AJR FOCUS ON:

Biomarkers and Imaging of Breast Cancer

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OBJECTIVE. The goals of this review are to provide background information on the definitions and applications of the general term "biomarker" and to highlight the specific roles of breast imaging biomarkers in research and clinical breast cancer care. A search was conducted of the main electronic biomedical databases (PubMed, Cochrane, Embase, MEDLINE [Ovid], Scopus, and Web of Science). The search was focused on review literature in general radiology and biomedical sciences and on reviews and primary research articles on biomarkers in breast imaging over the 15 years ending in June 2017. The keywords included "biomarker," "trial endpoints," "breast imaging," "breast cancer," "radiomics," and "precision medicine" in the titles and abstracts of the papers.

CONCLUSION. Clinical breast care and breast cancer–related research rely on imaging biomarkers for decision support. In the era of precision medicine and big data, the practice of radiology is likely to change. A closer integration of breast imaging with related biomedical fields and the creation of large integrated and shareable databases of clinical, molecular, and imaging biomarkers should allow the field to continue guiding breast cancer care and research.

The launch of the Precision Medicine Initiative by President Obama in 2015 provided official recognition of the already strong scientific paradigm of finding patient-centric preventive, screening, diagnostic, and treatment options, depending on a person's individual biologic and environmental characteristics. The perfecting of "omics" molecular technologies in basic biomedical research, the increase in computer analytic and computational capabilities, and the development of advanced imaging technologies all came together to give rise to a new field of radiomics. In radiomics, imaging goes far beyond its conventional descriptive function and can be integrated with multiple individual patient parameters ranging from genomic patterns to environmental exposures. This requires a multidisciplinary approach and has the potential to position radiology at the crossroads of precision medicine in many biomedical fields [1–6].

In the collaborative setting of precision medicine, the term "biomarker" becomes a central concept for developing study methodology, formulating research hypotheses, and selectively applying scientific discoveries in the clinic. Only a subset of clinical, molecular, or imaging parameters have the capacity to serve as biomarkers and be relied on to correlate with underlying disease processes and other biomarkers. Therefore, it is important to understand the meaning of the term in biomedical research in general and its applications to radiology and breast imaging in particular.

Terminology

The term biomarker is ubiquitous in the modern scientific literature. A search for the keyword "biomarker" in the titles or abstracts of publications returned 213,550 results in Web of Science and 167,784 results in PubMed. A biomarker in the broad sense refers to an objective medical sign: a measurable and quantifiable indicator of a physiologic or pathologic state of a living organism. It is contrasted to a symptom, which is a subjective perception of health or illness [7]. The World Health Organization has defined a biomarker as "any substance, structure or process that can be measured in the body or its products and influence or predict the incidence or outcome of disease" [8].

This broad definition of the term may be applied to a great variety of biologic characteristics and molecules derived from many clinical, laboratory, or imaging tests, de-

Keywords: biomarkers, breast cancer, precision medicine, radiomics, trial endpoints

doi.org/10.2214/AJR.17.18708

Received July 1, 2017; accepted after revision September 9, 2017.

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AJR 2018; 210:271–278

0361–803X/18/2102–271

pending on the objectives and the biomedical field [9]. The exponential growth of scientific knowledge over the past several decades led to the discovery of a plethora of biomarkers and revolutionized clinical medicine and drug development. However, different biomedical disciplines developing in parallel accumulated their own definitions and applications of the term, which led to confusion and compromised interdisciplinary communication [10, 11].

The need to unify and precisely define the term biomarker became compelling after passage of the Food and Drug Administration Modernization Act of 1997, which allowed the use of biomarkers as surrogate endpoints in drug and medical device evaluation [7, 12, 13]. Over the past 2 decades there has been an ongoing effort to standardize the terminology and to clarify definitions in biomarker-related research, in particular in relation to clinical trials. For years only biologic molecules were considered biomarkers, thus restricting the role of imaging to measuring or characterizing a biomarker, rather than being a source of biomarkers itself [1]. This is no longer the case, as outlined in the latest glossary released in 2016 by the U.S. Food and Drug Administration (FDA)–National Institutes of Health (NIH) Biomarker Working Group in its Biomarkers, Endpoints, and other Tools (BEST) Resource. In this document [9] a biomarker is "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers."

Why Use Biomarkers?

