Next Generation Radiologic-Pathologic Correlation in Oncology: Rad-Path 2.0

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OBJECTIVE. The bedrock of radiology has been radiologic-pathologic (Rad-Path) correlation: the correlation of imaging to ex vivo gross and histopathologic findings of disease. This classical view is being challenged by our increasing understanding of the molecular basis of disease, particularly in oncology. The traditional lines in diagnostic sciences have blurred with the development of new in vitro diagnostic molecular assays and molecular imaging methods as well as the growing evidence that conventional diagnostic imaging has potential use in understanding genomic properties of disease. The purpose of this article is to make the case for a fundamental shift to the next generation of Rad-Path correlation (Rad-Path 2.0).

CONCLUSION. The future success of radiology will require not only continued technologic advances in physical and life sciences but also the convergence of previously distinct diagnostic disciplines.

Keywords: histopathologic findings, molecular imaging, radiologic findings, radiogenomics, radiologic-pathologic correlation

DOI:10.2214/AJR.11.7163

Received May 4, 2011; accepted after revision July 12, 2011.

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AJR 2011; 197:990–997

0361–803X/11/1974–990

Since its inception, diagnostic imaging has provided clinicians with increasingly sophisticated noninvasive visual representations of disease. This is nowhere more apparent than in the evaluation of cancer, where imaging is used in almost all facets of disease assessment [1–5]. The primary value of medical imaging is the information that imaging provides with respect to the underlying pathology being viewed. As gross specimen analysis followed by histopathologic analysis using light microscopy were the fundamental means of disease diagnosis before the discovery of x-rays, diagnostic imaging has always relied on pathology as ground truth.

The intrinsic relationship between radiology and pathology (Rad-Path 1.0) has persisted essentially unchanged in form to this day. Because histopathology has served as the reference point for imaging, the primary goal of imaging has accordingly been to achieve the equivalent of in vivo microscopy. The pursuit of this goal has been the motive of much of the research and development behind existing modern imaging technologies [6]. Indeed, with successive generations of imaging equipment enabling ever-greater temporal and spatial resolution, our ability to peer noninvasively into the human body and perceive disease has improved dramatically, moving us closer to this reference standard. With next generation high-field MRI, MDCT, and PET/CT tools as examples, we are able to acquire larger volumes of data at higher spatial resolution and lower acquisition time with which to better correlate to histopathology [7–10]. However, a revolution is underway in molecular diagnostics that challenges the value of this traditional approach. This is most evident in the study of cancer.

The Shift in Medical Diagnosis in the Postgenomic Era

The completion of the Human Genome Project and the availability of high-throughput genomic tools, such as gene-expression microarrays and next-generation sequencing, have set in motion new ways of understanding cancer with unprecedented detail and precision [11–14]. We are now able to evaluate molecular processes within the cell at greater depth, speed, and coverage and at genome scale. As one powerful illustration, by leveraging our knowledge of the complete catalog of genes provided by the Human Genome Project, we can now evaluate the global transcriptomic state of a tumor in a single assay using gene-expression microarrays [15]. The impact of such technologies on our understanding of disease has been far reaching, deepening our understanding of the cellular and genetic states that are present in and typify cancers [11, 16].

TABLE 1: Several Commercial Gene-Expression In Vitro Diagnostic Molecular Assays Available in Oncology

Name	Company	Tissue Type	Brief Summary
BluePrint	Agendia	Breast	Subclassifies breast cancers into basal, luminal, or *ERB2*
Breast Cancer Index	bioTheranostics	Breast	Predicts distant recurrence of estrogen receptor–positive/lymph node–negative breast cancer
ColoPrint	Agendia	Colon	Predicts the risk of distant recurrence of stage II and III colon cancer
MammaPrint[a]	Agendia	Breast	Predicts distant recurrence after surgery
Mammostrat	Clarient	Breast	Classifies risk of breast cancer recurrence during tamoxifen therapy
OncoDefender	Everist Genomics	Colon	Predicts recurrence of stage 1 or 2 colorectal cancer after surgery
OncoType DX	Genomic Health	Breast	Predicts likelihood of recurrence and chemotherapy benefit in estrogen receptor–positive/lymph node–negative breast cancer
OncoType DX	Genomic Health	Colon	Assesses the risk of recurrence of stage 2 colon cancer after surgery
Prostate Px	Aureon	Prostate	Assesses the risk of recurrence and disease state of prostate cancer in surgical candidates

[a]Food and Drug Administration approved.

