Expert Review of Anticancer Therapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iery20

How will artificial intelligence impact breast cancer research efficiency?

Gianluca Franceschini, Elena Jane Mason, Armando Orlandi, Sabatino D'Archi, Alejandro Martin Sanchez & Riccardo Masetti

To cite this article: Gianluca Franceschini, Elena Jane Mason, Armando Orlandi, Sabatino D'Archi, Alejandro Martin Sanchez & Riccardo Masetti (2021) How will artificial intelligence impact breast cancer research efficiency?, Expert Review of Anticancer Therapy, 21:10, 1067-1070, DOI: 10.1080/14737140.2021.1951240

To link to this article: https://doi.org/10.1080/14737140.2021.1951240

Published online: 09 Jul 2021.

EXPERT REVIEW OF ANTICANCER THERAPY
2021, VOL. 21, NO. 10, 1067–1070
https://doi.org/10.1080/14737140.2021.1951240

EDITORIAL

How will artificial intelligence impact breast cancer research efficiency?

Gianluca Franceschini [a,*], Elena Jane Mason [a,*], Armando Orlandi [b], Sabatino D'Archi [a], Alejandro Martin Sanchez [a] and Riccardo Masetti [a]

[a]Multidisciplinary Breast Center, Dipartimento Scienze della Salute della Donna e del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; [b]Division of Medical Oncology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

ARTICLE HISTORY Received 16 April 2021; Accepted 21 June 2021

1. Introduction

Artificial Intelligence (AI) is a fascinating discipline that has captured our imagination since its birth in the 1950s [1]. Its function in society's life has grown exponentially in the last decade, to a point where many of its manifestations such as face recognition or digital voice assistants are taken for granted and generate little or no astonishment in everyday users. Interest for AI application in health care began in the 1990s and soon turned to oncology. Given the large number of women diagnosed with breast cancer every year, this field is an optimal setting for the development of a technology largely based on processing significant amounts of data.

Computer-aided detection (CAD) was the first software announced for clinical use in breast cancer diagnosis, and was burdened with significant expectations which were not entirely met since its introduction in the late 1990s [2]. This technology relied on algorithms programmed to analyze digital mammograms in search of the same features of malignancy that radiologists look for when reading an exam (i.e. shape, size, asymmetry etc): 'old' AI was therefore conceived as an enhancement of human intelligence that could be matched with the artificial benefit of processing large quantities of data. Despite encouraging initial results, years of CAD clinical application revealed no significant improvement in comprehensive screening performance, and general hype deflated until a new deep learning (DL) revolution generated a second wave of enthusiasm from the early 2010s [3].

2. Discussion

Deep learning is a new AI technology that uses sophisticated architectures initially inspired by human neurobiology, such as convoluted neural networks (CNN), to model complex, non-linear relationships. The main difference with CAD systems is that DL models are not limited by the human understanding of what a breast cancer looks like, but teach themselves what to look for after being exposed to many examples of normal and pathological images.

This revolution will have a significant impact on breast cancer research in three crucial fields: tumor diagnosis, identification of prognostic and predictive factors, and clinical trial development (Figure 1).

2.1. Diagnosis: from enhancing screening to avoiding surgery after neoadjuvant therapy

Today, several commercial FDA-approved AI applications for breast cancer diagnosis are available, and preliminary data examining the case-level performance of these systems are encouraging [4,5]. These algorithms can be used as a 'second opinion' to support the radiologist's decision during the evaluation of a dubious breast mammogram, and other AI applications in breast imaging interpretation are being tested. For example, digital breast tomosynthesis (DBT) has been shown to have a higher cancer detection rate compared to digital mammography alone, but its use in breast screening is currently limited by factors such as higher costs and longer evaluation time [6]: AI can come in aid of radiologists performing screening with this technique by easing lesion detection in DBT images, therefore shortening reading times and allowing utilization of both techniques during screening. Furthermore, given that breast cancer prevalence is generally <1% in the screening population, AI could set a certain threshold of malignancy probability and sift through images to identify mammograms with a high probability of containing no abnormalities, therefore significantly diminishing the radiologist's burden and allowing clinicians to concentrate only on suspicious cases and DBT evaluation [7].

