The Role of Pathologists in the Era of Personalized Medicine

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Although the field of oncology has made significant progress in improving the duration and quality of life for patients with cancer, response rates to traditional chemotherapeutic agents remain unacceptably low when compared with response rates in other disease areas.1 This situation, combined with the disturbing trend of decreasing annual new drug applications despite increasing drug development spending,2 has accelerated the adoption of the personalized medicine concept in several areas of medicine but most significantly in oncology. In this field, in the past 5 to 10 years, the terms personalized medicine, biomarkers, and translational medicine have gone from being hypothetical concepts to being widespread actualities in drug development, basic and clinical research, and clinical practice. Once obscure points of discussion at cancer conferences, these topics now dominate many congresses and have spawned dozens of biomarker meetings around the world each year.

In its simplest form, personalized medicine seeks to do away with the cancer treatment paradigms of “one drug fits all” and “trial and error,” replacing them with a model centered on the pairing of molecularly classified cancer subgroups with new generations of chemotherapeutic molecules targeting the specific pathogenic mechanisms that drive the respective neoplastic processes in each subgroup. The objective is to administer the right drug to the right patient at the right time and at the right dose. This model is entirely dependent, however, on a new generation of cancer tests that accurately and comprehensively characterize patients’ tumors at the DNA, RNA, and protein levels, thereby allowing physicians to identify likely responders before beginning treatment.

These tests have been designated companion diagnostics to acknowledge that, in the personalized medicine model, the pharmaceutical compound and the diagnostic assay become inexorably linked. That is, without the drug, there is no need for the companion diagnostic; and perhaps more conceptually provocative, without the companion diagnostic, there may be no utility for the drug. Thus, while targeted therapies often demonstrate dramatic responses in diagnostic-driven patient subsets, the therapy’s efficacy in unselected patient cohorts is typically too low for regulatory approval. The US Food and Drug Administration has published a guidance document in draft form on the codevelopment of drugs and diagnostics.3 A major point of emphasis in that document is the need to begin development of the diagnostic assay early in the drug development process, ideally in the preclinical stage, to best ensure that a robust assay can be approved by the US Food and Drug Administration and be commercialized in conjunction with the pharmaceutical compound.

If one considers the large and growing number of molecularly targeted therapies that are either available commercially or in development,4 as well as the enormous amount of ongoing translational research in oncology, it becomes clear that the personalized medicine concept is not going to be a short-lived trend but rather a true paradigm shift and a new way of diagnosing and treating cancer as a disease.

At the same time, the personalized medicine concept faces a number of significant challenges before its potential can be fully realized. At the scientific level, although our knowledge surrounding the molecular underpinnings of cancer continues to expand at a rapid pace, we are a long way from having a complete understanding of how cancer cells are driven, how they evolve over time, how they interact with the host microenvironment and how they react to therapeutic intervention. In drug development, we face the challenges of developing therapies against targets we do not completely understand and of selecting optimal trial designs, clinical endpoints, and biomarker strategies. In the clinic, we need to deal with the reality of acquired drug resistance, even in patients who have had dramatic initial responses, and with a previously underestimated degree of intrapatient and intratumoral heterogeneity. Although the combination of targeted therapies appears to be one solution to the latter challenges, clinical trials that include adaptive designs and combinatorial approaches have only recently been initiated, and it remains to be seen whether toxicity will be a limiting factor. At the logistic level, sample collection, especially tissue collection, continues to be challenging in the context of clinical trials. This is due to cost, patient enrollment impact, preanalytic variables, and lack of standardization.

Given that the entire concept of personalized medicine is predicated on the interdependence of drugs and diagnostics, how will each of these critical components be valued,
priced, and reimbursed, so they are widely available and best serve the needs of patients?

The solutions to these issues will depend on a coordinated approach from a variety of disciplines, including oncology, molecular biology, and certainly, pathology.

THE ROLE OF PATHOLOGISTS IN PERSONALIZED MEDICINE: THE NEED FOR CHANGE

As personalized medicine takes hold and revolutionizes the way we diagnose, characterize, and treat cancer, there is a tremendous opportunity for pathologists to make major contributions to this emerging new paradigm and to dramatically improve the care of patients with cancer. Some significant changes, however, need to occur within the field of pathology for this to become a reality. Pathology, as a field, has been occupied primarily with the diagnosis, classification, and subclassification of disease. Certainly, pathologists also provide prognostic information in the form of histologic grade, and in a small number of cases, they provide information, such as HER2 status, that is directly related to therapy. For the most part, however, pathologists have not played an active role in driving forward personalized medicine. Pathology, as a field, needs to move beyond the realm of diagnosis and mere classification/subclassification of diseases, to become the field responsible for providing personalized medicine information. Pathologists need to be the experts in the medical system who answer the following questions for patients and their treating physicians:

- Does the patient have an indolent disease or one that threatens his or her life?
- If the patient has a malignancy, how aggressive is it?
- What is the expected patient survival rate in the absence of therapy?
- Which specific genes are dysregulated and are responsible for driving the tumor? How many signaling pathways are involved, either directly or as compensatory or parallel mechanisms? Based on this information, which targeted therapy or targeted therapy combinations will be effective in the patient?
- If the patient becomes resistant to initial therapy, what additional pathways need to be shut down?