We now recognize the tremendous molecular diversity present in different tumors and even within what was previously believed to be a single tumor type. For example, a seminal gene-expression profiling study revealed the presence of molecularly distinct cancer populations within what was previously believed to be a single tumor type (in this case, diffuse B cell lymphoma) on the basis of observations that these phenotypically similar tumors under the light microscope were often quite inconsistent in clinical outcome [17]. Additional studies have since allowed further subclassification of B cell lymphoma into three distinct molecular classes that differ not only in their clinical outcome but also in therapeutic sensitivity [17, 18].

Moreover, studies have also shown that gene-expression patterns can be used for the deconvolution of distinct signaling pathways involved in tumorigenesis [19]. Hence, gene-expression profiling of cancer potentially answers a number of biologically and clinically important questions: it can be used to help predict clinical course, assess response to treatment, and potentially identify key pathways involved in a given molecular phenotype [20]. A wide variety of other cancer types including lung, breast, brain, renal, melanoma, colon, and prostate have similarly undergone genome-wide expression analysis identifying important molecular subclasses [21–32]. These subclasses further separate patients with the same histologic diagnosis, revealing that molecular heterogeneity is a conserved feature of all cancers and that histopathology alone is insufficient to guide patient management.

The concept of genomic profiling has begun to see realization in the form of commercialized molecular diagnostic assays in a number of different applications and tumor types. For example, a growing number of institutions are beginning to incorporate the MammaPrint assay (Agendia) and OncoType DX (Genomic Health) tests for breast cancer, both of which are multiplex gene-expression assays indicated in predicting a patient's outcome and response to treatment [33–37]. Studies are also underway in assessing the use of a similar test in colorectal cancer [38]. Table 1 summarizes several of the commercially available gene expression–based molecular diagnostic tests available in solid tumor oncology. This trend will only continue with expansion into new indications in existing tumor types as well as more broadly into different cancers. Thus, although still in their relative infancy, genomic approaches are showing increasing relevance and utility in clinical decision making beyond traditional histopathology, thereby challenging the current basis of imaging and its anachronistic reliance on the existing Rad-Path 1.0 correlation.

New Information, New Questions

The principal role of imaging in the overall assessment of cancer resides in its ability to detect tissue-level abnormalities relative to normal tissue, characterize the likely benign or malignant basis, postulate as to the cell type, and then define both the location and anatomic extent of disease and whether the disease burden is broadly changing in the face of therapy. Newer cross-sectional imaging modalities such as CT, MRI, and PET/CT are rapidly improving in their ability to perform these tasks by providing finer temporal and spatial resolution. Such information has played a valuable role in cancer management in which it continues to serve as the primary basis for clinical staging and response assessment, informing clinicians of broad estimates of survival, and providing guidelines on modality and intensity of therapy to be used [10, 39–41]. However, driven in large part by the promise of human genome sequencing, there has been a shift in pharmaceutical development toward therapies targeting specific driver mutations and molecular pathways and away from broader chemotherapeutics, representing yet another challenge for imaging and its role in the evaluation of cancer. Defining the presence, location, and extent of disease, although still extremely valuable, is not enough when faced with the critical decision of which molecular targeted agent to apply in a given patient population.

This evolution toward targeted therapeutic development has ushered in an era of personalized medicine in which molecularly targeted therapies are intimately linked to molecular diagnostics critical for efficient selection of patients. This paradigm has become an increasingly compelling strategy for the treatment of cancer, largely beginning with the success of trastuzumab for the treatment of metastatic *ERB2* (formerly *HER2*) positive breast cancer [42]. The origins of targeting tumors overexpressing this receptor were based on observations that gene amplification and protein overexpression of *ERB2*, which are found in 25–30% of breast cancers, were associated with a shorter disease-free interval and worse overall survival [42, 43]. Trastuzumab, a monoclonal antibody that targets the *ERB2/neu* receptor, has since proven effective in treating patients with *ERB2*-positive metastatic breast cancer with respect to both of these outcome measures [42–44]. The discovery of this unique molecular phenotype and the subsequent success of administering a targeted therapy against it illustrate how molecular markers can play a crucial role in determining the appropriate course of treatment of individual patients. As a result,

