BREAST CANCER

The Way of the Future: Personalizing Treatment Plans Through Technology

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overview

Advances in tissue analysis methods, image analysis, high-throughput molecular profiling, and computational tools increasingly allow us to capture and quantify patient-to-patient variations that impact cancer risk, prognosis, and treatment response. Statistical models that integrate patient-specific information from multiple sources (e.g., family history, demographics, germline variants, imaging features) can provide individualized cancer risk predictions that can guide screening and prevention strategies. The precision, quality, and standardization of diagnostic imaging are improving through computer-aided solutions, and multigene prognostic and predictive tests improved predictions of prognosis and treatment response in various cancer types. A common theme across many of these advances is that individually moderately informative variables are combined into more accurate multivariable prediction models. Advances in machine learning and the availability of large data sets fuel rapid progress in this field. Molecular dissection of the cancer genome has become a reality in the clinic, and molecular target profiling is now routinely used to select patients for various targeted therapies. These technology-driven increasingly more precise and quantitative estimates of benefit versus risk from a given intervention empower patients and physicians to tailor treatment strategies that match patient values and expectations.

INTRODUCTION

Individualization of patient care has long been the goal of medicine. The Ebers Papyrus written in Egypt in 1500 B.C. provides the following personalized treatment recommendations "…for a person who suffers from abdominal obstruction and you find [on physical examination] that it goes-and-comes under your fingers like oil-in-tube, then prepare for him fruit-of-the-dompalm, dissolve in semen, crush and cook in oil and honey…," on the other hand if a person suffers from abdominal obstruction "…and his stomach is swollen and his chest asthmatic, then make for him wormwood, elderberries, sebesten, sesa chips, crush and cook in beer."[1] One could argue that the history of medicine is the history of increasingly more sophisticated personalization of treatment that involves progressively narrower definitions of disease and selective treatments based on understanding of biology. Most of our current disease terminologies date back to the 19th century and are based on anatomic and microscopic observations paired with clinical descriptions of symptoms. However, dramatic advances in molecular and cell biology, medical imaging, and computer science, as well as increasingly rigorous standards for clinical research, are fundamentally changing how we think about cancer and formulate treatment strategies for our patients. Oncology has reached an inflection point; many of the classic disease definitions started to lose practical value, and for good reason. Generic disease terms like "breast cancer" became so vague and imprecise in the context of contemporary knowledge and diagnostic technologies that it has almost lost its value in determining how to act on this diagnosis. Contemporary state-of-the-art diagnoses increasingly capture the large patient-to-patient variations that impact cancer risk, prognosis, and treatment response. This article briefly reviews advances in imaging technologies and the use of molecular tests to guide treatment selection; focusing on breast cancer as an example, we also discuss the rapidly emerging field of artificial intelligence (AI) to aid diagnosis and reduce undesirable interobserver variance in clinical activities.

OPTIMIZING ADAPTIVE IMAGING IN THE CLINICAL MANAGEMENT OF BREAST CANCER

Imaging is a standard diagnostic procedure in the clinical management of breast cancer; however, its application to personalized treatment is rapidly evolving and requires reassessment of how imaging is performed and how information is derived. The growing field of quantitative imaging biomarkers recognizes the need for standards that address each of the stages of imaging technology, including the imaging device itself ("scanner"), the image reconstruction process, and the method of image quantification.[2-4] Each of

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PRACTICAL APPLICATIONS

- The most accurate cancer risk and prognostic risk models integrate variables from multiple sources. Do not guesstimate; use a validated multivariable model if available.
- Molecular variables and anatomic tumor (T, N) stage tend to provide independent information about clinical outcome and, therefore, complement each other. Use all information that is available to provide the most accurate outcome estimates.
- Quantitative estimates of probable clinical outcome and predicted benefit from a given intervention are now available for many clinical situations. These tools enable patients to tailor treatment strategies to their own risk/benefit tolerance level.

these elements contributes to the overall performance of the imaging biomarker and has to be considered in the optimization process. In breast cancer care, much is being learned in the neoadjuvant treatment setting where the status of the tumor can be monitored during systemic treatment. MRI has evolved as an effective imaging method for assessing tumor response during neoadjuvant treatment and is used here as an example of the benefits and challenges of adaptive imaging. This application highlights several overarching considerations for optimizing imaging markers for use in personalized treatment strategies, including the need to balance potentially competing requirements for clinical assessment and biomarker performance and the need for subtype-specific optimization of imaging markers.