If pathologists do not embrace personalized medicine, other fields and various nonpathology biotechnology companies will provide answers to these questions, but they will do so in the absence of morphologic data, ultimately generating information that will be inherently of less value. In a recent article, Thomas Giordano, MD, outlines what he calls personalized predictive pathology and appropriately asks, “Will molecular profiling become part of the routine pathologic assessment of cancers performed by surgical pathologists, or will it become the domain of subspecialty labs, either academic or commercial, with surgical pathologists observing from the sidelines?” 5p402 He adds, “Prediction of therapeutic response by molecular profiling is the logical and natural extension of the work of surgical pathologists.” 5p403

Pathologists are the only professionals in the health care/scientific system that can interpret genomic, gene expression, and proteomic data in the context of tumor morphology. Only the pathologist can comment on the presence, absence, and differential expression of biomarkers in tumor cells versus normal cells, in situ tumors versus invasive tumors, and in different grades and patterns of a tumor present within one sample. Only the pathologist can provide a comprehensive assessment of companion diagnostics and other biomarkers on a per patient, per clone, and per cell basis. The correlation of biomarker data with traditional histomorphologic data adds, “Prediction of therapeutic response by molecular profiling is the logical and natural extension of the work of surgical pathologists.” 5p403

THE NEED FOR NEW TOOLS

Pathologists will certainly require novel tools and technologies to enable this promise. For decades, pathologists have had the ability to correlate the expression of proteins with histomorphologic patterns by using immunohistochemical methods. Recently, because of the advent of light microscopy-based in situ hybridization methods, gene amplification has been added to the brightfield repertoire of the surgical pathologist, allowing pathologists to visualize individual copies of genes and amplification states in the context of morphology. Unlike fluorescence in situ hybridization, these technologies use traditional counterstains and generate high-quality cellular morphology, allowing for distinction between different aspects of the specimen, such as invasive and in situ tumor components. This type of technology is a critical advance for the field of pathology because, for the first time, pathologists are able to generate genomic profiles of patients’ tumors that incorporate histologic pattern information. For example, in a breast cancer case that contains both an invasive ductal and an invasive lobular component, pathologists can use these novel technologies to observe separately the HER2 gene status of the 2 components. Several studies have investigated the frequency and extent of heterogeneity in breast cancer,5-7 and it will be important for pathologists to continue to further this type of work by correlating intratumoral biomarker heterogeneity with differential clinical responses to targeted therapies.

Although the visualization of amplification status in the context of histomorphology represents a major advance in the field of pathology, it is only the first of many types of molecular genomic technologies that pathologists will need to acquire. As we expand our knowledge of the differences between cancer cells and their normal counterparts at the DNA, RNA, and protein levels, it is becoming clear that the characterization of tumors as part of the personalized medicine paradigm will need to occur in a comprehensive manner and will not be possible with single markers or technologies. The evolving picture of personalized medicine for non–small cell lung cancer is a recent example supporting this notion.

To varying degrees, numerous studies have demonstrated the usefulness of epidermal growth factor receptor (EGFR) mutations, copy number/amplification status, and to a lesser extent, protein expression by immunohistochemistry to predict responses to EGFR-specific therapies, such as erlotinib (Tarceva, Genentech, South San Francisco, California and OSI Pharmaceuticals, Melville, New York) and gefitinib (Iressa, AstraZeneca Pharmaceuticals, Wilmington, Delaware), in patients with advanced non–small cell lung cancer.8-10 Although not perfect, these markers can be used to enrich patient cohorts for responders, and in some cases, the clinical responses in patients with metastatic disease have been dramatic. One notable patient subset that is immediately resistant to this approach (ie,
primary resistance) is that of patients harboring mutations in the \textit{KRAS} gene. Activating mutations in this parallel pathway serve to bypass EGFR inhibition and to maintain downstream signaling through growth and proliferation pathways.