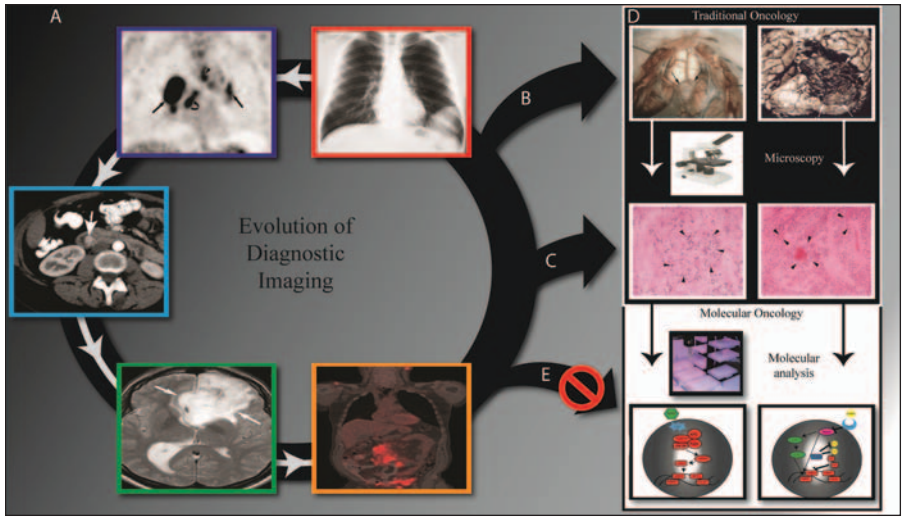

Fig. 1—Illustration of rad-path 1.0 paradigm. Broad evolution of diagnostic imaging technologies is depicted counterclockwise in (A). In rad-path 1.0, primary goal of diagnostic imaging in oncology is to serve as noninvasive surrogate for gross (B) and microscopy (C). However, "traditional oncology" is evolving beyond these broad diagnostic measures toward more sophisticated and resolved molecular analysis in molecular oncology (D), which is not accounted for in rad-path 1.0 (E).

a given patient's eligibility for receiving trastuzumab is now dependent on the tumor's *ERB2/neu* status, rather than the anatomic burden of the disease, node or estrogen receptor status, or line of therapy, as would have been the case for nontargeted chemotherapy.

Traditional staging systems continue to provide clinicians with important information; however, the emergence of specific molecular markers has begun blurring the role of anatomic measures, such as disease burden, as the sole drivers of therapy selection and patient outcome. Indeed, a growing number of molecular markers, such as *ERB2/neu*, are now being established as the critical primary decision nodes in therapy determination, such as epidermal growth factor receptor (*EGFR*) and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*) in lung cancer, *K-ras* in colon cancer; isocitrate dehydrogenase (*IDH*) 1 and 2 as well as O6-methylguanine-DNA methyltransferase (*MGMT*) in glioblastoma multiforme (GBM), *CD20* in lymphoma, and the protooncogene B-Raf (*BRAF*) in melanoma, to name just a few [45–54]. Early and midterm clinical trial data from these and other studies are increasingly supporting the value of upfront patient stratification on the basis of molecular markers tied to selection of a particular targeted therapy. The list of targeted agents will continue to grow as will the need for diagnostic molecular stratification of patients to guide therapy selection. Therefore, it should be evident that there is a growing disconnect between the anatomic-microscopic based Rad-Path 1.0 information that imaging is currently providing and the information referring clinicians now require to guide patient management driven by advances in molecular diagnostics and personalized medicine. If molecular markers are increasingly being embedded in the diagnosis and classification of cancers, is imaging, which is still based on gross and histopathology, providing adequate information to guide management? It would appear that diagnostic imaging in its current Rad-Path 1.0 form is ill-prepared to meet these broad and expanding challenges.

The Case for Change

Medicine, oncology in particular, is undergoing changes toward molecular- and genomic-guided decision making. It should also be evident that diagnostic imaging, although advancing technologically, is not doing so in a manner synchronous with the changes taking place in molecular diagnostics. This growing incongruence is highlighted in Figure 1. As medicine continues to transition from a tissue and cell-type basis toward a molecular basis, it is only logical that diagnostic imaging technologies also shift in a parallel manner. Indeed, this transformation is slowly taking shape in a handful of research laboratories, with powerful new technologies in development that are capable of imaging cellular and even molecular events in vivo. Molecular imaging approaches are maturing to the point that they are making their way into human testing. Readers who are interested in understanding these technologies and their implications are referred to recent articles on molecular imaging [55–60]. However, as with all potentially disruptive technologies, a number of significant technical, economic, and integration hurdles must be overcome before acceptance in the clinic. Until that time, important questions remain: How can we as medical information providers continue to remain relevant in a world that is rapidly evolving around us? What will be the role of diagnostic imaging in the emerging era of molecular medicine?