The ultimate goal of medicine is "the relief of pain and suffering, the promotion of health and the prevention of disease, the forestalling of death and the promoting of a peaceful death, and the cure of disease when possible and the care of those who cannot be cured" [14]. Every new drug, medical device, test, or intervention has to prove that it is in line with this main goal to be approved for clinical use. That means that ideally the primary outcome measures of any biomedical research, cancer-related research in particular, should be clinically meaningful, patient-centric, and reflective of how patients feel, function, and survive [15].

Overall survival is the reference standard of outcome measures; however, using it as the primary endpoint in clinical trials would make the trials extremely complex, protracted, costly, and in some instances, unethical [7, 16, 17]. To obtain results faster with more flexibility and smaller sample sizes, alternative endpoints, such as progression-free survival, disease-free survival, or objective response, were developed as surrogates for the primary clinical endpoints [9, 16, 17] (Table 1).

There are different levels of surrogacy of outcome measures, depending on the strength of clinical evidence. For the purpose of drug or diagnostic test development, the FDA requires evidence that a particular surrogate endpoint is reasonably likely to be predictive of clinical benefit on the basis of epidemiologic, therapeutic, pathophysiologic, or other evidence [7, 9]. Biomarkers are widely used in this capacity as surrogate outcome measures in biomedical research. They are especially useful for efficacy and safety evaluation, providing early results for drug development and enabling timely termination of a study if the biomarkers indicate that the intervention in question is potentially harmful [7, 17].

Diagnostic Accuracy

The endpoint definitions and the four phases of clinical trials were developed for studying the outcomes of therapeutic interventions. The situation is different for diagnostic tests, because they are designed to provide information to guide subsequent interventions rather than to directly affect the outcomes themselves [18]. For the purpose of evaluating new imaging technologies, diagnostic accuracy is considered an acceptable surrogate endpoint in lieu of a long-term outcome such as disease-specific mortality. This is the case, first, because the effects of a diagnostic test would be mediated by other confounding factors, such as the biologic mechanisms of the disease, the efficacy of treatment, and patient compliance. Second, with the current rate of technologic progress, the diagnostic method in question is likely to be obsolete by the time a long-term study would be completed [18, 19].

Characteristics of Useful Biomarkers

Biomarkers are by definition objective and quantifiable medical signs. To serve as surrogate endpoints for research and as actionable clinical parameters they must be measurable with a high degree of accuracy and reproducibility. They also must be relevant and valid. A relevant biomarker should be capable of reliably characterizing a clinically meaningful endpoint in question. Validity of a biomarker means that there is substantial evidence that it is a suitable substitute for a clinical outcome and that a change observed in a biomarker would reflect a change in the clinical endpoint it is meant to represent [7, 15, 17].

Medical imaging is a conditional exception to this rule, allowing the use of qualitative markers in addition to quantitative ones, provided that their use is clinically validated [1]. For example, BI-RADS descriptors are widely used examples of validated qualitative biomarkers.

An ideal biomarker would be disease specific, and its relation to the clinical problem in question would be understood on the basic biologic level. Unfortunately, no existing biomarker meets these criteria [7, 15, 17, 20, 21], and most biomarkers can be found in multiple physiologic and pathologic conditions [20]. Some biomarkers may not even be a part of the causative pathophysiologic mechanism but rather change in parallel with the clinical outcome in question [17]. These are among the reasons that most individual biomarkers do not have sufficient sensitivity and specificity to be clinically useful in isolation. However, when combined in panels, such as the TNM staging system or Oncotype DX score (Genomic Health), they can have much greater discriminatory power [21, 22].

Types of Biomarkers

Biomarker-related research has become extremely prolific and fast paced. New biomarkers and biomarker panels are continually discovered and offered for an ever-increasing array of clinical and translational applications. The FDA and NIH have undertaken an ongoing effort to unify and harmonize biomarker-related terminology and to keep abreast of the current state of the field. The most current BEST [9] divides biomarkers into seven subcategories depending on their role in research and clinical practice (Table 2).

Medical imaging can be a source of diagnostic, predictive, prognostic, and monitoring biomarkers [6], and has already been used extensively in these applications as a clinical tool.

