The Future of Imaging Biomarkers in Radiologic Practice: Proceedings of the Thirteenth Annual ACR Forum

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The 2013 ACR Forum focused on the emerging field of imaging biomarkers and how best to integrate imaging biomarkers into clinical practice, promote research into imaging biomarkers, and leverage advances in bioinformatics. The recommendations generated from the Forum seek to inform ACR leadership on the best strategies to pursue to ensure that radiologists secure a preeminent role in the new era of precision and personalized medicine.

Key Words: ACR Forum, imaging biomarkers, precision medicine, informatics, research, radiology value chain

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INTRODUCTION

Each year, the ACR assembles a diverse group of experts and thought leaders from within and outside the specialty to discuss a specific topic of long-range importance to the practice of radiology. This initiative, known as the ACR Forum, began in 2001 and has included topics ranging from disruptive technologies (2005) to future physician payment models (2009) to, most recently, the projected future of radiology in 2022 (2012). This year, the organizing committee chose to focus on the emerging importance of imaging biomarkers (IBs) in the era of precision and personalized medicine. Participants invited to this year's Forum included physician and nonphysician leaders in imaging from both medicine and industry. Additionally, experts in the application of advanced informatics to promote research into IBs were also present. After a keynote address presented by Daniel Sullivan (Duke University Medical Center), the 2-day program included brief presentations by Neil Rofsky (University of Texas Southwestern Medical Center), Donald Rosen (ACR), and Keith Dreyer (Massachusetts General Hospital), as well as informal breakout sessions. However, most of the time was devoted to focused discussions on (1) the integration of imaging biomarkers into clinical practice, (2) research into imaging biomarkers, and (3) bioinformatics. In the final session, the Forum participants produced a list of consensus recommendations to be presented to the ACR Board of Chancellors on how to prepare the radiology community, both academic and private practice, for the emerging role of IBs in radiologic practice.

This article summarizes and synthesizes the proceedings of the meeting and is organized around the general topics of integrating IBs into clinical practice, education and training, bioinformatics, and promoting IB research in radiology.

BACKGROUND

The evolution of Western medicine is marked by inflexion points at which fundamental shifts occur in the manner in which diseases are categorized. As we move further into the 21st century, we are on the precipice of the next inflexion point, whereby a new taxonomy of disease is being developed, driven by advances in genomics and a greater understanding of the molecular pathways of illness [1]. Understanding the classification is important because it directly influences the creation of therapeutic interventions that ultimately cure or alleviate illness.

In the age of Hippocrates, at the dawn of Western medicine, little was understood regarding the etiologies of disease. Diseases were categorized by symptoms, and only those symptoms were treated, leading to unreliable and often poor outcomes. As Western medicine progressed and greater knowledge of anatomy, physiology, and pathology was gained, physicians and scientists began to establish relationships among diagnosis, treatment, and

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outcome. This led to a method to study the impacts of a variety of therapies on illness (clinical trials) and publication to share those results, leading to the current era of evidence-based medicine. Although evidence-based medicine has succeeded in defining effective therapeutics for large populations, it is lacking when applied to small subpopulations ("precision medicine") and ultimately to the individual level ("personalized medicine") [2].

In the era of evidence-based medicine, the process of drug development, beginning with preclinical trials and ending with the gold standard of large randomized prospective controlled trials, has proved to be too time consuming and cost prohibitive to effectively bring new therapies to the bedside. Moreover, the traditional end points used in these trials, mortality and morbidity, are fraught with limitations [3]. In response to these shortcomings, the scientific community has sought new approaches, in particular the development of surrogate end points in the form of biomarkers. Biomarkers are defined as "any detectable biologic parameter, whether biochemical, genetic, histologic, anatomic, physical, functional or metabolic" [3]. More recently, the scientific and regulatory communities have embraced biomarkers as acceptable surrogate end points for clinical trials, paving the way for their widespread use in medicine [4]. Specifically, IBs were defined by Smith et al [4] as any "anatomic, physiologic, biochemical, or molecular parameter detectable with one or more imaging methods used to help establish the presence and/or severity of disease."

At the dawn of the era of precision and personalized medicine, radiology is at a crossroads. For radiologists to secure a preeminent role in this new era, IBs must be incorporated into clinical practice, the challenges described in this summary addressed, greater education efforts pursued, and new avenues of research actively explored.

IBs IN CLINICAL PRACTICE

Integrating IBs into clinical practice presents a unique opportunity to contribute to the radiology value chain. The utility of IBs is particularly relevant as the field of medical imaging undergoes a paradigm shift from qualitatively assessing changes in gross anatomic structures, best exemplified by the traditional "Roentgen signs," to a more quantitative approach that can leverage emerging modalities ability to characterize the physiology of the microenvironment. These advances dovetail with a larger movement in medicine that is exploring the impact of genotypes and individual observable characteristics (phenotypes) and their interplay with therapeutics. One such imaging technology currently in use across the globe is ^{18}F-fluorodeoxyglucose PET in oncologic imaging, whereby the information gleaned from this imaging tracer is driving treatment algorithms. Advances in "molecular theranostics," as described by Lee and Li [5], are leading to "improved therapy selection on the basis of specific molecular features of disease, greater predictive power for adverse effects, and new ways to objectively monitor therapy response." However, ^{18}F-fluorodeoxyglucose PET only scratches the surface of Lee and Li's criteria for a true molecular theranostic because it does not exploit a specific molecular mechanism amenable to targeted therapy. As newer imaging techniques and agents allow systems that bridge data generated from diagnostic tests with molecularly targeted therapeutic interventions, it will be critical for both community and academic radiologists to incorporate these systems into their practice to become more tightly integrated into clinical care teams.

However, before widespread integration of IBs can occur within the radiology community, certain hurdles, including standardization, must be overcome. Standardization and rigor must be applied to all aspects of the imaging cycle, including image acquisition, image processing, and report generation. For IB data to be included into clinical care pathways, they must be reproducible and held to the same standards set forth by the National Institute of Standards and Technology definition of a measurement, which notes that a "measurement result is complete only when accompanied by a quantitative statement of its uncertainty." Moreover, "the uncertainty is required in order to decide if the result is adequate for its intended purpose and to ascertain if it is consistent with other similar results" [6]. Accurate, reproducible quantitative measurements are a requirement to reduce error and variability if IBs are to play a role in the era of precision and personalized medicine. Standardization is also critical in imaging report generation and dissemination. Imaging reports that are of high value must be structured, use standardized terminology, be limited in their variability especially with regard to recommendations, and convey actionable information.

On the basis of the above discussion, Forum participants developed the following consensus recommendations regarding the integration of IB into clinical practice, the ACR should take the following steps:

1. Identify clinical practice needs for standardization for all practice types.
2. Identify, prioritize, and incorporate into clinical use a working list of current biomarkers by liaising with subspecialty societies.
3. Convene the relevant stakeholders (payers, industry, and specialty societies, including international) to implement IBs.
4. Support RSNA and other efforts on report standardization relative to IBs: support standardized reports and promote by all means possible their implementation.
5. Work within the regulatory system to provide incentives for standardized reporting.

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