

CONFLICT OF INTEREST

The author declared no conflict of interest.

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Educating for Personalized Medicine: A Perspective From Oncology

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The personalized-medicine concept represents the future of oncology medicine. **New genomics technologies will characterize patients biologically in ways that will drive more efficient and effective cancer treatment. Yet the introduction of these technologies is disruptive to current practices in clinical oncology, as well as to current regulatory and reimbursement strategies. The efficient introduction of personalized medicine will require education in addition to behavioral and policy changes by the various involved stakeholders.**

Personalized medicine: premise and promise

The concept of an individualized approach to patient treatment is not new in medicine. Treatment decisions for individual patients have always involved an integration of complex clinicopathological, technical, and socioeconomic considerations, and nowhere is this more important than in treatment decision making for cancer. When the evidence is supporting, oncologists have long been willing to base treatment decisions on laboratory measurements of a patient's tumor, the use of hormonal therapy in women with breast carcinoma being a decades-old example. The more recent premise of truly “personalized medicine,” however, extends much further. **The new**

genomics technology increasingly allows the characterization in detail of the relevant biology of an individual tumor and the patient with that tumor—potentially **before, during, and after** treatment. The clinical meaning of this biological characterization will come most efficiently from the **careful study of patients** while they are being treated with targeted therapeutics in clinical trials. **Tumor classifications will be radically revised to reflect clinically relevant biology; they will be linked more closely with biologically targeted therapeutics use and will therefore inform treatment decisions more effectively.** It is entirely possible that the concept of tumor “classification”—at least for the purposes of treatment decision making—will

evolve into one of tumor “characterization” at the individual patient level.¹

This new concept of personalized oncology medicine affects every stakeholder in the cancer treatment community. **How quickly the new biological information is transformed into better patient care and more efficient health-care delivery will greatly depend on the education of these stakeholders regarding the meaning and the implications of personalized medicine.**

Educating for personalized medicine and overcoming the hurdles to its introduction

The challenges regarding the development and introduction of the new genomic technologies and their potential for improvement of health care have been the focus of a number of recent activities and reports. The US Department of Health and Human Services (DHHS) Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) produced a report in May 2008 entitled “**Realizing the Potential of Pharmacogenomics: Opportunities and Challenges**” (http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_PGx_report.pdf). **This report recognized the many challenges in integrating pharmacogenomic information into the health-care and public health systems and made a series of recommendations related in particular to the education and guidance of the multiple involved parties.** Additionally, the President's Council of Advisors on Science and Technology (PCAST) produced a report, “**Priorities for Personalized Medicine**,” in September 2008 (http://www.ostp.gov/galleries/PCAST/pcast_report_v2.pdf). PCAST gathers advice from the private sector, including the academic community and industry. In its study, PCAST examined eight major policy areas affecting personalized medicine. Recommendations were made only in the areas of technology/tools, regulation, and reimbursement. Particularly with respect to the issues of physician and patient education and economics, the report pointed out that policy recommendations have not been made because personalized-medicine product development is still in early stages.

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Speaking to a principally Canadian audience, Hudson recently called for a transformative approach to how medical research is conducted and translated into improved clinical care.² He described the “waves of translation” in the introduction of this new technology. The first wave was the description of the complex underlying biology—the genes, proteins, and pathways involved. The second wave, which is under way, involves the integration of genomic knowledge into clinical trials and population research, bringing clinical meaning to this new biology. According to Hudson, it will be the activities of the third wave that will determine how quickly and how effectively these changes will be introduced. This third wave entails the necessary health-services research, policy making, adoption by health-care providers of this new technology, education, and communication to health-care providers. In this article, we explore the role of education in the development and implementation of personalized medicine by the various stakeholders in the cancer treatment community.

Patients and patient advocates

Patient advocacy groups and individual malignancy-focused foundations are powerful voices for patient and physician education and can champion the introduction of new diagnostic tests in routine patient care once supporting evidence has been developed. The Multiple Myeloma Research Consortium, for example, has funded a myeloma tissue bank containing clinically annotated samples and supported the conduct of clinical trials that include appropriate biomarker correlates. Web-based resources from these organizations as well as commercial websites such as Medscape can play an important role in both patient and physician education and in providing continually updated information.