CNNs are a technology particularly apt at interpreting images. It is therefore unsurprising that its application in oncology has gained particular momentum in the fields of radiology and pathology, two strongly image-related disciplines. The distribution of growingly affordable technology has contributed to the development of virtual microscopy and digital pathology, opening the way to a considerable amount of imaging data that is more and more shareable thanks to biobanks and cloud systems. DL CNN models are

CONTACT Gianluca Franceschini gianlucafranceschini70@gmail.com Multidisciplinary Breast Center, Dipartimento Scienze della Salute della Donna e del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Largo Agostino Gemelli 8, Rome 00168, Italy

*These authors have contributed equally to this work.

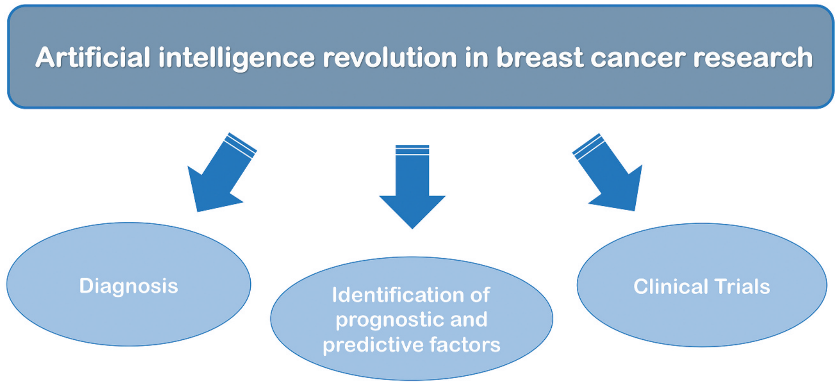

Figure 1. Expected impact of AI in breast cancer research areas.

being tested for automatic interpretation of pathological slides and are showing promising results in many areas applicable to breast cancer care, such as detection of tumor-infiltrating lymphocytes, mitoses, PDL-1 expression, molecular subtypes and HER2 status of breast lesions [4]. Some DL algorithms have been tested to compete with a panel of pathologists in interpreting whole-slide images of nodal metastases, and achieved better diagnostic performance [8]. It is therefore imaginable that AI will gain growing importance in histopathology and provide increasing support (and competition?) to pathology specialists.

In the coming years these acquisitions, in addition to having a clear impact on early diagnosis, could also have a significant role in clinical decision-making, for example in deciding whether or not to refer for surgery patients who obtain a complete clinical response to neoadjuvant treatments.

In recent years, some trials have failed to demonstrate how current diagnostic tools (such as histological analysis after needle biopsy) can select patients with a 'real' complete response, and who could therefore theoretically avoid surgery [9]. AI could perform a radiomic analysis and allow a better selection, to identify those patients who can be cured with the exclusive administration of drugs.

