fernandes BF**, Belfort RN, Di Cesare S, Burnier MN Jr. Circulating uveal melanoma cells: should we test for them? *Can J Ophthalmol* 2008; **43**: 155-158 [PMID: 18347616 DOI: 10.3129/i08-011]
63 **Li Y**, Shi J, Yang J, Ge S, Zhang J, Jia R, Fan X. Uveal melanoma: progress in molecular biology and therapeutics. *Ther Adv Med Oncol* 2020; **12**: 1758835920965852 [PMID: 33149769 DOI: 10.1177/1758835920965852]
64 **Blasi MA**, Laguardia M, Tagliaferri L, Scupola A, Villano A, Caputo CG, Pagliara MM. Brachytherapy Alone or With Neoadjuvant Photodynamic Therapy for Amelanotic Choroidal Melanoma: Functional Outcomes and Local Tumor Control. *Retina* 2016; **36**: 2205-2212 [PMID: 27124879 DOI: 10.1097/IAE.0000000000001048]
65 **Seibel I**, Cordini D, Rehak M, Hager A, Riechardt AI, Böker A, Heufelder J, Weber A, Gollrad J, Besserer A, Joussen AM. Local Recurrence After Primary Proton Beam Therapy in Uveal Melanoma: Risk Factors, Retreatment Approaches, and Outcome. *Am J Ophthalmol* 2015; **160**: 628-636 [PMID: 26133249 DOI: 10.1016/j.ajo.2015.06.017]
66 **Harbour JW**, Char DH, Kroll S, Quivey JM, Castro J. Metastatic risk for distinct patterns of postirradiation local recurrence of posterior uveal melanoma. *Ophthalmology* 1997; **104**: 1785-92; discussion 1792 [PMID: 9373108 DOI: 10.1016/s0161-6420(97)30025-6]
67 **Singh AD**, Shields CL, Shields JA. Prognostic factors in uveal melanoma. *Melanoma Res* 2001; **11**: 255-263 [PMID: 11468514 DOI: 10.1097/00008390-200106000-00007]
68 **Bell DJ**, Wilson MW. Choroidal melanoma: natural history and management options. *Cancer Control* 2004; **11**: 296-303 [PMID: 15377988 DOI: 10.1177/107327480401100503]
69 **Durante MA**, Rodriguez DA, Kurtenbach S, Kuznetsov JN, Sanchez MI, Decatur CL, Snyder H, Feun LG, Livingstone AS, Harbour JW. Single-cell analysis reveals new evolutionary complexity in uveal melanoma. *Nat Commun* 2020; **11**: 496 [PMID: 31980621 DOI: 10.1038/s41467-019-14256-1]
70 **Helgadottir H**, Höiom V. The genetics of uveal melanoma: current insights. *Appl Clin Genet* 2016; **9**: 147-155 [PMID: 27660484 DOI: 10.2147/TACG.S69210]
71 **Moore AR**, Ran L, Guan Y, Sher JJ, Hitchman TD, Zhang JQ, Hwang C, Walzak EG, Shoushtari AN, Monette S, Murali R, Wiesner T, Griewank KG, Chi P, Chen Y. GNA11 Q209L Mouse Model Reveals RasGRP3 as an Essential Signaling Node in Uveal Melanoma. *Cell Rep* 2018; **22**: 2455-2468 [PMID: 29490280 DOI: 10.1016/j.celrep.2018.01.081]
72 **Amirouchene-Angelozzi N**, Schoumacher M, Stern MH, Cassoux N, Desjardins L, Piperno-Neumann S, Lantz O, Roman-Roman S. Upcoming translational challenges for uveal melanoma. *Br J Cancer* 2015; **113**: 1249-1253 [PMID: 26505679 DOI: 10.1038/bjc.2015.269]
73 **Li J**, Liu X, Li C, Wang W. miR-224-5p inhibits proliferation, migration, and invasion by targeting PIK3R3/AKT3 in uveal melanoma. *J Cell Biochem* 2019; **120**: 12412-12421 [PMID: 30825222 DOI: 10.1002/jcb.28507]
74 **Talcott CL**. Formal executable models of cell signaling primitives. In: Margaria T, Steffen B, editors. Proceedings of the Leveraging Applications of Formal Methods Second International Symposium, ISoLA 2006; 2006 Nov 15-19; Paphos, Cyprus. IEEE, 2006: 298-302 [DOI: 10.1109/ISoLA.2006.66]
75 **Talcott C**, Eker S, Knapp M, Lincoln P, Laderoute K. Pathway logic modeling of protein functional domains in signal transduction. *Pac Symp Biocomput*2004: 568-580 [PMID: 14992534 DOI: 10.1142/9789812704856_0053]
76 **Santos-García G**, Talcott CL, Riesco A, Santos-Buitrago B, De Las Rivas J. Role of nerve growth factor signaling in cancer cell proliferation and survival using a reachability analysis approach. In: Mohamad MS, Rocha MP, Fdez-Riverola F, Mayo FJD, De Paz JF, editors. Volume 477 of Advances in Intelligent Systems and Computing. 10th International Conference on Practical Applications of Computational Biology & Bioinformatics, PACBB 2016; 2016 Jun 1-3; Sevilla, Spain. Springer, 2016: 173-181 [DOI: 10.1007/978-3-319-40126-3_18]
77 **Talcott CL**. Symbolic modeling of signal transduction in Pathway Logic. In: Perrone LF, Lawson B, Liu J,