Image-Acquisition Considerations

A challenge to the adoption of imaging markers in clinical practice is the need to control for variabilities at the time of image acquisition that can compromise quantitative measurements, even if they do not adversely impact diagnostic accuracy. This is particularly critical if repeated measures are used to assess change over time. Imaging technologies for breast cancer are designed primarily for cancer screening. MRI image acquisition methods for screening have been engineered to emphasize anatomic clarity and speed. This can often involve the use of image enhancements and filters to improve contrast-to-noise and improve lesion conspicuity; however, these strategies can introduce errors and site-to-site variability to the measured signal. Scan time reduction strategies are used to improve efficiency in the clinic, often at the expense of measurement fidelity. In the clinical setting it is commonplace to adjust image acquisition protocols on a patient-by-patient basis to accommodate differences in body habitus or anatomy. Intelligent software systems on many scanners will often accommodate these adjustments by automatically modifying other image acquisition parameters. These measures improve diagnostic efficiency, but biomarker imaging requires that acquisition techniques also prioritize quantitative accuracy. Controllable errors must be minimized, and this can often come at the expense of spatial resolution and scan time. Inter- and intrapatient variability are minimized using more restrictive protocols, controlled introduction of software and hardware upgrades, and limited allowances for patient-specific adjustments. These requirements are often at odds with the strategies used to optimize clinical imaging and can add steps to the clinical workflow. These conflicting incentives hinder the ability to ensure high-fidelity data for imaging biomarker development and testing.[2,5] A retrospective study performed in the I-SPY breast cancer neoadjuvant trial examined the influence of protocol adherence on the ability of functional tumor volume, a biomarker derived from breast MRI, to predict pathologic complete response (pCR). Functional tumor volume is used as part of the response-adaptive design of the I-SPY2 trial to adjust randomization in favor of arms showing early benefit over control.[6] Multicenter MRI data used in the study followed a prescribed protocol and met acceptance criteria. Protocol adherence was rated for seven technical and quality factors, including acquisition duration, early phase timing, field of view, spatial resolution, contralateral image quality, patient motion, and contrast administration. The area under the receiver operating characteristic curve was used to measure the performance of functional tumor volume change in predicting pCR. Functional tumor volume changes with adherent image quality in all factors had higher estimated area under the receiver operating characteristic curve than did those with nonadherent image quality, although the differences did not reach statistical significance. The study highlighted the impact of protocol adherence and data quality on predictive performance.[7]

MRI of Neoadjuvant Response

Of breast imaging methods, MRI is particularly effective for visualizing the effects of neoadjuvant treatment on breast tumors. MRI signals reflect spatial and functional properties of tissue and provide noninvasive information about tumor burden and biologic heterogeneity, giving it great potential to serve as a biomarker. In the neoadjuvant setting, breast MRI has been evaluated in numerous studies for its ability to detect residual disease and to predict response. Accurate detection and delineation of residual disease has the potential to improve surgical outcomes and perhaps remove the need for surgery for women achieving pCR. There is growing interest in this goal as more effective treatments have led to higher rates of pCR. MRI has been found to be more effective than clinical examination and other routine

imaging modalities (mammography and ultrasound) for residual disease detection.[8,9] Studies examining agreement between MRI and residual disease size on histopathology have found it to vary by subtype, with higher agreement reported among HER2+ and triple-negative breast cancer (TNBC) tumors.[10] Initial studies reported lower agreement in hormone receptor–positive tumors, which often have more diffuse residual disease that is undetectable by MRI. However, a recent literature review on subtype-specific MRI performance in detecting pCR concluded that MRI accuracy in detecting pCR is not as clearly associated with subtype as individual studies initially suggested.[11]

It is well understood that the intrinsic resolving power of MRI limits its ability to detect microscopic residual disease and, thus, its ability to discern between true pCR and minimal residual disease. This limits the use of MRI as a definitive imaging surrogate for surgical exploration to confirm pCR, although several studies are investigating approaches combining imaging and biopsy to explore the potential to avoid surgery.[12-14]

Perhaps more relevant to the personalization of treatment is the ability of imaging to predict treatment outcome when measured early in the course of treatment. Early noninvasive indicators of treatment effectiveness could provide a basis for modifying treatment plans, making de-escalation possible for patients showing excellent response and a recommended change in therapy for those with minimal response. Although MRI has limited accuracy for verifying pCR, it is very effective at determining the extent of disease for large breast tumors and at measuring changes with treatment. Studies examining the early predictive ability of MRI have found greater accuracy compared with other imaging methods in predictive performance across breast cancer subtypes.[15] For early response prediction, functional characteristics can add information to measurements of tumor dimensions alone. A multitude of measurement methods, including radiomics approaches, can be used to quantify tumor properties. Timing of early assessment is an additional variable. Two systematic reviews of the literature that examined the accuracy of MRI for early prediction of subsequent pathologic response to neoadjuvant therapy found that the large heterogeneity of methodologic approaches made comparison of results difficult and precluded definitive conclusions.[16,17] It is likely that machine learning and AI technologies will be an integral part of the development and maturation of imaging markers and their integration into treatment response prediction models.[18]

The marked variability in neoadjuvant chemotherapy response among different molecular subtypes of breast cancer is well established. Biomarker development, including imaging biomarkers, requires optimization by tumor subtype to maximize their usefulness.[19] Subtype-optimized models developed in the I-SPY2 trial have been used to design a de-escalation strategy that combines subtype-specific MRI predictive probabilities with midtreatment percutaneous core biopsy pathology to select candidates who can be safely offered the option to skip the doxorubicin-cyclophosphamide component of their treatment, because the probability of achieving pCR after the initial 12 weeks of taxane-based chemotherapy is very high. The combined rule was found to result in a 91% positive predictive value and 61% sensitivity for pCR and is being evaluated in the I-SPY2 trial.[20]

To fully realize the potential of response-adaptive treatment strategies to truly personalize treatment, information from multiple sources, including clinical risk variables, imaging, genomic profiles, histopathology, and circulating tumor markers, will have to be combined and adjusted for the relative subtype dependencies of these variables. As with each variable in the model, imaging needs to provide measurements that are reliable, timely, cost effective, and independently informative. New standards for quantitative imaging are being developed along with new data-analytics techniques that will enable construction of clinically relevant tools to individualize treatment plans.