Unfortunately, even the group of patients with non–small cell lung cancer who initially respond to EGFR inhibitors inevitably relapse after a period of 2 to 3 years because of drug resistance. The mechanisms underlying this secondary or acquired resistance are being elucidated and are providing insight into the future of personalized medicine and the types of diagnostic and therapeutic approaches that will be necessary to overcome them. One mechanism of acquired resistance in this setting is the emergence of second-site mutations in the \textit{EGFR} gene, such as the T790M point mutation, which renders first-generation EGFR tyrosine-kinase inhibitors less effective competitors for adenosine triphosphate. A second mechanism involves the amplification of the \textit{MET} gene, which along with \textit{ERBB3}/\textit{HER3}, serves to bypass the inhibition of EGFR via the phosphatidylinositol-3-kinase pathway. Finally, a third mechanism of acquired resistance to EGFR tyrosine kinase inhibitors elucidated in A431 cell lines is the activation of the IGF1R pathway via IRS-1.

This example of acquired resistance via multiple mechanisms is being replicated with other targeted therapies in other indications, and suggests that therapeutic strategies incorporating combinations of pathway-specific targeted molecules will be required to overcome the redundancy and parallel nature of aberrant growth signaling in cancer. At the same time, if pathologists are to have a significant role in personalized medicine, they will need to have access to in situ and tissue-based diagnostic tools that span the gamut of genetic derangements in cancer. In addition to protein expression and gene copy number, pathologists may require tools that allow them to visualize point mutations, insertions, deletions, translocations, mRNA expression, methylation, and other epigenetic events, to name a few. The in situ detection of micro-RNAs has already been demonstrated and represents a positive development in the expansion of the pathologist’s tool kit.

In the era of personalized medicine, the practice of pathology will need to undergo some changes to remain aligned with the needs of oncologists and their patients. Traditional histomorphology and morphologic diagnosis will not disappear but, rather, will take on more importance as pathologists expand their ability to comprehensively profile patients’ tumors with next-generation, in situ methods. The pathologist’s role will be to integrate the data from these diverse technologies into a coherent stream of information for patients and clinicians (Figure 1). The pathology report of the future will contain not only diagnostic and prognostic information but also critical predictive information pertaining to which drugs will be effective in a particular patient. An interesting opportunity for pathologists that emerges from these changes is that of direct patient interaction. As the amount and complexity of data that directly affect the care of the patient increasingly falls under the purview of pathologists, patients are more frequently seeking the expertise of pa-

\textbf{Figure 1.} Concept for the role of the pathologist in the era of personalized medicine. Pathologists will integrate traditional histomorphology with data from existing and next-generation molecular assays to provide patients and clinicians with diagnostic, prognostic, and predictive information.
architects to best understand their diagnoses, tumor profiles, and resulting implications for treatment. Rather than infringing on the responsibilities of oncologists, pathologists who take on this patient-facing role can be seen as providing information that is complementary to, and synergistic with, the discussions that oncologists have with patients. Some pathology departments have begun to experiment with making pathologists available to patients a few hours a week for consultations with very positive results. Other pathologists have organized educational programs for cancer patients that focus on the interpretation of their surgical pathology reports.18,19

**IMPLICATIONS FOR PATHOLOGY-TRAINING PROGRAMS**

Pathology-training programs also need to change to ensure that pathology residents and fellows are aware of the developments taking place in personalized medicine. As the links between drugs and diagnostics continue to strengthen, it becomes increasingly important for pathologists to be knowledgeable about, or at least exposed to, developments in clinical oncology, molecular biology, and translational science. Developments in these areas have direct implications for the diagnosis and molecular profiling of cancer and, therefore, for pathology. According to Dr Giordano, “Most pathology training programs are not adequately preparing their trainees in molecular profiling.”5,p403 This deficiency needs to be addressed if we are to ensure that new pathologists are equipped with the skills and knowledge necessary for them to be active participants in the era of personalized medicine. There are existing activities in which pathology residents (and practicing pathologists) can participate to increase their exposure to these topics. Besides attending the annual conferences organized by the United States and Canadian International Academy of Pathology, College of American Pathologists, and International Academy of Pathology, pathology trainees can attend meetings organized by the American Association for Cancer Research and the American Society of Clinical Oncology, where the latest developments in cancer research and translational science are presented and discussed. Also recommended is this Futurescape of Pathology conference, an annual meeting focusing on technical and conceptual innovations that are transforming the field of pathology. Pathology trainees can also follow the latest discoveries and research relevant to personalized medicine by reading journals, such as Science, Nature, New England Journal of Medicine, Journal of Clinical Oncology, and Clinical Cancer Research.