We are faced with a number of challenges as we await the promise of molecular imaging technologies to mature. On a practical level, one of the major limiting factors to broad adoption of molecular imaging techniques in the near term is the large current installed base of radiologists whose knowledge is fundamentally rooted in the traditional Rad-Path paradigm. Furthermore, these same radiologists have invested billions of dollars in state-of-the-art imaging equipment that specifically functions to support this old Rad-Path 1.0 paradigm. In an ideal world, one could identify ways to leverage this existing intellectual and capital infrastructure but do so in a manner that is aligned with the current growth seen in molecular oncology and simultaneously facilitates the gradual transitioning toward pure molecular imaging–based approaches. In other words, the solution would primarily focus on changing the ways we currently view and use imaging technologies and the information they generate. In its bare form, this would primarily consist of redefining the Rad-Path paradigm to provide increasingly relevant molecular information.

Rad-Path 2.0

At its base level, redefining the Rad-Path paradigm, or evolving to a Rad-Path 2.0 paradigm, would entail realigning our current radiologic-histopathologic correlation basis to a radiologic-molecular or radiologic-genomic correlation. Rad-Path 2.0 will be about finding ways to extend correlation of the information already obtained from existing clinical imaging modalities, such as CT, MRI and PET, beyond conventional gross and histopathology to also include large-scale molecular or genomic information. The major advantage of such an approach lies in its ability to leverage the existing installed base of radiologists who are highly trained in image interpretation

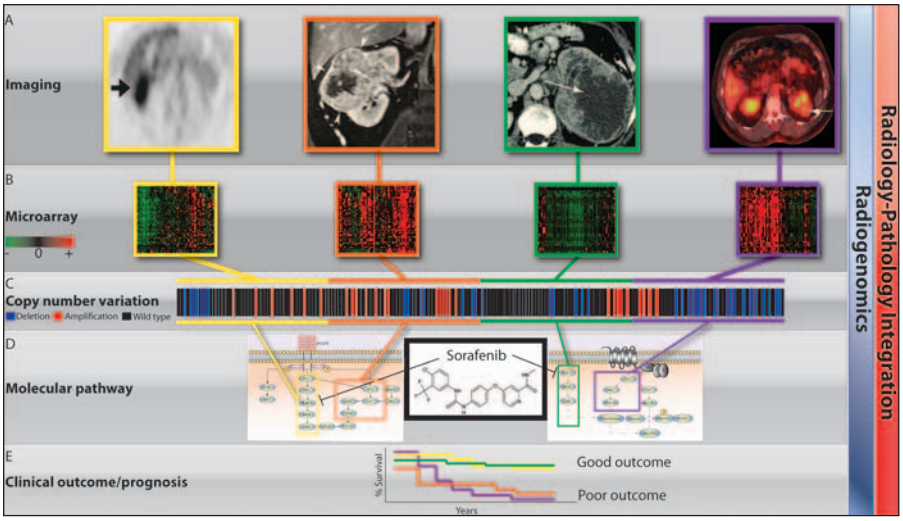

Fig. 2—Schematic diagram shows next generation Rad-Path 2.0 paradigm, which integrates imaging, molecular-genomic, and clinical data illustrated using renal cell carcinoma as example.
A–E, Multiscale biology includes imaging (**A**), gross and histopathology (not shown), gene expression (**B**), DNA copy number (**C**), signaling pathways (**D**), and clinical measures and outcomes (**E**), which are all leveraged in one unified platform, both conceptually (radiogenomics) and programmatically (radiology-pathology integration).

using existing imaging equipment. The field of radiogenomics is just one such implementation of this type of next generation Rad-Path 2.0, radiologic-molecular correlation, and is the focus of the remainder of this article.

Radiogenomics as a Means of Multiscale Imaging

The conventional thinking in radiology has been that the information captured by existing imaging modalities is insufficient to reveal molecular detail. Radiogenomics posits that much of the rich information generated by existing imaging methods is currently unaccounted for and inappropriately discarded by the current Rad-Path 1.0 paradigm, and by instead linking this information to the underlying molecular data, much richer associations can be obtained from the same images. Simply put, the thesis is that there is information extractable from conventional imaging methods that is sufficiently dense and structured that can be used to define stable relationships with the underlying associated large-scale molecular information. This would then potentially allow particular imaging phenotypes to serves as surrogates for the unique molecular programs that typify a molecular subtype of a cancer rather than just the bland cell type as is current practice.