UTILIZING MOLECULAR TESTS TO ASSESS RESPONSE TO THERAPY

Breast cancer is a clinically and molecularly heterogeneous disease; prognosis and treatment options vary widely between different subtypes and stages of disease. Hormone receptor and HER2 status are well-known markers for beneficial hormonal and HER2-targeted treatments. Yet, a substantial subset of patients experiences over- or undertreatment using only these markers for treatment selection. To improve outcomes, better patient selection is essential, which motivates the development of improved and new predictive markers to enable personalized treatment. Successful predictive biomarkers reflect a relevant biologic process, are accurate and reproducible, and enable identification of two or more patient subgroups with a differential outcome to a specific treatment.[21] These concepts of analytical validity, clinical validity, and clinical utility, which are applicable to all diagnostic, prognostic, and predictive markers, are summarized in Fig. 1. In this section, we briefly discuss predictive biomarkers in the context of breast cancer management; these illustrate the substantial progress and challenges that characterize molecular biomarker development in general.

HER2-Targeting Treatment

HER2 protein overexpression and gene amplification are predictive markers for HER2-targeting therapies.[22] Combining multiple HER2-targeting drugs has increased response rates, but there remains a subgroup of patients that does not benefit from these drugs despite HER2

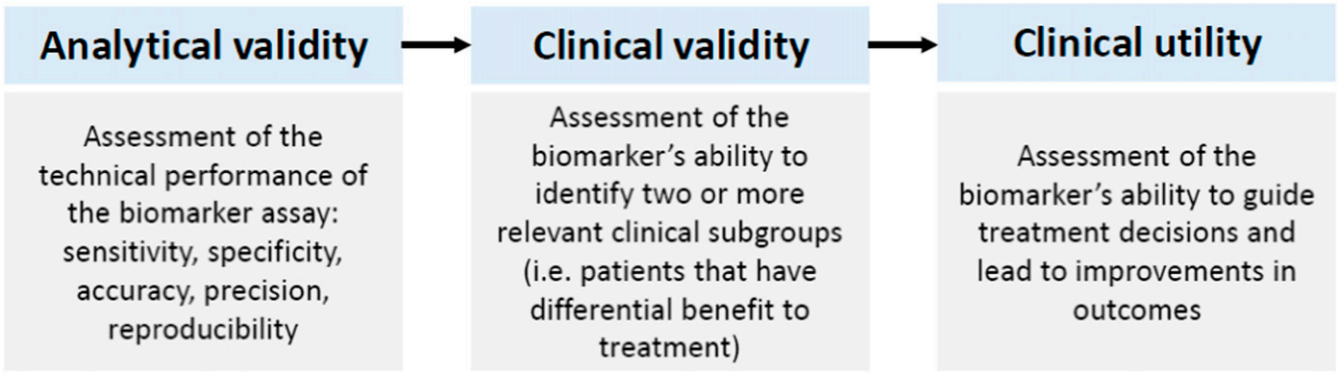

FIGURE 1. Criteria for the Evaluation of Biomarkers

amplification. Identifying these patients may spare them from unsuccessful treatment, and understanding the mechanisms of resistance could lead to more effective new drugs. Novel markers that might refine the predictive values of HER2 protein expression/gene amplification include HER2 messenger RNA expression level, HER2-enriched molecular subtype, and various immune-related markers that are each associated with higher pCR rates and better survival following HER2-targeted therapies.[23,24] A multigene model using messenger RNA expression data from patients with HER2$^+$ inflammatory breast cancer who were randomly selected to receive paclitaxel and trastuzumab, with or without lapatinib, was predictive of pCR, with an impressive area under the receiver operating characteristic curve of 0.76 in the CALGB 40601 trial.[25] However, standardization and independent validation of this and other gene signatures are yet to be accomplished. How to predict the need for, and benefit from, individual components of multidrug HER2-targeted regimens also remains unsolved. In the NeoALTTO trial, a substantial interaction was found between immune and stromal gene expression signatures and pCR with trastuzumab plus lapatinib combined with paclitaxel versus one HER2-targeted drug and paclitaxel; however, this interaction was not seen for survival outcomes.[24] In the NeoSphere study, patients with HER2 membrane protein expression above the median had a marked benefit from the addition of pertuzumab to docetaxel and trastuzumab, whereas there was no benefit for patients with expression that was below the median.[26] These are select examples of intriguing findings that will require independent validation.

Sensitivity to HER2-targeting agents does not completely rely on HER2 overexpression; activating mutations in the *HER2* gene can confer sensitivity to single-agent neratinib (HER2 kinase inhibitor), and neratinib may even have activity in the absence of *HER2* mutation or gene amplification. In the I-SPY2 trial, high *STMN1* gene expression was associated with response to neratinib (concurrent with paclitaxel) in 48 patients with HER2$^-$ tumors.[27] Further validation of this biomarker is necessary before implementation in the clinic.

