Molecular Diagnostics

AT THE NEXUS OF INDIVIDUALIZED MEDICINE, HEALTH CARE DELIVERY, AND PUBLIC POLICY

SCOTT A. WALDMAN, MD, PhD, AND ANDRE TERZIC, MD, PhD

Advances in decoding integrated biological processes; the surge in enabling technologies including the high-throughput platforms of genomics, proteomics, and metabolomics; and the emergent revolution in targeted drug discovery and development of companion diagnostics place the clinical enterprise on the threshold of individualizing disease management.

This innovation in health care is predicated on molecular biomarkers enabling disease prediction and prevention, diagnosis, and treatment of individual patients and populations. Biomarkers are quantifiable disease characteristics that yield information about pathophysiological processes to detect disease progression or predict therapeutic response. Traditional biomarkers include surrogate physiological measurements (heart rate, blood pressure, performance status), images (chest X-ray, mammograms), and individual protein molecules (prostate-specific antigen [PSA], carcino-embryonic Antigen [CEA]). A new generation of molecular marker technologies, including single nucleotide polymorphism (SNP) analysis, genomic and proteomic profiling, epigenetic profiling, and gene expression profiling have the potential to increase disease-specific sensitivity and specificity to ensure the accuracy necessary for individualized disease management.

This molecular revolution has stimulated a new generation of biotechnology to harness the application of biomarkers to individualized and population medicine. However, the potential of biomarker technology has yet to be fully realized, reflecting asynchronous development of discovery technologies and paradigms for their validation, early adoption, and broad application. The paucity in biomarker validation has engendered issues surrounding approval and marketing by regulatory agencies. This evolution in regulation, the emergence of requirements for robust analytic validation and clinical qualification, and the attendant patient- and capital-intensive resources required have produced substantial barriers to realizing the full potential of biomarkers in clinical practice.

Application in Personalized Patient Management

Individualization of disease management is predicated on biomarkers that subserve specific clinical domains. Preventive biomarkers prospectively identify individuals at increased risk for developing disease. Diagnostic biomarkers identify disease at the earliest stage, before clinical manifestation. Prognostic biomarkers stratify risk of disease progression in patients undergoing definitive therapy. Predictive biomarkers identify patients who are most likely to respond to a specific therapy. Therapeutic biomarkers provide a quantifiable measure of response to therapy in patients undergoing treatment. Finally, biomarkers identify patients at risk for developing adverse reactions to specific therapeutics.

Translation of Technological Advances

The development of analytic technologies for evaluating nucleic acids and proteins, in conjunction with the elaboration of the human genome, has provided the technological impetus to develop molecular biomarkers for disease management. In contrast, conceptual advances in elucidating the molecular mechanisms underlying pathogenesis have yielded a plethora of targets with expanding complexity to satisfy clinical needs for individualization of medical management, providing the associated “pull” for biomarker development. Initially, molecular markers evolved in the model of classical protein and genetic markers as single elements related to the presence of disease. Their clinical application was potentiated by the development of rapid nucleic acid sequencing technology coupled with mutation-specific polymerase chain reaction for high-throughput analyses. These linear initial approaches have dramatically evolved to capture systems-level alterations underlying pathophysiology. Panels of genetic markers and their disease-specific mutations are cataloged and their cumulative prognostic or predictive value established. Beyond panels of individual genes, the entire transcriptome can be assessed, distinguishing diseased and normal tissues with different risk profiles, to develop patterns of gene expression with prognostic and predictive value. Similar approaches are being examined with patterns of disease-specific SNPs and epigenetic changes associated with DNA methylation. Most recently, profiling the serum proteome using mass spectrometry has been employed to distinguish patients with cancer from those without.

The Unmet Promise of Molecular Markers

Although molecular markers represent the envisioned future for individualized medicine, their potential has yet to be realized, reflecting issues of technique, study design, and pathophysiology. The technologies producing these markers have been prolific as discovery engines but have not been systematically transitioned to generate robust assay performance consistent with requirements for routine clinical laboratories in the form of analytic validation, and defined disease-management value in the form of clinical qualification. It is not unusual for biomarkers to be assessed with the use of home-brew assays in individual laboratories that have not undergone rigorous analytic validation to define performance metrics, including reproducibility.
sensitivity, and precision. In addition, molecular analytes may be evaluated employing different technical platforms whose performances have not been cross-validated. This absence of assay performance standards reflecting rigorous analytic validation and standardization across laboratories and platforms underlies issues of irreproducibility. Additionally, quantitative and qualitative relationships between analytes and disease management have not undergone rigorous clinical qualification, and the evidence linking a biomarker with biology and clinical endpoints may not be readily available. These relationships describing the clinical utility of the marker should be assessed in appropriately designed and powered prospective blinded and randomized clinical trials and subsequently validated in follow-up trials.

