

Guest Editorial

The Association for Molecular Pathology's Approach to Supporting a Global Agenda to Embrace Personalized Genomic Medicine

Personalized genomic medicine will play an important role in future medical practice; today, however, it is still surrounded by uncertainty. The call to action for a national agenda for the future of Pathology in personalized medicine from the October 13–15 2010 meeting at the Banbury Conference Center, proceedings of which are being published this month in the *American Journal of Clinical Pathology*,¹ is a wake up call to pathologists and laboratory medicine practitioners. Whole genome analysis (WGA) testing, as well as variations such as whole exome and whole transcriptome analysis, broaden the scope of questions that can be asked in the clinical laboratory beyond traditional personalized medicine, enabling the adoption of personalized genomic medicine. Molecular pathologists and diagnosticians should be—and indeed have been since the dawn of molecular diagnostics three decades ago—at the forefront of embracing new technologies and the analytical opportunities that result. We have a responsibility to lead our colleagues in embracing this new era of genomic medicine or the discipline of Pathology may be left behind.

Adoption of New Technologies

When a new technology with the potential to revolutionize medical practice is widely used in the research setting, its translation into clinical care may engender intense competition among specialties for ownership. This issue is not new. Analogous to the recent Banbury meeting, a group of approximately 50 pathologists gathered in Bethesda, MD, in 1992. Their charge was to discuss the future of Molecular Pathology (ie, the application of novel molecular biology methods to the practice of medicine). The Bethesda meeting led to the establishment of the Association for Molecular Pathology (AMP) in 1995, the development of Molecular Genetic Pathology fellowship training programs accredited by the Accreditation Council for Graduate Medical Education, and the jointly administered specialty certification in Molecular Genetic Pathology by

the American Board of Pathology (ABP) and the American Board of Medical Genetics. In 1992, we faced many of the same issues discussed at the Banbury Conference Center in 2010: lack of expertise among practicing pathologists and laboratory medicine practitioners, an absence of quality standards for testing, uncertainty of regulatory oversight for testing, non-existent billing codes, and incomplete knowledge about many gene mutations identified by molecular tests.

The movement toward personalized genomic medicine is real and inevitable. The model human genome sequence was completed more than 10 years ago. Extraordinary and nearly continuous improvements in sequencing technologies are yielding faster and cheaper sequence information. These developments have brought us to the point where we are already sequencing the genomes of individuals and finding interesting and, at times, medically useful information. As the <\$1000 genome becomes a reality in the next two to five years, the number of individuals undergoing WGA will rapidly increase. As practitioners dedicated to laboratory and tissue-based diagnosis, pathologists and other clinical laboratorians will be leaders in the adoption of personalized genomic medicine. These practitioners will play central roles in setting quality standards for clinical WGA testing, performing clinical WGA tests, interpreting test results, effectively reporting and communicating the clinical significance of results to treating health care providers and to patients, and providing long-term specimen and/or data archiving. Moreover, pathologists and clinical laboratory practitioners will be the drivers for incorporating translational genomic research findings into clinical practice, as we have done and continue to do for single gene and disease-specific gene-panel testing in molecular pathology today.

The Banbury Conference Center Report

The specific proposed action list developed at the 2010 Banbury Conference Center articulates many of

the issues that must be addressed before Pathology can move the practice of personalized genomic medicine into reality. Most pathologists and clinical laboratory practitioners need additional education in genomics. Targeting current Pathology trainees is an obvious and necessary approach; however, education is also critical for other health care professionals to enable them to interpret and understand the clinical significance of WGA test results. Current multigene panels will provide excellent initial experience in the application of WGA technology as laboratories transition testing to WGA platforms. Establishment of effective and appropriate regulatory and reimbursement policies, including quality standards and billing codes, will encourage movement of WGA from research to clinical settings and will be essential for its widespread clinical use. One of the most challenging projects outlined in the Banbury Conference Center report¹ is the development of a clinical grade variant database. This effort not only requires the cooperation and consensus of many medical specialty groups, but it also demands the creation of novel, clinically efficient interfaces to aid pathologists and clinical laboratory practitioners in the interpretation of WGA results as well as the capability for continual curation and updating of information as our understanding of human genome variants grows.