Health-care providers

Improving outcomes in clinical practice is the ultimate goal of personalized medicine, and education of health-care providers to ensure that personalized medicine technologies are used appropriately will be essential to the achievement of that goal. As pointed out by the SACGHS report in the context of pharmacogenomics, busy

clinicians, uncertain about the nature and interpretation of these newly developed complex tests, may be slow to adopt them unless they are educated and uncertainty regarding payment for the administration of the tests is minimized.

The use of clinical care guidelines based on objectively assessed levels of evidence, particularly when they are used as a basis for reimbursement decisions, presents real opportunities to combine ongoing clinician education with improved patient care. For example, the National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium serves as a basis for UnitedHealthcare coverage for chemotherapy drugs used in outpatient settings; similarly, the Centers for Medicare and Medicaid Services uses these guidelines as one reference for establishment of coverage policy and coverage decisions regarding treatment. Both guidelines and payer policies affect clinical practice, and, again, Web-based resources represent a mechanism of providing the busy clinician with the most recent information and guidance. The evolution of NCCN guidelines for multiple myeloma and myelodysplastic syndrome, revised with ever greater frequency, exemplify the recent and increasing incorporation of cytogenetic and molecular genetics into clinical care algorithms.

The introduction of this new biology and technology to the characterization and management of patients will also have a major impact on pathologists, affecting every aspect of their practice from tissue collection and storage (the increasing importance of high-quality archiving of fresh-frozen tumor and even viable tumor cell preparations), through the reclassification of tumors, to more therapeutically relevant and biologically based classifications. Furthermore, introduction of the complex diagnostic tests behind personalized oncology medicine carries its own complexities. The business models with respect to the conduct and reimbursement of these highly specialized and increasingly complicated tests, their interpretation, and the translation of these results into patient care are still emerging. Radiologists similarly will also need to adapt to the evolving and increasingly linked diagnostic and therapeutics worlds. The value of functional imaging assess-

ment of tumor response to therapy using techniques such as fluorodeoxyglucose-positron emission tomographic scanning and dynamic magnetic resonance imaging is being assessed formally in clinical trials by the National Institutes of Health Foundation Biomarkers Consortium. In general, however, responsibility for formal evaluation and validation of such new techniques is unclear, and progress has been slow. As one mechanism to accelerate this process, the PCAST has called for establishment of a Personalized Medicine Coordination Office within the DHHS. Involved professional societies can also take an important role in evaluating these new technologies and the education needed for their implementation.

Therapeutics industry: research and development

The concept of more biologically homogeneous patient subsets within classic disease states is well understood by clinical drug developers, who have generally in recent years adopted a biomarker strategy to confirm drug proof of concept, inform dose and schedule selection, and identify responsive patient subsets. Most biomarker studies have been only partially successful, succeeding more often in the first two goals than the last. However, the application of technologies such as gene expression or multiparametric phosphoflow cytometry promises to more accurately match patients with therapy. As these tests are shown to be more accurately predictive, more efficient drug development with smaller, shorter, less expensive, and less ambiguous trials becomes possible.

Marketing organizations within drug companies are sophisticated channels for delivery of public health messages and as such can play important educational roles, championing and communicating the messages and value proposition of a new personalized medicine. The concept of “targeted therapy” has been carefully crafted and delivered by marketing organizations in the context of several new therapeutic drugs over the past few years. Extending these messages to incorporate the concept of biologically characterizing patients to ensure suitability for particular therapeutic approaches is therefore a natural extension.

Diagnostics industry

The diagnostics industry has had little regulatory or financial incentive to develop the kinds of complex high-clinical-value tests that we now anticipate with the personalized-medicine era. The advent of commercially successful complex tests that provide useful prognostic information, such as the **OncotypeDX (Genomic Health)** or **MammaPrint (Agendia)** gene expression prognostic tests in adjuvant therapy for breast carcinoma, has changed the picture somewhat. However, there remains considerable regulatory and reimbursement uncertainty concerning the levels of clinical validity and utility evidence expected.³ As the US Food and Drug Administration (FDA) increasingly exerts its authority to regulate these tests, and higher levels of evidence are required, the diagnostics industry will need to improve its evidence development, including partnering with therapeutics development companies in the development of companion diagnostics.