Wieland FP, editors. Proceedings of the Winter Simulation Conference, WSC 2006; 2006 Dec 3-6; Monterey, United States. WSC, 2006: 1656-1665 [DOI: 10.5555/1218112.1218414]

78 **Meseguer J**. Conditional rewriting logic as a unified model of concurrency. *Theor Comput Sci* 1992; **96**: 73–155 [DOI: 10.1016/0304-3975(92)90182-F]

79 **Santos-García G**, Palomino M, Verdejo A. Rewriting logic using strategies for neural networks: An implementation in Maude. In: Corchado JM, Rodríguez S, Llinas J, Molina JM, editors. Volume 50 of Advances in Soft Computing. Proceedings of the International Symposium on Distributed Computing and Artificial Intelligence, DCAI 2008; 2008 Oct 22-24; Salamanca, Spain. Springer, 2009: 424-433 [DOI: 10.1007/978-3-540-85863-8_50]

80 **Clavel M**, Durán F, Eker S, Lincoln P, Martí-Oliet N, Meseguer J, Talcott CL. All about Maude - A high-performance logical framework, how to specify, program and verify systems in Rewriting Logic, volume 4350 of Lecture Notes in Computer Science. Springer, 2007 [DOI: 10.1007/978-3-540-71999-1]

81 **Riesco A**, Santos-Buitrago B, Knapp M, Santos-García G, Galilea EH, Talcott CL. Fuzzy matching for cellular signaling networks in a choroidal melanoma model. In: Panuccio G, Rocha M, Fdez-Riverola F, Mohamad MS, Casado-Vara R, editors. Volume 1240 of Advances in Intelligent Systems and Computing. Practical Applications of Computational Biology & Bioinformatics, 14th International Conference (PACBB 2020); 2020 Jun 17-19; L'Aquila, Italy. Springer, 2020: 80-90 [DOI: 10.1007/978-3-030-54568-0_9]

82 Martí-Oliet N, Ölveczky PC, Talcott CL. Logic, Rewriting, and Concurrency - Essays dedicated to José Meseguer on the occasion of his 65th birthday, volume 9200 of Lecture Notes in Computer Science. Springer, 2015 [DOI: 10.1007/978-3-319-23165-5]

83 **Santos-Buitrago B**, Riesco A, Knapp M, Alcantud JCR, Santos-García G, Talcott C. Soft Set Theory for Decision Making in Computational Biology under Incomplete Information. *IEEE Access* 2019; **7**: 18183-18193 [PMID: 31788396 DOI: 10.1109/ACCESS.2019.2896947]

84 **Santos-Buitrago B**, Galilea EH. Signaling transduction networks in choroidal melanoma: A symbolic model approach. In: Fdez-Riverola F, Rocha M, Mohamad MS, Zaki N, Castellanos-Garzón JA, editors. Volume 1005 of Advances in Intelligent Systems and Computing. Practical Applications of Computational Biology and Bioinformatics, 13th International Conference, PABCC 2019; 2019 Jun 26-28; Ávila, Spain. Springer, 2019: 96-104 [DOI: 10.1007/978-3-030-23873-5_12]

85 **Krantz BA**, Dave N, Komatsubara KM, Marr BP, Carvajal RD. Uveal melanoma: epidemiology, etiology, and treatment of primary disease. *Clin Ophthalmol* 2017; **11**: 279-289 [PMID: 28203054 DOI: 10.2147/OPTH.S89591]

86 **Patel M**, Smyth E, Chapman PB, Wolchok JD, Schwartz GK, Abramson DH, Carvajal RD. Therapeutic implications of the emerging molecular biology of uveal melanoma. *Clin Cancer Res* 2011; **17**: 2087-2100 [PMID: 21444680 DOI: 10.1158/1078-0432.CCR-10-3169]

87 **Xu X**, Zong Y, Gao Y, Sun X, Zhao H, Luo W, Jia S. VEGF Induce Vasculogenic Mimicry of Choroidal Melanoma through the PI3k Signal Pathway. *Biomed Res Int* 2019; **2019**: 3909102 [PMID: 31380420 DOI: 10.1155/2019/3909102]

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