The Business of Molecular Markers

Biomarkers can influence the clinical decision making that profoundly affects health care economics. Screening for genetic mutations identifies patients at risk for developing breast or colon cancer; those patients then become new customers to the health care system. Prognostic tests to define the risk of recurrence in breast cancer identify patients who may not benefit from expensive chemotherapy. Predictive tests that examine the over-expression of Her2 receptors in breast tumors identify patients who will respond to expensive monoclonal antibody therapy directed to that target. The impact on clinical outcomes and the associated allocation of limited health care dollars have been used to justify profit margins for molecular diagnostics, comparable with those traditionally reserved for therapeutics. Their emergence as high-profit products has spurred biotechnology entrepreneurs and venture capitalists to launch new companies focused on developing biomarkers across the disease spectrum. Success depends on whether their products address substantial markets and direct clinical decision making regarding expensive, complex, or dangerous therapeutic interventions. At stake is a $5 billion market growing at 25% annually.

Historically, the developmental paradigm for biomarkers was to obtain approval for marketing of test kits by the Food and Drug Administration (FDA) that would then be sold to local clinical laboratories. Now, molecular tests forego FDA approval and implementation in local laboratories and, rather, are run in central laboratories. Offering diagnostic tests from a central laboratory, obviating the need for FDA approval, permits shorter and less expensive development timelines. However, these developmental efficiencies are associated with a reciprocal absence of definitive studies analytically validating and clinically qualifying the biomarker, which are mandated by the FDA for marketing approval. It is precisely this failure to provide clinical validation of biomarker value, analogous to safety and efficacy requirements by the FDA for marketing drugs, which contributes to lagging integration of molecular markers into patient management.

Regulation of Diagnostic Testing

Although molecular biomarkers have emerged as key indices for disease management, oversight and regulation of their safety and validity has not kept pace. Today, more than 1000 biomarkers are marketed as diagnostic tests, most offered as home-brew tests in central laboratories. The FDA does not regulate the conduct of diagnostic tests, their analytic validity, or their clinical qualification. Rather, validity, utility, and clinical interpretation of tests are relegated to individual laboratories. In 1988, Congress enacted the Clinical Laboratory Improvement Amendments (CLIA) to certify laboratories testing human specimens and reporting patient results. Under CLIA provisions, laboratories must adhere to requirements for quality control, personnel training, and validation procedures. Moreover, laboratories performing high-complexity testing must enroll in proficiency testing programs related to the quality of testing services offered. Of significance, there are no specific program or specific quality control, personnel qualification, or proficiency testing requirements for molecular testing. Indeed, the Centers for Medicare and Medicaid Services (CMS), within the Department of Health and Human Services, is responsible for the quality of CLIA-approved laboratories. It is significant that one third of CLIA-certified laboratories performing genetic testing fail to participate in proficiency testing. In that context, the inverse relationship between errors in diagnostic analyses and proficiency testing suggest that the current regulatory position may be some cause for concern.

The FDA has not had a consistent position regarding jurisdiction over molecular and genetic tests. Indeed, it has authority to regulate them but has exercised enforcement discretion. In 2006, the FDA issued a draft guidance extending regulatory enforcement authority to a subset of home-brew molecular tests termed in vitro diagnostic multivariate index assays (IVDMIA). Multivariate index assays measure multiple analytes and analyze data with algorithms or software programs. The agency targeted IVDMIA for regulation because the algorithms often are proprietary, making it difficult for physicians to interpret results. Most IVDMIA will require some level of FDA review, and some will require full regulatory approval before they enter the marketplace. Beyond IVDMIA, the FDA has not developed an overarching position regarding oversight of home-brew assays as a class.

Conclusion

Molecular markers offer a clear path from the current empirical, probabilistic model of clinical care to the development and implementation of preemptive, deterministic personalized medicine. However, their evolution into clinical practice is predicated on the development of strict paradigms focused on analytic validation and clinical qualification. In that regard, biomarker development and clinical application should have an established basis of preclinical and clinical evidence, reflecting clinical trial design, analytical methodologies, and statistical rigor. Moreover, there may be benefits in centralizing federal regulatory oversight of approval, marketing, and quality control.
in application in the FDA and/or CMS. Efforts should focus on collaborations across public and private sectors to facilitate the discovery and application of biomarkers that will support the development of new molecularly-targeted therapeutics to achieve a truly individualized approach to patient care.\textsuperscript{4,7,17-19}

Acknowledgements

Dr. Waldman is the Samuel M.V. Hamilton Endowed Professor of Thomas Jefferson University. Dr. Terzic is the Marriott Family Professor of Cardiovascular Research of the Mayo Clinic.