Payers

Payers increasingly influence the style of medicine practiced, and reimbursement patterns will be important drivers or constraints on the development of more complex diagnostic tests. As therapeutic agents become more biologically targeted and as diagnostic tests become more determinative relative to the use of therapeutic agents, the challenges for payers increase. As noted previously, payers are increasingly depending on clinical care guidelines such as those of the NCCN (<http://www.nccn.org>). Data on cost-effectiveness of the new complex tests are limited, often slowing adoption of testing.⁴ However, the potential benefits to payers are great, because expensive therapeutics will be used only in patients most likely to respond, with both patients and providers benefiting.

Current reimbursement for complex diagnostic tests is neither rational nor promoting of the development of the new generation of complex diagnostic tests. Progress in the science of personalized medicine has preceded recognition of the economic value, and it is generally recognized that current coverage and payment policies for these complex and expensive-to-develop tests are inadequate. Labora-

tory-based *in vitro* diagnostic tests have traditionally been treated as commodities with low and ever-decreasing reimbursement. The intense focus in reimbursement schema on analogy to existing tests and on cost as a basis for pricing has led to a situation in which “there is little reward for creating additional value and hence little incentive to create the evidence to support value creation.”⁵

Clearly, the current reimbursement systems provide no incentive for innovation, and therefore payer education is also essential to communicate the value of complex, clinically important, potentially high-value tests supported by strong clinical and health economic data.

Regulators

Regulators can both contribute to and benefit from a better match between defined individual-patient tumor biology and relevant therapeutics, which is the goal of personalized medicine. The FDA has recognized this fact with its Critical Path Initiative, which seeks to bring greater benefit to the drug development process through application of the new biological technology, and its guidance issued 19 June 2007, “Pharmacogenetic Tests and Genetic Tests for Heritable Markers” (<http://www.fda.gov/cdrh/oivd/guidance/1549.html>).

The FDA can also influence the drug industry to better characterize patient-responder phenotypes in drug development programs; examples include the testing for HER2/neu expression in breast carcinoma and *KRAS* mutation assessment for predicting responsiveness to epidermal growth factor receptor inhibitors in colorectal cancer (FDA, Oncologic Drugs Advisory Committee Meeting, 16 December 2008; <http://www.fda.gov/ohrms/dockets/AC/cder08.html>). As noted, the FDA, through its proposed “In Vitro Diagnostic Multivariate Index Assays” guidance (<http://www.fda.gov/cdrh/oivd/guidance/1610.pdf>), is moving to exert greater regulatory authority over the development and commercialization of personalized-medicine tests, and is therefore a powerful force in driving acceptance and behavior of these concepts and practices in the therapeutics community.

Summary

The personalized-medicine concept represents the future of medicine, the natural outcome of new pathophysiological insight into disease mechanisms and the need to match use of biologically targeted therapeutics with appropriately biologically characterized patients. In oncology, new genomics technologies are characterizing patients biologically, driving more effective cancer treatment and more efficient cancer drug development. The introduction of these technologies is disruptive to current practices in clinical oncology, as well as to current regulatory and reimbursement strategies. The efficient introduction of personalized medicine in oncology and any other field of medicine will require education as well as behavioral and policy changes of the various involved stakeholders. Among others, groups such as the **Personalized Medicine Coalition** (<http://www.personalizedmedicinecoalition.org>)—which describes itself as “representing a broad spectrum of academic, industrial, patient, provider, and payer communities” and seeking to “advance the understanding and adoption of personalized medicine concepts and products for the benefit of patients”—are fostering a multidisciplinary approach to educating for the personalized-medicine era in oncology and other disease areas.

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Both authors are employees of Nodality, a company dedicated to developing personalized medicine.

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