2.2. *Identification of prognostic and predictive factors*

The cost of genome sequencing is declining, and large amounts of data can be extracted from tumor genomic mutation analysis. Linking genomic variations to disease presentations is a challenge that has led to the creation of internationally accessible online databases such as TCGA [10] and COSMIC [11] datasets. With its ability to process and learn from large amounts of data, AI is becoming increasingly important in genomics and translational oncology. DL algorithms have successfully been applied to determine the correlation between tumor genotype and phenotype in whole-slide imaging, a method which could prove more cost-effective than mutational analysis [12]. Furthermore, the analysis of multidimensional 'omic' (multi-omic) data is leading to the characterization of new cancer subtypes, and dedicated repositories are being developed to help store and access the enormous volumes of data that come with it [13]. A comprehensive analysis of such huge amounts of data is beyond human power. In a recent paper by Ramazzotti et al. [14], the researchers developed a deep-learning algorithm to examine multiple data types recovered from TCGA (point mutations, copy number alterations, promoter CpG methylation and gene expression) in order to define breast cancer subtypes. They obtained 13 clusters, 10 of which were ER+, and three predominantly triple-negative. In both groups, they identified a cluster considerably more aggressive than its peers, a finding consistent with the clinical notion that treatment and survival outcomes vary greatly even between patients with the same tumor type. Multi-omic analysis therefore leads to the discovery of new kinds of breast cancer subtypes, and has shown its superiority over traditional classification methods, with a significant impact on patient prognostic scoring [15]. Predicting the tumor's response to drug administration is also a major field of artificial intelligence application, and computational resources integrating big data to discover efficient drug-response patterns are in development [16]. It appears therefore that traditional clinical features, such as tumor histopathology or immunophenotype, are rapidly reaching their limit, and artificial intelligence algorithms analyzing big multiomic data will become critical to predict patient outcomes and response to treatment in an era of precision medicine.

Another 'omic' area that is gaining special attention in breast oncology is radiogenomics – a discipline that researches correlation between the radiological and molecular or genetic features of a disease. This field of research is based on the idea that tumors carrying certain genotypes induce phenotypical alterations that can be extrapolated from radiological information. AI is being used to search for radiological features that, though invisible to the human eye, correlate with specific tumor subtypes, and encouraging results have been obtained in studies examining various imaging techniques [17,18]. CNN architectures have been applied to breast MRI to predict tumor histology and molecular data such as ER, PR, and HER2 status, or foresee disease upstaging in patients diagnosed with DCIS by core needle biopsy [19].

AI evolution will lead toward increasingly tailored approaches in both diagnosis and treatment of breast cancer patients. Radiologic, pathologic, and especially genomic information is leading to the classification of more and more disease subtypes, and several AI tools are in progress to better define prognosis, treatment strategies, and risk of recurrence based on molecular data. Several genomic assay tests such as Oncotype DX® and Endopredict® have been developed to predict risk of recurrence and potential benefit from chemotherapy in breast cancer patients, however to date most tests are only applicable to patients with ER+ tumors [20]. New AI strategies include the research of prognosis scoring systems that are applicable to all tumors, with the goal of avoiding potential overtreatment in women that routinely receive adjuvant chemotherapy, such as ER-negative or HER2-positive cancer patients [21]. IBM launched Watson For Oncology, a cognitive computing system designed to apply AI algorithms to deliver treatment strategies for breast cancer patients, and, while its general success remains controversial, a recent study has shown a high level of concordance between breast cancer treatment recommendations provided by Watson's artificial intelligence and a multidisciplinary, human tumor board [22]. There has also been interest in utilizing CNNs for radiotherapy treatment planning.

2.3. Clinical trials: improving acquisition, accrual, and analysis of big data

In all, the last few years of research in the field of AI have brought to the discovery and honing of new technologies that open the way to plenty of possibilities in the field of breast cancer. Research itself is a viable candidate for revolution, as AI holds the power of transforming every stage of a clinical trial: protocol development can be enhanced, enrollment can be improved by AI patient-trial matching thanks to growing diffusion of electronic health records (EHR), patient adherence can be monitored via real-time data collection offered by DL algorithms in wearable devices [23]. At the same time, breast care clinicians could also sensibly benefit by the introduction of AI in daily routine. While digital innovations such as EHRs or computerized prescriptions have been introduced in hospitals and healthcare facilities to implement patient security and keep track of clinical data, these changes have also led to unfortunate consequences for clinicians, such as augmented clerical work and endless hours spent at a computer instead of face to face with patients. Fortunately, AI technology could step up and take care of technology itself, releasing doctors from the grievous task of feeding data into the system: natural language processing (NLP) is a discipline born from linguistics and AI that enables computers to understand language, both spoken or written. Common examples of this new technology are mobile phone voice assistants or automatic 'chatbots.' NLP technology can read and extract data from medical records, and fed with the right amount of documents it can also learn how to interpret text, so that written expressions such as 'breast cancer,' 'breast tumor' or even 'BC' can be recognized and cataloged correctly as referring to the same concept. This solution has the potential to salvage a vast amount of data collected in documents or even hand-written notes before the advent of technology in hospitals, or from still non-computerized facilities [24].