Some biomarkers can belong to multiple categories, depending on the objectives of a particular study or the clinical question [9]. For example, estrogen receptor, progesterone receptor, and HER2 (also known as ERBB2) may serve as diagnostic, predictive, or prognostic biomarkers. Maximum standardized uptake value (SUV_{max}) at ^{18}F-FDG

TABLE 1: Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall survival	Clinical benefit for regular approval	Randomized studies essential Blinding not essential	Universally accepted direct measure of benefit Easily measured Precisely measured	May involve larger studies May be affected by crossover therapy and sequential therapy Includes noncancer deaths
Symptom endpoints (patient-reported outcomes)	Clinical benefit for regular approval	Randomized blinded studies	Patient perspective of direct clinical benefit	Blinding is often difficult Data are frequently missing or incomplete Clinical significance of small changes is unknown Multiple analyses Lack of validated instruments
Disease-free survival	Surrogate for accelerated approval or regular approval[a]	Randomized studies essential Blinding preferred Blinded review recommended	Smaller sample size and shorter follow-up necessary compared with survival studies	Not statistically validated as surrogate for survival in all settings Not precisely measured; subject to assessment bias, particularly in open-label studies Definitions vary among studies
Objective response rate	Surrogate for accelerated approval or regular approval[a]	Single-arm or randomized studies can be used Blinding preferred in comparative studies Blinded review recommended	Can be assessed in single-arm studies Assessed earlier and in smaller studies compared with survival studies Effect attributable to drug, not natural history	Not a direct measure of benefit Not a comprehensive measure of drug activity Not a comprehensive measure of drug activity Only a subset of patients who benefit
Complete response	Surrogate for accelerated approval or regular approval[a]	Single-arm or randomized studies can be used Blinding preferred in comparative studies Blinded review recommended	Can be assessed in single-arm studies Durable complete responses can represent clinical benefit Assessed earlier and in smaller studies compared with survival studies	Not a direct measure of benefit in all cases Not a comprehensive measure of drug activity Small subset of patients with benefit
Progression-free survival (includes all deaths) or time to progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval[a]	Randomized studies essential Blinding preferred Blinded review recommended	Smaller sample size and shorter follow-up necessary compared with survival studies Measurement of stable disease included Not affected by crossover or subsequence therapies Generally based on objective and quantitative assessment	Not statistically validated as surrogate for survival in all settings Not precisely measured; subject to assessment bias, particularly in open-label studies Definitions vary among studies Frequent radiologic or other assessments Involves balanced timing of assessments among treatment arms

Note—Reprinted from [22] and in the public domain.

[a]Adequacy as a surrogate endpoint is highly dependent on other factors, such as effect size, effect duration, and benefits of other available therapy.

TABLE 2: Types of Biomarkers by Use

Type of Biomarker	Function	Example
Diagnostic	Used for the detection or confirmation of a disease or condition and for identification of a specific disease subtype	BI-RADS descriptors, ER, PR, and HER2 (also known as ERBB2) status
Monitoring	Serially measured to assess the status of a disease or condition or to find evidence of exposure to, or effects of, a medical product or environmental agent; focus is on changes in a patient's condition	Tumor size and volume by imaging; prostate-specific antigen for monitoring of prostate cancer
Pharmacodynamic, response	Used for showing that a medical product, intervention, or environmental exposure results in a biologic response; may not be predictive of whether the intervention will have an effect on the future clinical outcome but rather show that the intervention had an effect	Blood pressure to assess response to antihypertensive drugs; standardized uptake value at FDG PET to monitor endocrine therapy in breast cancer [25]
Predictive	Used to identify individuals who are more likely to experience a favorable or unfavorable response to an intervention, medical product, or environmental exposure compared with individuals without the biomarker	Possibility that mutations in *BRCA* genes are predictive of response to PARP inhibitors in patients with advanced breast and ovarian cancer [83, 84]; likelihood that ER- and PR-positive breast cancers respond to endocrine therapy [85]; possibility that dense breast tissue is a biomarker predictive of the decreased sensitivity of mammography for detecting noncalcified breast cancer [51]
Prognostic	Reflect the likelihood of a clinical event, disease progression, or recurrence irrespective of an intervention	TNM stage, tumor grade, tumor receptor status
Safety	Indicate the presence of a harmful effect of an intervention if measured before and after the exposure	Serum creatinine and EGFR as safety biomarkers to monitor nephrotoxicity of IV contrast agents
Susceptibility, risk	Used to predict the potential of development of a disease or medical condition in individuals who do not currently have a clinically apparent disease or condition	*BRCA* gene mutations as indicators of increased lifetime risk of breast and ovarian cancers [86]; mammographically dense breast tissue as an independent risk factor for development of breast cancer [50, 87]

Note—Data from [9]. ER = estrogen receptor, PR = progesterone receptor, PARP = poly(adenosine diphosphate–ribose) polymerase, EGFR = estimated glomerular filtration rate.