**THE ROLE OF PATHOLOGISTS IN INDUSTRY**

Pathologists have important contributions to make in the practice of personalized medicine, including its key components, oncology therapeutics and companion diagnostics (Figure 2). Anatomic and clinical pathologists are increasingly being hired by pharmaceutical and diagnostic companies because these industries have recognized the importance of having pathologists’ input in the development of oncology drugs and companion diagnostics (Figure 3).

**Pathologists in the Pharmaceutical Industry**

In the pharmaceutical industry, pathologists are finding roles in all phases of drug development, including preclinical research, translational medicine, and clinical drug
development. The most common roles for pathologists are in the areas of research and translational medicine.

Roles in preclinical research are best suited to pathologists who have either an doctor of medicine or doctor of philosophy degree or an interest in basic science work. This work typically involves the use of cell line or xenograft models to evaluate the effectiveness of novel compound candidates, the discovery and evaluation of putative biomarkers, as well as experiments to understand the molecular epidemiology of therapeutic targets and, therefore, potential clinical indications. These roles typically are laboratory-based and include oversight of a laboratory.

Frequently, pathologists will also find roles in translational groups within the pharmaceutical industry. Besides the traditional research and development groups that have always existed at pharmaceutical companies, having a group or groups that work at the interface of research and development has now become standard practice. These groups are given various names, such as Translational Medicine, Experimental Medicine, and Molecular Medicine, and commonly have a pathologist as either a team member or the group leader. The term translational medicine is meant to convey the idea of rapidly translating novel basic science discoveries and scientific knowledge into clinical applications, going quickly from bench to bedside. Pharmaceutical companies now realize that it is no longer acceptable or feasible for basic science researchers to work in isolation from their clinical development colleagues. Generating a compound in the laboratory and “throwing it over the wall” to clinical teams for clinical trials and development is not an approach that will work in the era of targeted therapy and personalized medicine. Instead, research and development must work together from the very beginning of the drug discovery process, and in many pharmaceutical companies, translational medicine groups are bridging this gap. Pathologists who work in these types of groups will typically work with both research scientists and clinical development teams in developing and implementing biomarker strategies for several compounds or across a portfolio of compounds. For example, with early stage (ie, phase 0 or 1) compounds, this may include creating an immunohistochemical assay to measure a phosphorylated protein and to measure pharmacodynamic effects. For a later-stage compound, the objective may be to develop an assay panel that is predictive of drug response (ie, a companion diagnostic). These tasks may include working with in-house colleagues as well as outsourcing work to central laboratories and diagnostic companies.

Pathologists may also assist in writing the clinical trial study protocol or the study laboratory manual, especially for written sections that deal with sample collection and biomarker analysis and scoring. The collection of tissue samples, as a necessary component of biomarker development, is becoming commonplace in both early and late-stage clinical trials. In various clinical trial scenarios, the pathologist contributes critical expertise regarding the histopathologic subclassification of tumors, familiarity with histologic practices, and the feasibility of collecting different types of samples (eg, needle core biopsies vs archival formalin-fixed, paraffin-embedded blocks vs unstained slides). Inadequate, poorly planned or poorly executed sample collection can have a significant effect on the quality and robustness of clinical trial data. The collection of high-quality tissue biopsy samples has proven to be very challenging in large late phase clinical trials. For example, in the phase 3 registration trial for the drug erlotinib (Genentech and OSI Pharmaceuticals), only 44% of patients had usable slides for immunohistochemistry, and only 31% of patients had usable tissue available for sequencing or fluorescence in situ hybridization analysis. 10

Although positions in the clinical development phases of drug development are not typically available to pathologists without prior experience, once a pathologist has worked in one of the aforementioned roles, if interested, he or she may feasibly become a clinical project leader, overseeing the overall development of early or late-stage therapeutic compounds.

Pathologists in the Diagnostic Industry

In the diagnostics industry, pathologists can contribute to the entire life cycle of a diagnostic product, including discovery, development, technical validation, clinical validation, regulatory approval, commercial launch, marketing, sales, and customer support. The specific opportunities available to a pathologist will depend on the focus of the diagnostic company, with the greatest number of opportunities being at those companies that have tissue-based diagnostic products. Specific job titles could include staff pathologist, laboratory medical director, and chief medical officer.

In the discovery phase, a pathologist may be responsible for identifying, evaluating, and prioritizing the medical and scientific value of diagnostic opportunities. The pathologist may also design or participate in experiments to assess various novel or existing technologies or the technical feasibility of a novel assay concept. Pathologists can provide critical input during this phase to ensure that these 2 processes occur in the correct order. That is, new diagnostic products should begin with the identification of a medical value scenario or an area of unmet medical need, which in turn drives the search for appropriate enabling technologies. Reversing this order can lead to inefficiency, loss of focus, and ultimately, regulatory and/or commercial failure.