This type of indirect molecular imaging would allow radiologists to more fully explore the rich molecular heterogeneity that is known to typify cancer but that is currently inaccessible using standard methods. If this were feasible, it could then allow a relatively straightforward means with which to not only continue to provide structural and anatomic information at an organ, tissue, or cellular level for both disease detection and cell type diagnosis but could also add high-level molecular detail that could potentially be used for molecular characterization and targeted therapy selection. Thus, imaging could be leveraged across multiple scales of biology. However, to evaluate the actual potential utility of radiogenomics, it must first be shown that this concept is robust and stable. Therefore, a critical first step lies in showing that there is indeed a predictable and systematic relationship between features seen on imaging and the underlying molecular diversity present in the disease being imaged and that this molecular detail can be consistently deciphered from the images generated.

Aiming to address this question, Segal et al. [61] showed in a study involving 28 patients with hepatocellular carcinoma (HCC) that the information obtained in standard biphasic CT was sufficient to construct a stable association map revealing how CT image features are related to the global gene-expression profiles in HCC. Using this approach, they were able to reconstruct approximately 78% of the available HCC transcriptome (~6700 genes measured) with combinations of 28 predetermined CT image features. Diehn et al. [62] further showed that the radiogenomic approach is robust and scalable to other human tumors and imaging modalities. In this study, they sought to define whether imaging-based surrogates of predefined canonical gene expression programs using MR imaging data could be identified in patients with GBM. They were able to construct an association map linking 10 predefined MRI phenotypes with nine different gene expression programs (e.g., hypoxia, cell proliferation, *EGFR*), from a background of more than 2000 evaluated genes [62]. Thus, initial work in these and other studies suggest that information present in existing images can be linked with large-scale molecular information [63, 64].

Radiogenomics: Potential Areas of Utility

The applications of radiogenomics are extraordinarily broad. The association map allows one to define molecular targets of diagnostic interest, whether individual genes, groups of genes, or canonical gene expression programs, and to then specify those imaging features that best allow their prediction from the image. For example, Segal et al. [61] showed that if interested in identifying whether a particular HCC patient overexpressed genes related to angiogenesis, such as vascular endothelial growth factor (*VEGF*), a radiologist could use the association map to define those particular imaging features present in the CT image that would need to be evaluated to predict the approximate *VEGF* expression level in that patient's tumor. Thus, for a hypothesis-generating engine for selecting patients for an antiangiogenesis therapy trial, one could use the association map for selection on a patient-by-patient basis to include only those patients who had a high expression level of angiogenesis genes solely on the basis of CT. Similarly, the association map allows one to understand how gene expression patterns encode particular imaging phenotypes. In other words: What is the genotype-phenotype relationship behind a particular diagnostic image? For example, one could reference the association map to determine the molecular association or gene expression programs behind tumors that have a certain canonical image appearance, such as a CT capsule in HCC or a large degree of enhancement on contrast-enhanced MRI in GBM. Thus, radiogenomics shows how it is possible to convert information from images into global gene expression patterns to define patient groups and understand the molecular biology associated with an image phenotype.

Applications that could also potentially have direct clinical impact in predicting patient outcome have also been highlighted. Diehn et al. [62] showed that it was possible to identify a T2-weighted MRI phenotype called the "infiltrative" phenotype that was highly