REFERENCES

1. Cortese DA. A vision of individualized medicine in the context of global health. Clin Pharmacol Ther. 2007; 82:491–495.
2. Waldman SA, Terzic A. Individualized medicine and the imperative of global health. Clin Pharmacol Ther. 2007; 82:479–483.
3. Waldman SA, Terzic MR, Terzic A. Molecular medicine hones therapeutic arts to science. Clin Pharmacol Ther. 2007; 82:545–547.
4. Buckman S, Huang SM, Murphy S. Medical product development and regulatory science for the 21st century: the critical path vision and its impact on health care. Clin Pharmacol Ther. 2007; 81:141–144.
5. Piquette-Miller M, Grant DM. The art and science of personalized medicine. Clin Pharmacol Ther. 2007; 81:311–315.
6. Waldman SA, Terzic A. Therapeutic targeting: a crucible for individualized medicine. Clin Pharmacol Ther. 2008; 83:651–654.
7. Wagner J, Williams S, Webster C. Biomarkers and surrogate endpoints for development and regulatory evaluation of new drugs. Clin Pharmacol Ther. 2007; 81:104–107.
8. Licking EF, Longman R. The new diagnostics companies. Start-Up. 2006; March:12–19.
9. Dupuy A, Simon RM. Critical review of published microarray studies for cancer outcome and guidelines on statistical analysis and reporting. J Natl Cancer Inst. 2007; 99:147-157.
10. Simon R A check list for evaluating reports of expression profiling for treatment selection. Clin Adv Hematol Oncol. 2006; 4:219–224.
11. Hudson KL. Genetic testing oversight. Science. 2006; 313:1853.
12. Hudson KL, Murphy JA, Kaufman DJ, Jassat GH, Kattanis SH, Scott J. Oversight of US genetic testing laboratories. Nat Biotechnol. 2006; 24:1083–1085.
13. Dalton WS, Friend SH. Cancer biomarkers—an invitation to the table. Science. 2006; 312:1165–1168.
14. Jadon SY. Emerging molecular markers of cancer. Nat Rev Cancer. 2002; 2:210–219.
15. Petricoin EF, Ardekani AM, Hitt BA, Levine PJ, Fusaro VA, Steinberg SM, Mills GB, Simone C, Fishman DA, Kohn EC, Liotta LA. Use of proteomic patterns in serum to identify ovarian cancer. Lancet. 2002; 359:597–577.
16. Wilson JF. The rocky road to useful cancer biomarkers. Ann Intern Med. 2006; 144:945–948.
17. Williams SA, Slavin DE, Wagner JA, Webster CJ. A cost-effectiveness approach to the qualification and acceptance of biomarkers. Nat Rev Drug Discov. 2006; 5:997–1002.
18. Woodcock J. Molecular medicine: how, what, and when? Clin Pharmacol Ther. 2007; 82:376–378.
19. Woodcock J. The prospects for “personalized medicine” in drug development and drug therapy. Clin Pharmacol Ther. 2007; 81:164–169.
20. Mathis ET, Bredley KJ, Oehmig CM. A clinician’s guide to hereditary colon cancer. Cancer J. 2004; 10:280–287.
21. Meijers-Heijboer H, van Geel B, van Putten WL, Henzen-Logmans SC, Seynaeve C, Menko-Fluytman MB, Bartels CC, Verhoog CC, van den Ouweland AM, Niemeijer MR, Berekelsma CT, Klijn JG. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2001; 345:159–164.
22. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher EB, Wickerham DL, Bryant J, Wolmark N. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med. 2004; 351:2817–2826.
23. FDA. Draft guidance for industry, clinical laboratories, and FDA staff: In vitro diagnostic multivariate index assays. Available at: www.fda.gov/cder/cydex/guidance/1610.pdf. Accessed August 28, 2008.

EDITORIAL continued from pg. 1

faced with difficult times, and it becomes critical for all of the members of the clinical and translational medicine community to work collaboratively to educate our representatives and leaders regarding the important role that translational medicine can play in improving the health of our population while at the same time reducing health care costs. Such an effort requires collaboration and organization across the many diverse stakeholders in the field of translational medicine as well as financial support. These stakeholders include basic scientists, clinical investigators, health policy analysts, health economists, epidemiologists, community practitioners, private insurers, governmental regulatory agencies, members of the pharmaceutical and device industry, representatives of the research supply industry, and academic leaders. At present, our community does not have a central organization around which it can focus its collaborative efforts.

This journal was begun with the recognition that the community of investigators and scholars who were interested in the broad and diverse elements of clinical and translational science needed a platform on which they could communicate with each other and share new ideas and discoveries. However, a journal can only go so far in linking the members of a community and cannot provide a platform for the public relations, lobbying, and scientific exchange that come about from the formation of a society or association. Over the past half century, we have seen societies begin and grow as new fields of scientific or clinical interest have evolved. The growth of some societies has led to the creation of national meetings at which scholars can exchange and critique new information. In other cases, societies have grown to support both the financial and clinical missions of groups of specialists or subspecialists by lobbying federal regulatory agencies for higher reimbursements for clinical services and lobbying Congress for higher allocations to federal health insurance agencies, including Medicare and Medicaid. Because of its breadth and diversity, the translational medicine community needs a society that can effectively serve multiple needs and be representative of the many interests of its stakeholders. It must be able to work collaboratively with existing societies to support their efforts in lobbying Congress for additional research funds and the need to support personalized medicine. Just as the country has reached a time when there is a need for “change,” the community of clinical and translational scientists must come together to organize themselves to enhance the education of the next generation of translational scientists, provide a forum for discussion of common challenges and provide a voice to advocate for infrastructure support and for the inclusion of our community in public policy analysis.