PET can be used for prognosis [23, 24], monitoring, or tumor response [25, 26]. Tumor volume may serve as a prognostic or monitoring biomarker [27].

Biomarkers can be derived from multiple clinical and imaging sources with various techniques. They can also be roughly subdivided by their nature or origin [28] (Table 3).

Breast Imaging Biomarkers

Radiologic findings were only recently officially recognized as biomarkers [1, 9]; however, imaging in general and breast imaging in particular have been widely applied for decades in correlative biomarker-driven research, and the results have been promising [29–31].

Quantitative Imaging Biomarkers

One of the established functions of imaging is to provide in vivo 2D and 3D measurements of anatomic structures. Measurements are true quantitative biomarkers and are indispensable in research and clinical decision making [1]. They are used in diagnosis, staging, evaluating prognosis, and monitoring treatment of breast cancer. The monitoring and pharmacodynamic capabilities of imaging measurements are widely used in the Response Evaluation Criteria in Solid Tumors (RECIST) for cancer treatment [32].

RECIST has been particularly useful for monitoring the effects of cytotoxic chemotherapy, which is expected to cause cell death and decrease tumor size [33]. Progressive understanding of the pathophysiologic and molecular biologic characteristics of breast cancer led to the discovery of new cellular signaling pathways, such as estrogen receptor, HER2 (ERBB2), phosphatidylinositol 3–kinase, insulinlike growth factor 1 receptor, cyclin-dependent kinases (CDKs), and others. These biomarkers are either already used for therapy or being actively studied as potential therapeutic targets [34, 35].

Unlike conventional cytotoxic chemotherapeutic agents, many of the new agents targeting molecular signaling pathways are cytostatic and inhibit tumor growth rather than cause its regression [33, 36, 37]. For example, the new CDK4/6 inhibitors palbociclib and ribociclib are cytostatic agents that have been approved for treatment of naive hormone receptor–positive advanced breast cancer in combination with hormonal therapy [38]. The cytostatic effect can be achieved by various mechanisms, including altering neoplastic angiogenesis and vascular permeability [33, 36, 37]. In this context, detecting changes in the vascular microenvironment of the tumor becomes more important than documenting a change in tumor size. This can be achieved with quantitative biomarkers derived from functional imaging. Dynamic contrast-enhanced MRI (DCE-MRI) can be used for quantitative assessment of the vascular microenvironment and tissue permeability by measurement of such quantities as the volume transfer constant K^{trans}, the initial area under the gadolinium concentration-time curve [33, 37], and DWI and apparent diffusion coefficient (ADC) parameters [33, 39].

Molecular imaging, such as PET, positron emission mammography, and SPECT, can provide quantitative biomarkers that reflect tumor receptor status, the degree of tumor heterogeneity, and treatment response [3]. It is established that SUV_{max} and metabolic tumor volume are more reproducible quantitative parameters than are tumor size measurements [40]. Molecular imaging enables in vivo assessment and monitoring of tumor receptor status. Estrogen receptor–negative status can be evaluated with 16α-^{18}F-fluoro-17β-estradiol (^{18}F-FES). Zirconium-89-labeled

TABLE 3: Sources of Biomarkers Used in Breast Cancer Care

Category	Source	Biomarker Type	Examples
Clinical	Patient history	Environmental exposures Lifestyle factors Age Family history	Mantle chest radiation High alcohol consumption Older age First-degree relative with breast cancer
Laboratory	Whole blood Serum Plasma Tissue	Genomic Transcriptomic Proteomic Metabolomic	*BRCA* mutations Long noncoding RNAs PI3K/Akt/mTOR pathway Threonine, glutamine
Imaging	Mammography Ultrasound Dynamic contrast-enhanced MRI MIBI scintigraphy FDG PEM	For-presentation images CAD Radiomics	BI-RADS descriptors Kinetic enhancement curves Energy, homogeneity, entropy, skewness, and kurtosis

Note—PI3K = phosphatidylinositol 3–kinase, RNA = ribonucleic acid, Akt = protein kinase B, mTOR = mammalian target of rapamycin, MIBI = methoxyisobutylisonitrile, PEM = positron emission mammography, CAD = computer-aided detection.

trastuzumab is an example of a radiolabeled HER2 antibody currently under investigation for HER2 targeted therapeutic response [3].