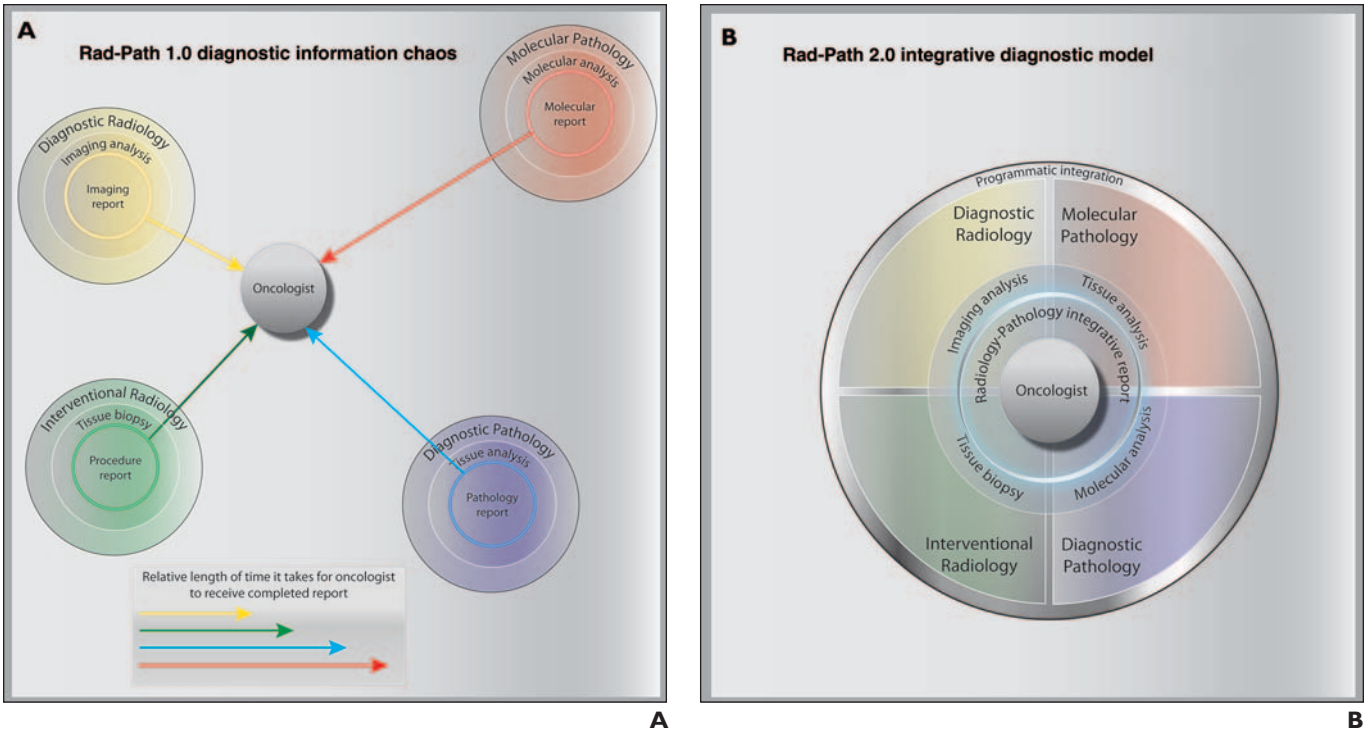

Fig. 3—Drawings show different radiology-pathology (Rad-Path) paradigms.
A and **B,** Drawings highlight differences in diagnostic information flow, integration, and reporting between Rad-Path 1.0 (**A**), in which each information-generating unit works almost independently, and Rad-Path 2.0 (**B**), in which the units are programmatically integrated.

correlated with a previously characterized unique survival expression signature that predicted outcome independent of histologic and clinical variables. The authors then showed in independent datasets of patients with GBM that they were able to stratify patients solely based on the presence or absence of this infiltrative image trait (which is a surrogate marker for the survival gene-expression signature) into different prognostic groups that had significant differences in overall survival times.

Segal et al. [61] showed that in HCC it was possible to identify an aggressive molecular phenotype a priori and, using the association map, identify those imaging features that are predictive of this expression signature. From this, they were able to identify those patients who expressed the venous invasion gene-expression signature and were likely to have microscopic venous invasion and thus a poor outcome. They were also able to use this information to then build a second imaging phenotype predictor of overall prognosis for HCC. These examples show how a radiogenomic approach could provide clinical benefit by allowing a radiologist to use imaging to noninvasively determine the molecular diversity inherent in cancer and thereby stratify patients into molecular subclasses with different prognostic associations on the basis of their imaging phenotypes.

The therapeutic implications of radiogenomics have also been explored in cancer. As improvements in our understanding of signal transduction pathways result in the development of newer targeted therapies, biomarkers will need to be developed in parallel that best allow identification of those patients for whom the targeted therapeutic agent will be effective. Along these lines, Diehn et al. [62] evaluated whether a radiogenomic approach could be used to identify an image biomarker of *EGFR* expression that is commonly dysregulated in GBM and for which a number of *EGFR*-targeted therapies currently exist. Having identified from the initial GBM radiogenomic association map an image trait termed "contrast necrosis" phenotype that was highly associated with an *EGFR* gene-expression program, they went on to evaluate its ability to also predict *EGFR* protein expression, which is the cognate target of *EGFR*-inhibitor therapies. That they were able to select patients with GBM who overexpressed the *EGFR* protein from this MRI phenotype provided initial proof of the principle that a radiogenomic approach could be potentially useful in selecting patients for targeted therapies [62].