The Banbury Conference Center report¹ drives home the need for Pathology to embrace personalized genomic medicine and outlines specific steps toward achieving that goal. We would extend the term Pathology to include not only ABP-certified pathologists but also other specialists engaged in molecular diagnostics (eg, from such diverse disciplines as genetics, clinical chemistry/microbiology/immunology, and bioinformatics, to name a few) to comprise the full breadth of laboratorians and practitioners engaged in WGA testing. It is also important to recognize that personalized genomic medicine is an issue for the entire field of medicine. The human genome carries information that will impact every medical specialty. While Pathology must embrace WGA testing and interpretation, every medical specialty must understand the implications of genomic variants for the care of their patients. The education and training of today's practicing physicians includes little preparation on the human genome and the clinical significance of genomic variation to health and health care. The medical community now has the task of integrating this new domain into medical practice, but Pathology cannot accomplish this alone. Partnerships across multiple specialties will be essential for the care of individual patients because the results of a single patient's WGA will hold significance for multiple medical disciplines. Paradoxically, Pathology and Laboratory Medicine can only assume and maintain leadership in personalized genomic medicine by partnering across the whole of medicine to reap the full benefit of this promising future.

Cautions for the Future

Although the eventual application of WGA for clinical care is inevitable, the details and paths to their resolution are unclear. As sequencing technology becomes faster and less expensive and with higher density of coverage of the genome, it is not clear whether storage of sequence data for reinterpretation will be more costly than repeating WGA, emphasizing the pivotal role of bioinformatics in genomic medicine. Moreover, with an estimated one quarter of human genes covered by one or more patents, the impact of gene patents on molecular pathology practice and the complexities of related licensing and infringement issues are exponentially amplified when patients' entire genome sequences are considered. For more information on this topic, see AMP's position statement on gene patents, available at http://www.amp.org/publications_resources/position_statements_letters/Gov/GenePatentPositionStatement_Final_Nov2008.pdf. Failure to resolve the patentability of human gene sequences and variant-phenotype associations in a medically responsible way risks the imposition of an insurmountable barrier to the implementation of WGA.

Furthermore, the limited availability of genetic counseling resources must be considered. An increased number of variants will be identified, a significant proportion of which are likely to be familial or private variations of uncertain clinical significance. The inability to ascertain and to provide meaningful cumulative risk estimates for carrier or affected disease status following WGA or whole exome analysis will pose particular problems. Therefore, in addition to clinically validated standardized databases, interpretive algorithms that consider variables such as age of disease onset, penetrance, presence of pseudogenes, and likelihood of phenocopies of the disease being evaluated must be developed to facilitate accurate interpretation and patient counseling.

Finally, in addition to physician and health care provider education, public education will be key to empowering broad interest and participation in personalized genomic medicine by patients and their families. Hand-in-hand with public education come the ethical issues raised by the ability to sequence an individual's genome and potentially to predict medical risks as well as other personal characteristics. These issues deserve, if not require, a public engagement process to increase awareness and understanding as well as to facilitate recognition and design of public policies to prevent unanticipated negative side effects. Attention to these and other issues that will certainly arise as we move forward will be essential to our success and the realization of this bright future.

AMP Position

AMP stands alongside other organizations and stakeholders in supporting an agenda to promote this new

era of personalized genomic medicine. As a premier group of molecular diagnostics experts, we will spearhead initiatives that ensure both a leading role for Pathology and engagement of all health care providers. As evidence of this, AMP formed the Whole Genome Analysis Working Group in June 2010 to respond to the health care and biomedical research communities and to provide education and practical guidelines for the application of WGA to personalized genomic medicine. AMP position statements on various topics can be found at http://www.amp.org/publications_resources/position_statements_letters/index.cfm. The ultimate objectives of personalized genomic medicine are better patient outcomes and healthier lives for everyone. This is a global enterprise, and, as an organization

with members from more than 30 countries, AMP pledges to stress these goals and to continue to develop and influence this exciting transition to personalized genomic medicine.

AMP Whole Genome Analysis Working Group

Reference

1. Tonellato PJ, Crawford JM, Boguski MS, Saffitz JE: A national agenda for the future of pathology in personalized medicine: report of the proceedings of a meeting at the Banbury Conference Center: genome-era pathology, precision diagnostics and pre-emptive care: a stakeholder summit. *Am J Clin Pathol* 2011, 135:668–672

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*The following individuals disclosed relevant financial relationships: P.C. is employed by and owns stock in Illumina, Inc.; M.F. is employed by and owns stock in Life Technologies/Applied Biosystems; T.H. is employed by Illumina, Inc.; E.L. receives consulting fees from Novartis and Canon; N.N. is employed by Esoterix Genetic Laboratories, LLC, successor to Genzyme Genetics[†]; V.P. is employed by and owns stock in Quest Diagnostics.

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