Immune Checkpoint Inhibition

Immune checkpoint inhibition emerged as a promising new treatment modality, particularly for TNBC (reviewed in Radosa et al[28]). However, overall response rates to single-agent therapy are low, indicating a pressing need for a predictive marker. In the metastatic TNBC setting, PD-L1 protein expression emerged as a U.S. Food and Drug Administration–approved predictive marker to select patients with TNBC for immune checkpoint therapy. In the randomized IMpassion130 trial, only PD-L1 immune cell–positive cancers (with SP142, 22C3, or SP263 assays) showed improved progression-free survival when atezolizumab was added to nab-paclitaxel. In the KEYNOTE-119 trial, objective response rates and progression-free survival with single-agent pembrolizumab increased almost linearly as PD-L1 positivity (22C3 assay) increased. The KEYNOTE-355 trial that compared pembrolizumab plus chemotherapy with chemotherapy plus placebo for metastatic TNBC also demonstrated improvement in progression-free survival in the pembrolizumab arm, but only in PD-L1$^+$ cancers (combined positive score $\geq$ 10 with 22C3 assay). The SAFIR02 trial randomly assigned patients with metastatic breast cancer who had response or stable disease after six to eight cycles of chemotherapy and did not have any actionable mutations to receive maintenance single-agent durvalumab or continuation of chemotherapy. Maintenance durvalumab had inferior progression-free survival in the entire trial population but resulted in improved overall survival in the PD-L1$^+$ (SP142 assay) subset of cancers. In contrast to the metastatic setting, it has not been possible to identify predictive biomarkers that identify stage II to III TNBC that selectively benefits from inclusion of immune checkpoint therapy with neoadjuvant chemotherapy. High tumor-infiltrating lymphocyte count, high expression of PD-L1 protein, and a broad range of immune-related genes all

predict for a higher pCR rate with chemotherapy alone, as well as with chemotherapy plus immune checkpoint therapy. Unlike in metastatic TNBC, PD-L1 protein expression does not define the population that selectively benefits from neoadjuvant immune checkpoint therapy. The biologic reasons behind the distinct predictive functions of PD-L1 in metastatic versus early-stage TNBC are unclear. However, overall, metastatic lesions have a more immune-attenuated tissue microenvironment, even when immune cells are present, compared with primary tumors.[29]

It is important to note that the performance of PD-L1 as a predictive biomarker for response to anti–PD-1/PD-L1 therapy shows low predictive accuracy with an area under the receiver operating characteristic curve of 0.65, even in metastatic disease. This can be explained by the fact that PD-L1 status is difficult to assess because of the very low thresholds applied (1% immune cell positivity with the SP142 assay or a combined positive score > 10 with the 22C3 assay), intratumor heterogeneity in expression, variable assay sensitivity, and large interobserver variability.[30] Tumor mutational burden has emerged as a complementary assay to define patients, regardless of cancer type, who might benefit from pembrolizumab immune checkpoint therapy. The FoundationOne next-generation sequencing assay is approved by the U.S. Food and Drug Administration for this purpose. Immune gene signatures, multiplex immunohistochemistry, and various spatial features of immune cell infiltration are also actively being investigated as potential complementary predictive markers for immunotherapy.[31]

Homologous Recombination Deficiency and Systemic Therapy

Homologous recombination is the primary pathway that is responsible for high-fidelity repair of double-strand DNA breaks. Patients with TNBC and homologous recombination deficiency due to a biallelic BRCA loss of function (usually through a combination of germline and somatic events) respond well to agents that cause double-strand DNA breaks, such as platinum or anthracycline-containing chemotherapies. Consequently, it was hypothesized that patients without BRCA mutations but with genomic "scars" or gene expression features resembling BRCA-mutant tumors may also have a defect in homologous recombination and, therefore, might be sensitive to these agents.[32] Subsequently, studies in metastatic breast cancer showed that patients with TNBC that harbor homologous recombination deficiency (i.e., germline BRCA mutation or homologous recombination deficiency assay positive) have greater benefit from platinum chemotherapy than from a microtubule inhibitor, whereas patients with nonhomologous recombination deficiency have no such differential sensitivity.[33] However, this relationship is not seen in neoadjuvant trials.[34]

Clinical trials also demonstrated substantial single-agent activity of PARP-1 inhibitors in breast cancers that harbor germline BRCA1, BCRA2, or PALB2 mutations or somatic BRCA mutations.[35,36] Several methods exist for detection of homologous recombination deficiency, such as analysis of sporadic or germline homologous recombination mutations, copy number signatures, single-nucleotide polymorphism–based assays, and transcriptional signatures.[32,35] Currently, only germline and somatic BRCA sequencing assays and the Myriad homologous recombination deficiency assay are used in the clinic in the United States to select patients for PARP-1 inhibitor therapy.

Rare Actionable Mutations

Next-generation sequencing assays of a few dozen to a few hundred potential therapeutic target genes are being used increasingly in the clinic to identify patients with metastatic cancer for targeted therapies. In estrogen receptor$^+$ metastatic breast cancer, detection of PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) mutations became important after the SOLAR-1 trial demonstrated a benefit from adding the PIK3CA inhibitor alpelisib to endocrine therapy with fulvestrant, but only in cancers with somatic mutations in the *PIK3CA* gene (median progression-free survival, 11.0 months vs. 5.7 months).[37] Other rare, but potentially actionable, mutations in breast cancer that are supported by clinical trial data include somatic BRCA mutations (for PARP inhibitors), HER2-activating mutations (for neratinib), and *NTRK1* (tropomyosin receptor kinase A) fusion genes (for larotrectinib). Mutations in the *ESR1* (estrogen receptor 1) gene are also commonly encountered in estrogen receptor$^+$ metastatic breast cancer, particularly after prior therapy with aromatase inhibitors. However, the clinical relevance of this finding is limited to recommending fulvestrant over exemestane.