Similarly, Kuo et al. [65] showed that it is possible to identify CT image phenotypes associated with specific treatment response gene-expression programs in HCC. Given that transarterial chemoembolization with doxorubicin as the primary chemotherapeutic component has become a staple for the treatment of intermediate and advanced HCC, identifying potential responders to this agent could be of great benefit for patient treatment preselection and stratification [66, 67]. In the same study, the authors identified a CT imaging phenotype, termed the "tumor margin score," relating to the character of tumor margins that was correlated to a previously characterized unique doxorubicin treatment response gene-expression program [68]. Highlighting the ability of radiogenomics to serve as a noninvasive means to potentially integrate biology at multiple scales, they then went on to define the tumor margin score phenotypic associations at gene-expression, histopathologic, and clinical levels. Here they found that patients with a nonresponder doxorubicin imaging phenotype (a high tumor margin score), tended to be associated with a poor doxorubicin response gene-expression signature, the venous invasion gene expression signature, a poor hepatocyte differentiation gene-expression program, the presence of histologic microscopic venous invasion, and a high tumor stage. Simply put, tumors with a high tumor margin score on CT tended to activate multi-

ple gene-expression programs corresponding to an aggressive phenotype that was also reflected by histopathology and clinical staging. Thus, although early and still requiring additional validation, the initial data suggest that a radiogenomic approach appears both robust and scalable, capable of integrating data from the molecular to the microscopic and macroscopic levels, and supports the overall feasibility of the Rad-Path 2.0 concept.

Radiogenomics: The Case for a New Type of Diagnostics Convergence

As one probes deeper into the implications of a radiogenomic Rad-Path 2.0 correlation, the previously distinct lines between conventional tissue-based in vitro diagnostic molecular assays and noninvasive imaging begin to blur. The ideal diagnostic test clearly lies somewhere between these two conventional polar extremes. At its simplest, Rad-Path 2.0 would provide the high molecular specificity and accuracy that conventional tissue-based approaches offer while still providing structural and dynamic physiologic and contextual cues in a noninvasive manner, which current radiologic approaches afford. By enabling large-scale genomic features to be elucidated with imaging, radiogenomics shows that a potential middle ground exists in which knowledge from distinct clinical disciplines can be seamlessly integrated into a single common platform. However, taken a step further, radiogenomics, and molecular imaging in general, would additionally imply that gradual clinical convergence of in vitro and imaging-based diagnostic disciplines is both rational and feasible (Fig. 2). Thus, a further interpretation of Rad-Path 2.0 would include the merging of molecular diagnostics and imaging into a single diagnostic discipline.

The case for an integrated diagnostics approach is not a new one [69, 70]. Although radiologists and pathologists both analyze the same diseases in the same patients, their perspectives and the types of information they each provide to referring clinicians can differ greatly. With radiologists operating most efficiently at the macroscopic end of the biologic spectrum and pathologists most comfortable in the microscopic domain, each has a tendency to drive interpretations through a particular diagnostic lens. This situation can clearly lead to gaps in knowledge and an inability to create a global perspective in diagnosis; at its worst, it is analogous to the fable of the three blind men describing different parts of the same elephant but coming to vastly different conclusions.

This is no different from what we are seeing in molecular oncology with the diagnostic sciences. Rapid technologic advances in both radiology and pathology are increasingly driving subspecialization. This results in the generation of more diagnostic data but also an inability for one subspecialty to communicate with other subspecialties. The result is the generation of disparate diagnostic data streams, which cannot be integrated by any one diagnostic subspecialty, for which, ultimately, the burden is unfairly shifted to the referring clinician. Because tumor biology can be analyzed across a continuum of biologic scale—from molecules, genes, and proteins to tissues, organs, and organ systems, with each level providing important and distinct value—clearly there is untapped potential in being able to extract value across multiple, if not all, levels. This potential could only be achieved by understanding the many parts of the complete diagnostics universe and how those parts connect. This understanding would be afforded by a seamless diagnostics platform, such as radiogenomics, but also though an integrated diagnostics team of molecular and tissue pathologists and molecular and diagnostic radiologists who share a common knowledge base and speak a common language (Fig. 3).

Such an approach could have an impact on many levels in the near term. First, an integrated diagnostic unit could provide efficiencies in reporting that have been sorely lacking. The use of a single combined reporting scheme could mitigate the confusion associated with separate imaging, tissue diagnosis, and molecular testing results. A clinician could receive a single integrated report detailing the diagnostic imaging findings, description of the imaging-guided tissue biopsy, gross and microscopic evaluations, and immunohistochemistry and molecular analysis in one document. In current practice, each of these reports is received asymmetrically, adding to the challenge for referring physicians to integrate all of the data. Thus, an interdisciplinary approach, as afforded by radiology-pathology programmatic integration, allows information to be consolidated across the entire diagnostic spectrum into a single coherent and comprehensive information unit.

At another level, programmatic integration also directly improves diagnosis at the patient level by streamlining information acquisition and communication. By better understanding how diagnostic information is obtained, processed, analyzed, and used at each level, significant overall improvements can be made and inefficiencies removed from the system. An obvious existing example of this is in bone tumor diagnosis, where both pathology and radiology must work in concert to provide a correct diagnosis. By doing so and obtaining a better understanding of the strengths and limitations that each approach brings to the table, inefficiencies can be removed from the equation, with a concordant decrease in misdiagnoses, unnecessary biopsies, and errant surgeries in orthopedics oncology.