Qualitative Imaging Biomarkers

Owing to the American College of Radiology BI-RADS initiative, breast imaging benefits from the first and the best validated system of imaging descriptors in radiology [41, 42]. Multiple morphologic, distribution, and enhancement descriptors from the BI-RADS lexicon have been to varying degrees proved to reflect the probability that an imaging finding indicates breast cancer [41, 43–46]. These descriptors can be considered qualitative biomarkers because they are representative of an underlying biologic process [1, 9]. For example, of all mammographic calcifications, the ones with fine linear branching morphologic features have the greatest chance of being malignant [47]. The same biomarker can serve different purposes in different clinical scenarios: as a diagnostic biomarker, a spiculated margin of a mass is a strong predictor of malignancy on mammography, ultrasound, and MRI [44, 45, 48]. At the same time, as a prognostic biomarker, it may be indicative of a favorable prognosis in patients with breast cancer [49].

Breast imaging also provides ordinal biomarkers, which are categories with intrinsic rankings that can be arranged in a meaningful order. Mammographic breast density and the perceived degree of background parenchymal enhancement at breast MRI are examples of useful ordinal biomarkers [1]. Mammographic breast density is an established risk biomarker because of its association with the patient's lifetime risk of breast cancer [50]. It may also be considered a predictive biomarker of the utility of mammography for breast cancer detection [9, 51].

The types of breast imaging biomarkers by characteristics are summarized in Table 4.

Better Together: Biomarker Panels

Like most known biomarkers, individual imaging features do not carry sufficient discriminatory power to be used in isolation. Yet when combined with other imaging parameters into panels or scoring systems, they can perform significantly better [20, 21]. This is true in the case of mammographic calcifications: using morphologic and distribution descriptors together improves specificity [47, 52]. Another example is the increased predictive power of a combination of DCE-MRI and DWI parameters, as opposed to a single parameter, for predicting pathologic complete response after the first cycle of neoadjuvant chemotherapy for breast cancer [53].

Imaging biomarkers can be combined in panels with biomarkers of different origins, ranging from clinical information to omics technologies. For example, imaging findings and anatomic measurements combined with clinical data are used as composite biomarker systems, such as TNM [1] and the Neoadjuvant Response Index for breast cancer [54].

Much scientific effort has been directed at investigating correlations between imaging biomarkers and the underlying tumor biology. The most discriminatory imaging biomarkers of triple-negative breast cancer (TNBC) at DCE-MRI are large tumor size, solitary mass, smooth margin, and progressive enhancement kinetics [29, 30]. Rim enhancement on DCE-MR images is proposed as a helpful diagnostic marker in breast cancer, being associated with a higher tumor grade, estrogen receptor–negative status, and triple-negative biologic characteristics [29, 31]. Rim enhancement may also serve as a prognostic biomarker in TNBC, because it is associated with a higher rate of tumor recurrence and worse patient survival [31]. ADC has been found to be helpful for pre-

TABLE 4: Types of Breast Imaging Biomarkers

Type of Biomarker	Characteristics	Examples
Quantitative	Measurable, quantifiable, and reproducible parameters	Linear and volume measurements; SUV_{max}, metabolic tumor volume, K^{trans}, DWI, ADC, gadolinium AUC
Qualitative	Perceived descriptive characteristics representative of the underlying pathologic condition	BI-RADS descriptors (e.g., tumor shape and margins, morphology, and distribution of calcifications)
Ordinal	Categories with intrinsic rankings that can be arranged in a meaningful order	Mammographic breast density, perceived degree of background parenchymal enhancement

Note—SUV_{max} = maximum standardized uptake value, K^{trans} = volume transfer constant, ADC = apparent diffusion coefficient.

dicting tumor grade in estrogen receptor–positive breast cancer [55] and for discriminating ductal carcinoma in situ and invasive breast cancer [56].

Radiomics

The traditional qualitative imaging biomarkers, although useful, heavily rely on the radiologist's perception, which makes them subjective, descriptive, and prone to intraobserver and interobserver variability [57–60]. To qualify as a true biomarker, to serve as a meaningful substitute for a biologic process, and to be able to be statistically correlated with other biomarkers, any imaging biomarker has to be objective, reproducible, and quantifiable [60–62].