3. Expert Opinion

While there could be concern of AI gradually growing to replace doctors, current evidence suggests that it could instead be employed to enhance clinical performance while relieving physicians from the burden of bureaucracy. Of course, several issues remain to be addressed. The most discussed limitation in the application of AI to health care in general is the availability of large volumes of datasets, which are crucial for machine learning. However, the growing use of EHRs, NLP technology, and internationally accessible data repositories, together with the notion that breast cancer is the cancer with the highest prevalence in the world, make this issue seem of little relevance. On the contrary, the same cannot be said for the potential ethical and legal implications of directly involving AI in patient management [25]. Who should be held responsible in the case of AI mistakes? A concern all the more preoccupying considering that AI decisions are elaborated in hidden layers, and therefore the logic behind them cannot be verified by a human observer. This is called the 'black box problem,' and it clashes particularly with healthcare practice because clinicians are used to discussing the rationale behind every decision made for a patient. Furthermore, with technology growing more complex every day, doctors will grow less and less accustomed to understanding its principles. To prevent the knowledge gap between physicians and data science experts from growing wider, medical training programs should begin to include AI education and computational skills courses. Only then will future doctors be ready for the coming revolution in oncology.

Funding

This paper received no funding.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Gianluca Franceschini http://orcid.org/0000-0002-2950-3395
Elena Jane Mason http://orcid.org/0000-0003-0152-049X
Armando Orlandi http://orcid.org/0000-0001-5253-4678
Sabatino D'Archi http://orcid.org/0000-0002-0223-9635
Alejandro Martin Sanchez http://orcid.org/0000-0002-4840-507X
Riccardo Masetti http://orcid.org/0000-0002-7520-9111