During the development phase, pathologists can contribute to the verification and validation of assays and diagnostic testing platforms. During this phase, experiments are conducted to ensure that the diagnostic product meets the required technical specifications and customer needs and demonstrates an acceptable level of intrarun, interrun, interinstrument, and interlaboratory reproducibility. The validation phase typically includes external validation studies during which the pathologist may interact with outside pathologists or other physicians who are serving as the primary investigators for these studies.

Pathologists can also play an important role in the regulatory approval of a diagnostic product, contributing to or overseeing the medical affairs process of designing and executing clinical diagnostic trials that will serve as the basis for approval by the US Food and Drug Administration and other regulatory agencies worldwide. In certain situations, pathologists can play a valuable role during and after the launch of the diagnostic product by contributing to the marketing campaign, serving as a consultant and expert to the sales and marketing teams, and meeting with pathologists and other physicians to assess market reaction to a product. Pathologists may also be responsible for initiating and maintaining collaborations with thought leaders to better understand the potential medical value
of assays that are launched as research-use only products or to understand the medical need for new products. This type of role can be attractive to pathologists who want to maintain academic activities, including publishing and presenting data from their collaborations.

CAREERS IN INDUSTRY VERSUS TRADITIONAL PATHOLOGY PRACTICE

Compared with traditional practices in a community, academic, or reference laboratory, the role of a pathologist in either the pharmaceutical or diagnostic industry is different in focus, culture, working environment, and time frames. Rather than conducting macroscopic and microscopic evaluations of individual patient cases, a pathologist in industry contributes to the development of a therapeutic compound, a diagnostic/companion diagnostic assay, or both. Rather than working as an individual in a department, a pathologist in industry generally has a position that requires close collaboration with colleagues in a multidisciplinary team and often in a “matrixed” environment. Rather than being the sole authority figure in a laboratory, pathologists in industry need to become accustomed to working in a collaborative and hierarchical environment in which they will have a direct manager. Instead of completing cases in days or perhaps weeks, pathologists in industry work on projects that typically take months or years to complete, and in some cases, they will work on projects that ultimately do not make it to market. Positions in industry frequently require domestic and international travel, 30% to 40% of the time or more in extreme cases. Financial compensation for pathologists in industry is typically in the form of a base salary, an annual bonus with both company and individual performance multipliers, and an equity component that may include stock or stock options. Physicians typically experience an initial drop in salary when they enter a corporate environment. Rather than working as an individual in a department, a pathologist in industry generally has a position that requires close collaboration with colleagues in a multidisciplinary team and often in a “matrixed” environment. Rather than being the sole authority figure in a laboratory, pathologists in industry need to become accustomed to working in a collaborative and hierarchical environment in which they will have a direct manager. Instead of completing cases in days or perhaps weeks, pathologists in industry work on projects that typically take months or years to complete, and in some cases, they will work on projects that ultimately do not make it to market. Positions in industry frequently require domestic and international travel, 30% to 40% of the time or more in extreme cases. Financial compensation for pathologists in industry is typically in the form of a base salary, an annual bonus with both company and individual performance multipliers, and an equity component that may include stock or stock options. Physicians typically experience an initial drop in salary when they enter a corporate environment; however, the long-term financial potential in industry can exceed that of typical clinical practice environments.20 Although some pathologists may perceive these differences as advantages, others may perceive them as disadvantages. These differences certainly should be considered before a pathologist entertains the idea of a career in industry. Pathologists who have made the transition from clinical practice to a career in industry universally describe a reduction in stress related to the absence of threat of medical malpractice liability.

CONCLUSION

In light of an ongoing revolution in the understanding of cancer and the approaches necessary to treat molecularly defined patient subsets, the field of pathology finds itself at a crossroads. For the field of pathology to remain relevant in an era of personalized medicine, pathologists need to become the providers of personalized-medicine information, delivering critical answers to questions relating not only to diagnosis but also to prognosis and response prediction. By driving the clinical practice of molecular predictive pathology and taking on new roles in pharmaceutical and diagnostics development, pathologists have the opportunity to create and adopt innovative tools that allow the in situ characterization of patient tumors in a comprehensive way that directly informs specific treatment decisions. By embracing these concepts and delivering molecular genomic data in the context of traditional histomorphology, pathologists will play a leadership role in the era of personalized medicine and will directly improve the lives of patients with cancer.

References