Liquid Biopsy Biomarkers

Circulating biomarkers may better reflect intratumor heterogeneity than do tissue-based biomarkers and are amenable to repeated assessment during treatment. Analyses of mutations in circulating tumor DNA in the MONALEESA-2 trial suggested that patients with an alteration in receptor tyrosine kinase genes in breast cancer have less benefit from letrozole plus ribociclib compared with wild-type cancers.[38] In the PALOMA-3 trial, the ratio of baseline/cycle 5 circulating mutated *PIK3CA* gene copies was predictive of progression-free survival benefit with palbociclib.[39] In a phase I study of elacestrant, patients with estrogen receptor mutations in circulating tumor DNA had a much higher objective response rate than those who did not.[40] In the CirCe T-DM1 trial, patients with HER2$^-$ primary tumors, but HER2-amplified circulating tumor cells, were treated

with trastuzumab emtansine; unfortunately, only one of 11 patients achieved a partial response.[41] These studies highlight that there may be a lot of potential for liquid biopsies in response prediction, but major challenges must be overcome.

Challenges and Future Outlooks

Finding clinically useful predictive biomarkers is highly challenging because of a number of issues, including inter- and intratumor heterogeneity, variability between assays, lack of robustness, and insufficient discriminatory accuracy. Many biomarkers show associations with response to broad classes of therapeutic agents (e.g., chemotherapy, endocrine therapy, HER2-targeted agents, immunotherapy), but it has been very difficult to find drug-specific biomarkers. Furthermore, existing biomarkers are better at identifying who will not have a response to treatment (i.e., high negative predictive values) than predicting actual response to treatment (i.e., modest positive predictive value). With the increasing availability of genomic, transcriptomic, and proteomic data and the integration of these, we hope to come closer to developing clinically useful biomarkers.

OPPORTUNITIES AND CHALLENGES TO IMPLEMENTING ARTIFICIAL INTELLIGENCE IN HEALTH CARE

The past few years have seen an explosion of technologies powered by AI in health care, from triage and early detection to diagnosis to therapy.[42] Artificial intelligence–powered imaging and laboratory devices, medical robots, and mobile services, to mention just a few, almost certainly will improve the reach of high-quality health care across medical offices and countries, accelerate precision medicine, and help patients to proactively manage their health (Fig. 2). This section introduces promising developments in AI, followed by an overview of the challenges that still must be addressed in this field before reaching widespread use.

Decreasing Reader Variability While Improving Workflow Efficiency Through Artificial Intelligence

Medical imaging plays an important role in cancer diagnosis, treatment, and monitoring, but it is highly dependent on the interpretation of readers and their levels of expertise. The requirement of interpreting large amounts of complex data has exceeded the capacity of available specialists and brings new challenges to health care providers, especially in low- and middle-income countries. Recent advances in AI algorithms have resulted in substantial strides in the assessment of radiographic characteristics in medical images,[9] offering considerable promise for improving the efficacy and quality of clinical care. Deep learning is one form of AI that achieves great success in automated learning of imaging features when large, well-annotated databases are available to train the algorithms.[43]

Artificial intelligence–based computer-aided diagnosis and detection systems have shown promising results in the early screening of multiple diseases, including lung cancer, breast cancer, and prostate cancer, when evaluated against human operators.[42-44] This creates an opportunity to reduce the variability in screening quality by introducing AI systems as decision support for radiologists at various levels of training and experience. Artificial intelligence systems are also being developed to assist the image reading workflow. For instance, an AI-based software has been introduced to automatically process multiparametric MRI scans of the prostate, allowing radiologists to identify lesions and facilitate targeted biopsies more easily.[44] Radiation oncology is also greatly benefiting from AI.[45] Delineation of organs at risk is one of the most time-consuming manual tasks performed by radiation oncologists. Artificial intelligence has demonstrated promise in providing comparable autosegmentation of organs at risk to that of human experts. Additionally, dose

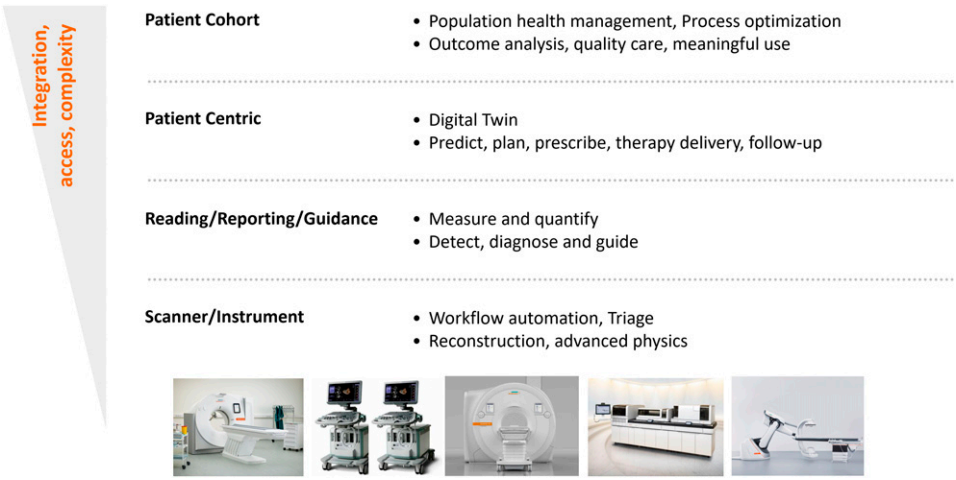

FIGURE 2. Hierarchy of Artificial Intelligence Systems in Health Care

distribution can be potentially optimized by AI approaches via integrating patient anatomy information and treatment machine parameters.