A parallel case in the Rad-Path 2.0 paradigm could be made with imaging-guided tissue targeting for molecular analysis. If existing imaging heterogeneity can be systematized and spatially linked to molecular heterogeneity, as was shown by Diehn et al. [62] in their radiogenomic analysis of GBM, then a better mechanistic understanding of these molecular alterations and where they tend to be localized in the image could prove critical for imaging-guided acquisition of tissue for molecular analysis and diagnosis. This could lead to benefits in patient care by allowing improved targeted tissue acquisition of lesions—or even of particular regions within a tumor—of high molecular or cellular relevance that could be informed by pathology at the time of tissue acquisition. Thus, vertical integration of diagnostic knowledge across the continuum of care has the potential to add efficiencies and gains in knowledge previously unaffordable by any one diagnostic unit alone

True programmatic rad-path integration offers numerous benefits. Although beyond the scope of this article, it makes sense that benefits in overall capital asset deployment and utilization, billing, research, trainee education, and human resources could all be derived over the long term in such a paradigm. Indeed, a small number of academic institutions including our own have begun to explore and implement aspects of the Rad-Path 2.0 concept outlined herein, both at the conceptual radiogenomics and radiology-pathology programmatic integration levels. Although still in its infancy and with many remaining issues to be resolved, the initial feedback both internally and from referring clinicians and researchers has been positive. For example, simple but fundamental changes, such as the creation of an integrated diagnostic workspace with shared resources among radiologists and pathologists, where tissue biopsy and initial analysis are performed in the same suite, can result in improved real-time communication and decision making at the point of care while simultaneously reducing overall cost. Additionally, broader integration of research units

enhances idea exchange and spurs innovation in areas of research currently unaddressed by either program alone.

Conclusion

We have sought to describe the evolving landscape in medicine, and oncology in particular, and its impact on the field of medical diagnosis. There is clearly a shift toward genomic and molecular characterization of disease fueled by an evolving body of knowledge confirming the tremendous molecular diversity present within cancer and even within what has previously been assumed to be a single cell type. This shift has led to entirely new perspectives spanning almost every facet of disease management.

Because diagnostic imaging is by its nature a science built on correlation, the key determinant of its value rests on establishing the proper standard with which to build this framework. With ex vivo gross and histopathology serving as its reference standard (Rad-Path 1.0), radiology has excelled in its goal of serving as an increasingly refined surrogate for in vivo microscopy over the past century. However, with the science of diagnostics clearly moving beyond such measures and fully embracing molecular information, radiology must reevaluate its stance. Continued reliance on this increasingly outmoded correlation without awareness of or adaptation to the changing landscape puts the field at risk of becoming helplessly engaged in a red queen's race, where one must constantly run to stay in the same place [71].

To avoid this fate, we have briefly outlined the central tenets our specialty must embrace to maintain relevance. Chief among these are the need to update the rad-path correlation to incorporate the expanding molecular and genomic diagnostic universe. This new paradigm must allow a meaningful and pragmatic transition.

We have highlighted several means with which this change can come about by defining a Rad-Path 2.0 paradigm that is based on integration occurring at two fundamental levels. The first level is conceptual or technologic integration, with radiogenomics serving as an example of a unifying platform that is able to leverage existing radiology infrastructures as a means to provide multiscale imaging across the entire continuum of biology from the macroscopic to the microscopic and even to the molecular. The second level incorporates programmatic convergence, which is to say, practical and real interdisciplinary integration between diagnostic specialties. We briefly highlighted this case using radiology and pathology as a clear example of such programmatic fusion. Ultimately, regardless of means or mechanism or shape or form, convergence and integration will prove to be key features integral to any paradigm shift.

As specialists, radiologists must be ever vigilant and constantly reassess our value proposition amid an increasingly competitive and evolving marketplace. Among the many relevant lessons is the observation that one is never "too big to fail" and that there are often clear signs that can be identified that foreshadow the eventual decline of an organization, culture, or civilization [72]. Although only time will tell how Rad-Path 2.0 will ultimately be conceptualized and reduced to practice, it is patently evident that a change in paradigm is needed. It is our belief that a broad interpretation, as outlined herein, incorporating both a technologic and programmatic framework for integration is the fundamental requirement for stakeholders in diagnostic medicine who desire to remain competitive in a rapidly evolving world.

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