One of the first attempts to use computers to objectivize radiologic findings was the application of computer-aided detection (CAD) technologies to medical imaging. CAD is pattern recognition software developed for a particular diagnostic task [63]. Morphology-based based CAD has been most widely used in mammography. Contrast enhancement–based CAD has also been successfully used in DCE-MRI [64].

The recent application of high-throughput computing together with automated pattern recognition software to medical imaging has resulted in rapid advancement of imaging analytics. It has given rise to the new field of radiomics, "the conversion of images into mineable data and the subsequent analysis of these data for decision support" according to Gillies et al. [6]. Comprehensive reviews of radiomics can be found in the literature [6, 65–67]. Radiomics allows automated quantification of multiple levels of image-derived data. Some quantifiable features, such as tumor shape and margin, can be visually correlated with the image by a radiologist, but most parameters are entirely computational and cannot be perceived by humans. These calculated parameters have the potential to be ideal true biomarkers, because they are objective, quantifiable, and reproducible in standardized settings.

Radiomic imaging features can be correlated with biomarkers from other sources, notably from the information provided by omics technologies. For instance, patients' genomic profiles can be combined with radiomic features in the field of radiogenomics, proteomic data in radioproteomics, metabolites in radiometabolomics, and so forth [68].

The radiomic approach to breast imaging has yielded promising results for the identification of quantitative imaging biomarkers predictive of molecular subtypes of breast cancer [69–71], risk of recurrence [72–74], metastatic potential [75], and pathologic complete response [76], among others. Quantitative analysis of DCE-MR images may prove helpful in discriminating positive and negative lymph node status in breast cancer [77].

Discussion

Breast imaging technologies have been playing an integral role in clinical breast care and breast cancer–related research for decades. They are indispensable for breast cancer screening, diagnosis, staging, and monitoring, thus providing a framework for informed medical decision making. In the era of personalized medicine, with its fast-paced development of omics technologies, machine learning, and big data, the role of imaging is being redefined to embrace new opportunities, address challenges, and continue guiding clinical medicine and biomedical research in the 21st century [6, 78, 79].

All branches of biomedical science have accumulated a tremendous amount of specialized knowledge about different aspects of health and disease, and all of them are redefining their role in the scientific process as a whole [80]. Because biologic systems are inherently complex, it has been increasingly recognized that solutions to the most pressing biomedical problems lie in collaboration among multiple disciplines. The field of systems biology was introduced to bring together interdisciplinary teams to develop multiscale models of biologic processes and to evaluate a system as a whole rather than as the sum of its parts [68, 80–82]. Radiomics is radiology's contribution to the field of systems biology [68] and its means of integration into the multidisciplinary holistic approach to pathologic processes.

The new field of radiomics has its challenges, which are as complex as the field itself. The lack of standardized image acquisition and reconstruction techniques among imaging units and facilities limits reproducibility of the findings. The ever-expanding number of potential imaging and molecular biomarkers that seemingly correlate with the pathologic processes in question has the potential to produce lists of random statistical parameters, disperse scientific efforts, and drive up the cost of health care. A deep understanding of the pathophysiologic basis of the correlation between a biomarker and the underlying condition gained through basic research could help focus the biomarker discovery and validation process and have a more meaningful impact on individual patient care.

The limited specificity of any single biomarker and the insufficient understanding of the underlying molecular mechanisms can be partially overcome by the creation of extremely large imaging, clinical, and omics datasets for biomarker discovery, which can produce statistical correlations of multiple parameters. These datasets will be difficult to compile within a single institution and will require multisite, national, and international research databases. This then creates a need for integrated and shareable databases of patient data, which is an extremely difficult task. Nevertheless, given the tremendous potential of the field and the concerted efforts of multiple organizations directed at overcoming these obstacles, the field of radiomics will continue to expand and is likely to find applications in all aspects of medical imaging in the near future [6, 65, 79].

Conclusion

Breast imaging provides a wide range of biomarkers useful for clinical decision support in breast cancer care and for biomedical research. As a result of the introduction of radiomics, the number of useful imaging biomarkers in breast imaging is bound to dramatically increase in the near future, expanding the role of breast imaging in these areas. Breast imaging radiologists should be familiar with the changing environment in medicine and with the new questions that are likely to be posed to us by our clinical and research colleagues. This will enable breast imaging to remain "the eyes" of breast cancer care and continue to guide the clinical breast care decision-making process.

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