From Outcome Prediction to Patient-Specific Digital Twins

The RECIST criteria are widely used in oncology to assess treatment response. However, these size-based metrics are questioned because they oversimplify the complex imaging features of tumors.[46] Radiomics analysis was introduced to comprehensively characterize and compare tumor geometric and textural appearance in images.[46] High-dimensional hand-crafted features can be automatically computed from images to predict the overall survival of patients with non–small cell lung cancer in response to radiotherapy, chemotherapy, or immunotherapy.[46,47] Recently, a deep-learning method, DeepProfiler, was introduced to automatically learn tumor-imaging characteristics that are associated with prognosis.[47] Using the consolidated information from imaging and clinical variables, DeepProfiler provided an estimation of local failure of stereotactic body radiation therapy and enabled individualized dosing to increase tumor control. Studies have also shown the capability of AI to predict gene mutations from histopathology images.[48] Building on these achievements, researchers are actively investigating methods that combine radiomics and genomics information for individualized outcome prediction.[49]

Digital twins of patients are also being developed, inspired by their industrial counterpart. Fueled by the increased digitalization and broad range of biologic measurements of functions of the human body, digital twins combine AI with computational models of human physiology to generate patient-specific models from medical data (Fig. 3). By integrating multimodal information, digital twins have the potential to quantify a patient's pathophysiology (e.g., tumor growth rate) more precisely.[50,51] The hope is that digital twins could enable in silico simulation of various interventions and assess their potential effects on the patient before any treatment begins. For example, an individualized model of the liver, estimated from images, was used to predict ablation extent and tumor coverage.[52] Digital twins is also being explored to model multiscale multi-omics interactions for drug discovery and treatment efficacy prediction.[53]

Artificial Intelligence–Assisted Automation and Services to Improve Access of Care

One of the biggest challenges in health care, within a country and globally, is to provide equal access to the same high-quality care. Staff shortages, differences in levels of provider training and skill, and dissimilarities in infrastructure and availability of equipment have created variable levels of care, including areas known as "medical deserts." Digitalization and AI could address some of these challenges. Artificial intelligence–assisted image reading aims at improving interrater variability for a more consistent and precise diagnosis throughout clinical sites. Medical systems are being reinvented with more intuitive and simplified user experiences thanks to AI-assisted automation. Minimally invasive procedures are benefiting from automation to simplify their execution, making them safer and more cost effective (e.g., through fully automatic multimodality image fusion).[54] Robotics solutions are assisting surgeons with performing more precise procedures; they may even enable highly specialized surgeons to operate on patients remotely in geographically isolated areas with modest assistance from a local health care provider.[55] Strides are being made in the capability of mobile and wearable devices to provide consumers and their care providers with actionable quantitative health information, from wellness to home monitoring of physical activity and vital signs after procedures or discharge from the hospital.

Challenges Ahead

Despite the tremendous progress of the past few years, many challenges still remain to fully harness the potentials of AI in health care.[50] First, scaling up the development of multimodal AI solutions requires more consolidated access to data that are still stored in a variety of systems that do not necessarily share a common data-exchange interface. To address this challenge, electronic medical records and standards like Fast Healthcare Interoperability Resources are facilitating interconnectivity, whereas clinical-decision support solutions are being deployed to integrate data from multiple sources into a single common system.[56]

Second, data privacy needs to be thoroughly ensured. While regulations are being updated to protect patients and consumers (e.g., Health Insurance Portability and Accountability Act [United States], California Consumer Privacy Act, General Data Protection Regulation [Europe]), privacy-by-design AI technologies are actively being investigated. For instance, federated learning proposes to train AI algorithms locally and only pool the resulting models centrally, alleviating the need to share patient data with researchers. Homomorphic encryption techniques are being investigated to encrypt data such that AI processing can be done on the encrypted file directly, whereas blockchain architectures are being explored to ensure full decentralization.[57]

Third, AI in oncology is challenged by the inherent variability of the disease and therapies. Each cancer is unique, with many therapy options possible, making large-scale data acquisition for AI training challenging. Artificial intelligence is already contributing to more precise screening and diagnosis of the most common cancers (e.g., breast and lung cancers). Yet, progress in AI theory and engineering is needed to enable precision medicine at scale, where

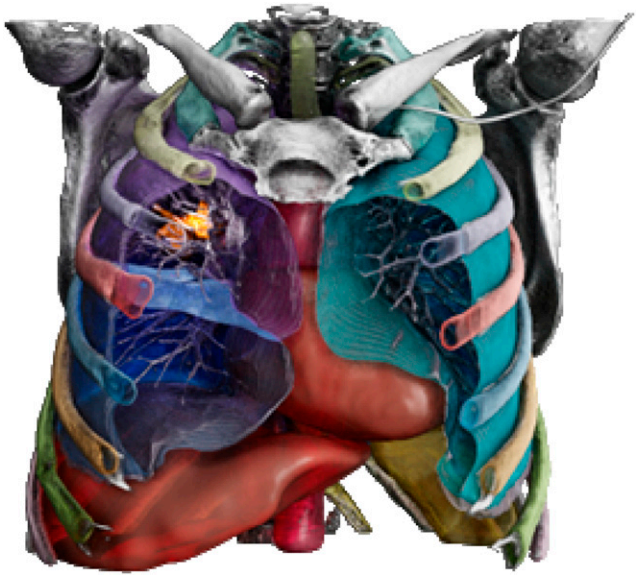

FIGURE 3. Rendering of CT Scans With Artificial Intelligence–Based Automatic Organ Segmentation (in colors) and Lesion Detection (in yellow)
Data courtesy of University Hospital Erlangen, Erlangen, Germany.