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Turing AM. Computing machinery and intelligence. Mind. 1950; LIX:433–460.
2. McKinney SM, Sieniek M, Godbole V, et al. International evaluation of an AI system for breast cancer screening. Nature. 2020;577 (7788):89–94.
   - • **These authors have contributed substantially to studying AI application in particular aspects of breast cancer care.**
3. Lecun Y, Bengio Y, Hinton G. Deep learning. Nature. 2015;521 (7553):436–444.
   - •• **These studies represent landmarks or are particularly efficient in explaining the history and current applications of AI in particular aspects of breast cancer care.**
4. Shimizu H, Nakayama KI. Artificial intelligence in oncology. Cancer Sci. 2020;111(5):1452–1460.
   - • **These authors have contributed substantially to studying AI application in particular aspects of breast cancer care.**
5. Rodriguez-Ruiz A, Lång K, Gubern-Merida A, et al. Stand-alone artificial intelligence for breast cancer detection in mammography: comparison with 101 radiologists. J Natl Cancer Inst. 2019;111 (9):916–922.
   - •• **These studies represent landmarks or are particularly efficient in explaining the history and current applications of AI in particular aspects of breast cancer care.**
6. Skaane P, Bandos AI, Gullien R, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population based screening program. Radiology. 2013;267 (1):47–56.
7. Sechopoulos I, Teuwen J, Mann R. Artificial intelligence for breast cancer detection in mammography and digital breast tomosynthesis: state of the art. Semin Cancer Biol. 2021;72:214–225.
   - •• **These studies represent landmarks or are particularly efficient in explaining the history and current applications of AI in particular aspects of breast cancer care.**
8. Bejnordi BE, Veta M, Van Diest PJ, et al. Diagnostic assessment of deep learning algorithms for detection of lymph node metastases in women with breast cancer. JAMA. 2017;318(22):2199–2210.
   - • **These authors have contributed substantially to studying AI application in particular aspects of breast cancer care.**
9. Li Y, Zhou Y, Mao F, et al. The diagnostic performance of minimally invasive biopsy in predicting breast pathological complete response after neoadjuvant systemic therapy in breast cancer: a meta-analysis. Front Oncol. 2020;10:933.
10. Blum A, Wang P, Zenklusen JC. SnapShot: TCGA-analyzed tumors. Cell. 2018;173(2) Cell Press:530.
11. Tate JG, Bamford S, Jubb HC, et al. COSMIC: the catalogue of somatic mutations in cancer. Nucleic Acids Res. 2019;47(D1): D941–D947.
12. Trivizakis E, Papadakis GZ, Souglakos I, et al. Artificial intelligence radiogenomics for advancing precision and effectiveness in oncologic care (Review). Int J Oncol. 2020;57(1):43–53.
13. Xie B, Yuan Z, Yang Y, et al. MOBCdb: a comprehensive database integrating multi-omics data on breast cancer for precision medicine. Breast Cancer Res Treat. 2018;169(3):625–632.
14. Ramazzotti D, Lal A, Wang B, et al. Multi-omic tumor data reveal diversity of molecular mechanisms that correlate with survival. Nat Commun. 2018;9(1). DOI:10.1038/s41467-018-06921-8
15. Biswas N, Chakrabarti S. Artificial Intelligence (AI)-based systems biology approaches in multi-omics data analysis of cancer. Front Oncol. 2020;10. DOI:10.3389/fonc.2020.588221
16. Vougas K, Sakellaropoulos T, Kotsinas A, et al. Machine learning and data mining frameworks for predicting drug response in cancer: an overview and a novel in silico screening process based on association rule mining. Pharmacol Ther. 2019;203:107395.
17. Hamidinekoo A, Denton E, Rampun A, et al. Deep learning in mammography and breast histology, an overview and future trends. Med Image Anal. 2018;47:45–67.
18. Ha R, Mutasa S, Karcich J, et al. Predicting breast cancer molecular subtype with MRI dataset utilizing convolutional neural network algorithm. J Digit Imaging. 2019;32(2):276–282.
19. Zhu Z, Harowicz M, Zhang J, et al. Deep learning analysis of breast MRIs for prediction of occult invasive disease in ductal carcinoma in situ. Comput Biol Med. 2019;115:103498.
20. Breastcancer.org. Oncotype DX: genomic test to inform breast cancer treatment. 2018 [Cited 2021 Jun 4]. Available from: https://www.breastcancer.org/symptoms/testing/types/oncotype_dx
21. Shimizu H, Nakayama KI. A 23 gene–based molecular prognostic score precisely predicts overall survival of breast cancer patients. EBioMedicine. 2019;46:150–159.
22. Somashekhar SP, Sepúlveda MJ, Puglielli S, et al. Watson for oncology and breast cancer treatment recommendations: agreement with an expert multidisciplinary tumor board. Ann Oncol. 2018;29 (2):418–423.
   - • **These authors have contributed substantially to studying AI application in particular aspects of breast cancer care.**
23. Cesario A, Simone I, Paris I, *et al*. Development of a digital research assistant for the management of patients' enrollment in oncology clinical trials within a research hospital. J Pers Med. 2021;11(4):244.
24. Kann BH, Thompson R, Thomas CR, et al. Artificial intelligence in oncology: current applications and future directions. ONCOLOGY (United States). 2019;33(2):46–53.
25. Carter SM, Rogers W, Win KT, et al. The ethical, legal and social implications of using artificial intelligence systems in breast cancer care. Breast. 2020;49:25–32.
   - • **These authors have contributed substantially to studying AI application in particular aspects of breast cancer care.**