therapy can be tailored to the individual. To that end, researchers are investigating methods based on causality, reasoning, and self-supervision (e.g., to be able to train robust and performant AI systems on small data sets).[58]

Lastly, AI systems are required to provide insights and confidence estimates about their decision. On one hand, uncertainty-quantification techniques are being researched by the community. On the other hand, collaborative systems of AI modules are being implemented instead of end-to-end neural networks, to increase transparency and controllability. Similarly, strategies to minimize biases in AI, a very important issue, are currently being defined, such as guidelines for the definition of diverse training cohorts.[59] Finally, educational programs in AI for medicine will be crucial to increase physicians' literacy in AI, teaching them about AI's ever-evolving capabilities and potential limitations.[60]

In conclusion, AI and digitalization are poised to transform health care as we know it. Although challenges still lie ahead, the community is working tirelessly to find solutions for safe, privacy-centric, and trustable AI solutions that have the potential to reduce variability in care throughout regions, enable more precise diagnosis and therapy, and increase the reach of high-quality care worldwide.

ADAPTING INDIVIDUALIZED TREATMENT PLANS TO CARE FOR EACH PATIENT

Individualized treatment plans have come a long way since the Ebers Papyrus. Personalized recommendations are incorporated into the entire spectrum of cancer management (Fig. 4). For example, multivariate risk-prediction models (e.g., The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, BRCAPRO breast cancer risk assessment tool, International Breast Cancer Risk Assessment Study) that incorporate various combinations of personal information, including age, ethnicity, age at menarche, parity, age at first birth, menopausal status, body mass index, history of benign proliferative breast lesions, mammographic density, and detailed family history, can provide individualized percentage risk estimates of developing breast cancer in the next 5 to 10 years.[61] This information can be used to guide genetic testing and breast cancer–screening decisions. Breast cancer mammographic screening also evolved toward increasingly individualized strategies: women with dense breasts now routinely undergo supplementary screening with annual ultrasonograms or MRI, and individuals with very high risk have more frequent screening than do women with average risk. The reporting of breast imaging results has been standardized (Breast Imaging Reporting and Data System, BI-RADS; www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Bi-Rads), and the terminology guides subsequent recommendations for follow-up procedures. If the diagnosis of invasive breast carcinoma is established by a breast biopsy, patients are triaged into one of the three major clinical subtypes of breast cancer: hormone receptor$^+$, HER2$^+$, or TNBC with distinct therapeutic implications. The percentage probabilities of recurrence and overall survival can be estimated for an individual by combining information from age at diagnosis, menopausal status, hormone receptor and HER2 status, tumor proliferative activity (i.e., Ki-67 status), tumor size, number of positive nodes, histologic grade, and detection method (i.e., mammographic screening vs. self-palpated) using a validated multivariate prognostic model (breast.predict.nhs.uk/tool).

After understanding the baseline risk of recurrence, an individualized estimate of percentage benefit from various treatment modalities can be calculated and discussed with the patient. In hormone receptor$^+$ disease, additional gene expression–based molecular tests can further refine the prognostic risk and identify patients who would have excellent long-term disease-free survival with endocrine therapy alone.[62] These molecular diagnostic tests (e.g., Oncotype DX Recurrence Score, MammaPrint, Prosigna, EndoPredict, Breast Cancer Index) have enabled hundreds of thousands of women to avoid adjuvant chemotherapy without jeopardizing their survival. Randomized clinical trials continue to refine our understanding of how to use these molecular assays. Most recently, the first interim results of the RxPONDER trial demonstrated that, even among patients with one to three positive lymph nodes,

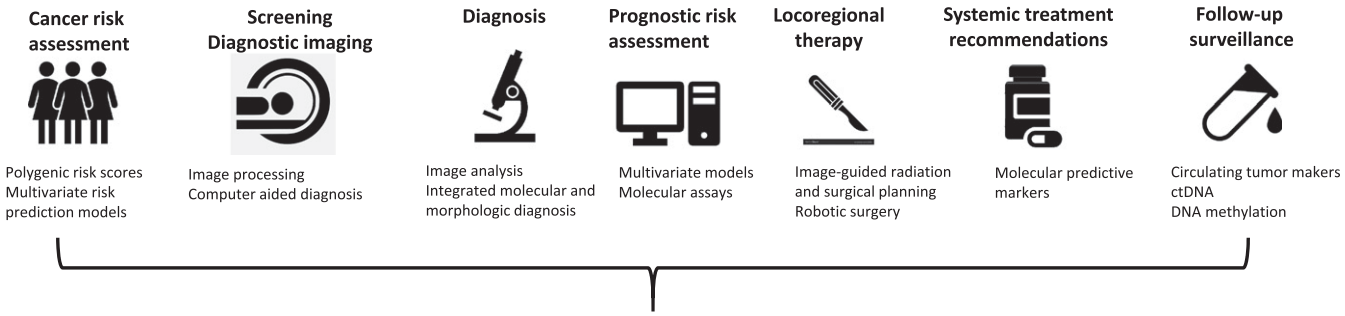

FIGURE 4. Personalization of Treatment Plans Through Technology Across the Spectrum of Disease Management
Abbreviation: ctDNA, circulating tumor DNA.

a subset of postmenopausal women who have a recurrence score less than 26 do not derive benefit from adjuvant chemotherapy and can be safely treated with adjuvant endocrine therapy alone.[63] By using molecular diagnostic tests, we can also make individualized predictions about the probability of benefit from extending adjuvant endocrine therapy beyond 5 years.[64] The increasing use of preoperative chemotherapy in HER2$^+$ and TNBCs allows further customization of postoperative adjuvant chemotherapy based on the extent of residual cancer found at the time of surgery.[65] Patients with substantial residual cancer burden after neoadjuvant chemotherapy can receive further treatment that improves their recurrence-free survival.

Individualized treatment plans do not end at selecting systemic adjuvant therapies for early-stage breast cancer; the previously rather uniform radiation therapy and surgery treatment strategies are also increasingly flexible and tailored for patient age and risk of locoregional recurrence. Clinical nomograms can be used to estimate the probability of finding positive axillary lymph nodes at diagnosis or after an initial positive sentinel node biopsy, and this information can guide decisions about subsequent axillary lymph node dissection or even skipping lymph node sampling altogether.[66] Accelerated postlumpectomy radiation treatment plans also exist that can shorten the traditional 5 weeks of radiation therapy for selected patients.[67]

A truly individualized treatment plan cannot be formulated without input from the patient. We all have different risk-benefit tolerance; perhaps one of the most important contributions of the existing prognostic and predictive tools is that they empower patients to make an informed decision about the various alternative treatment strategies that are available to diagnose and treat early-stage breast cancer.

What Is Next?

The past 20 years have seen remarkable progress in diagnostic technologies, coupled with the introduction of several dozen new drugs to treat cancer that have translated into improved survival for many cancer types. Survival of early-stage breast cancer has improved by 25% to 40% during this time period; unfortunately, it continues to show large variations between regions of the world, as well as by race and socioeconomic status within the United States.[68] Progress in individualizing treatment plans will accelerate further in the coming years. Adding polygenic risk scores derived from germline sequencing to clinical risk-prediction models will likely improve predictions of cancer risk, which will improve individualization of cancer-screening strategies. An example is the ongoing WISDOM study (NCT02620852), which is an adaptive randomized clinical trial comparing a comprehensive risk-based personalized screening with traditional annual breast cancer screening. Artificial intelligence–driven improvements in image analysis are expected to improve the precision of breast imaging to distinguish benign lesions from malignant lesions.[69] Novel molecular diagnostic tests are emerging in TNBC and HER2$^+$ breast cancers to refine prognosis beyond the clinical stage, the same way that gene expression profiling assays did in hormone receptor$^+$ disease. The extent of lymphocytic infiltration is showing clinically meaningful prognostic risk stratification in TNBC,[70] and a combination of HER2 expression, PIK3CA mutation, and molecular subtype may identify HER2$^+$ breast cancers with excellent prognosis.[71] Clinical trials are underway in HER2$^+$ breast cancer (CompassHER2-pCR, NCT04266249) and are planned in TNBC, to explore the potential of using pathologic response to neoadjuvant chemotherapy to optimize chemotherapy intensity. Patients with pCR even after a short minimally toxic therapy may not need more aggressive systemic therapy, whereas those with residual disease could receive more treatment after surgery to improve their survival. Molecular target profiling, which is already used in metastatic breast cancer to identify potentially targetable molecular abnormalities, will likely be explored in the adjuvant/neoadjuvant treatment setting to accelerate the introduction of effective targeted therapies in the early-stage curative setting.

Monitoring of circulating tumor DNA is perhaps one of the most exciting new technologies that could bring about

a paradigm shift in monitoring of patients with early-stage disease who have completed local and systemic therapies. Multiple small studies demonstrated that the presence of tumor-derived DNA in the blood during follow-up of asymptomatic clinically cancer-free patients heralds metastatic recurrence in 70% to 80% of patients within 6 to 10 months. Detection of molecular relapse before clinically apparent metastatic recurrence raises the tantalizing possibility that early intervention with a "second-line" adjuvant therapy might avert the impending clinical recurrence. Molecular monitoring for residual disease in hematologic malignancies, or for prostate-specific antigen failure in prostate cancer, followed by early systemic therapy improved recurrence-free survival in leukemias and in prostate cancer. A clinical trial is now underway to explore this strategy in estrogen receptor$^+$ early-stage breast cancer (DARE, NCT04567420).

Most of the examples in this article are taken from the breast cancer literature because there are extensive data to support screening of asymptomatic individuals, several clinically validated prognostic risk-prediction models exist, and molecular diagnostics tests are used to select patients for adjuvant chemotherapy. These advances clearly illustrate the evolution of individualizing treatment recommendations over the past 20 years, enabling personalized screening and de-escalation of care for many patients, while selecting patients at risk for recurrence who would benefit from more aggressive therapy. These same advances are also happening in most other cancer types and no doubt will accelerate in the coming years.

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