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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

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Overview

In October 2010, representatives and thought leaders from major national pathology organizations and a diverse group of other stakeholders gathered at the Banbury Conference Center in Lloyd Harbor, New York to examine opportunities and challenges facing the discipline of pathology and its future role in the rapidly developing field of personalized medicine. A major focus of the meeting was assessment of the potential impact of next generation sequencing (NGS) and whole genome analysis (WGA)[1] in medicine and, specifically, in clinical laboratory practice. The clearly articulated goal of the pathologists in attendance was to develop a national strategy to ensure that the performance, interpretation and regulation of genome-based clinical testing come directly under the purview of pathologists and their national organizations.

In devising a strategy to guide the development of “Genome Era” pathology, three fundamental themes emerged from the discussions:

1. A lifetime of genomic information

NGS is a ‘disruptive’ technology capable of catalyzing fundamental changes in medical care. It is increasingly plausible to anticipate that healthy individuals, including newborns, will have their genomes sequenced as the foundation of personalized programs of life-long health promotion, disease prevention, and when necessary, disease management. This

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paradigm shift in clinical laboratory testing presents the discipline of pathology with an unprecedented opportunity to reinvent itself as a *primary care discipline*. At the least, pathologists have the opportunity to provide expert support to every physician – primary care or otherwise – who care for individuals whose genomic information is known. There is also an opportunity for pathologists to be curators of genomic information over the course of each individual's lifetime, providing up-to-date interpretations of genomic information in the context of intercurrent health events and needs.

2. Pathology scope-of-practice

Pathologists have no "birth-right" to this technology and area of testing. We are witnessing significant challenges to our traditional role as laboratory physicians from other medical disciplines and private interests outside the usual boundaries of clinical medicine. To establish pathology's primary place in genome-era medicine, we must *acquire and demonstrate expertise* in this rapidly evolving era of personalized and patient-centered health care. At the outset, there is desperate need for organized, coordinated programs of training and education in genomic medicine in all ACGME-accredited pathology residency training programs and for established practicing pathologists. We must also ensure that regulation and oversight of genome-based laboratory testing fall under the jurisdiction of pathologists and their national accreditation organizations.

3. Demonstration of value

Adequate reimbursement for genome-based diagnostic testing in personalized medicine requires a *clear demonstration of value*. Pathologists must take the lead in proving that genome-based clinical laboratory testing can be cost-effective by truly optimizing evidence-based precision diagnostics, and thereby reducing the propensity for mistakes based on "trial-and-error" clinical management of patients requiring expensive health care resources. Put differently, we must actually demonstrate that the involvement of pathologists in the delivery of medical care informed by genomic information improves patient health outcomes, and is a more cost-effective way of delivering personalized healthcare than current practices that depend on testing for individual molecular deviations.

At Banbury, we began to address these overarching themes by proposing a set of highly targeted pilot projects to test WGA technology in a controlled setting, gather evidence to shape the evolution of pathology practice, and identify and address the key barriers to the wide spread use of genetic sequencing in routine pathology practice. This report summarizes the conclusions of the meeting and presents a 'Call to Action' designed to change the nature and practice of pathology in the genome era.

Background

Historically, the discipline of pathology has played a central role in the detection, classification and interpretation of cellular, biochemical, molecular and microbiological markers of disease to guide physicians in the care and management of patients. There has always been a rich tradition of investigation in pathology and we have contributed importantly to the use of high-throughput genome-wide technologies in scientific

discoveries. We have also played a leading role in clinical molecular diagnostics and genetic testing.[2,3] We have not, however, responded in an organized, concerted effort to claim ownership of the most recent wave of technological innovation in genome sequencing, particularly as it applies to deployment in clinical laboratory testing. Indeed, no single discipline in medicine has yet positioned itself at a national level to lead in the rapidly developing area of personalized medicine and genomics testing. At the present time, clinical genetic testing is fragmented among various specialties (pathology, clinical genetics, oncology, others) which, in general, provide laboratory testing of one or only a few risk alleles for the disease of interest. In some cases, such molecular testing is offered by private concerns that hold patent rights to certain genetic tests. In other cases, private, non-hospital based, CLIA-certified laboratories have begun to offer genetic testing that bypasses the traditional involvement of pathologists and, potentially, any physicians (via direct-to-consumer marketing and testing).[4,5]

Regardless of the route by which molecular testing may be delivered, Banbury Conference participants believe that the current model of limited “one-off” genetic testing will not survive. The patenting of gene sequences has come under intense scrutiny recently by the US Patent Office[6] and the entire landscape of genomic testing is changing rapidly. It seems inevitable that the current model will be supplanted by the advent of NGS and WGA at costs that will significantly undercut current charges for single gene testing.[7] In the near future, we anticipate that the entire genome will be sequenced, and a variety of validated soft-ware “filters” will then be used to glean clinically relevant information from the panoply of genetic variations that will inevitably be identified. There is no current paradigm for *who* will then interpret such filtered genomic information in ways that are useful to clinical physicians.

Primary Care Pathology

Traditionally, the discipline of pathology has acted in a passive or reactive mode. With few exceptions, laboratory testing and interpretation is initiated through the treating physician, and the pathologist does not engage in the selection of laboratory tests or in patient management decisions that inevitably follow upon obtaining test results. Moreover, we have generally not participated in efforts to practice preventive medicine, despite the fact that laboratory tests constitute one of the fundamental readouts in screening for chronic diseases or cancer. Rather, we rely on our clinical colleagues to send us specimens from patients who have come to medical attention for a specific problem; then, and only then, do we act to perform a test and prepare a report.

With the advent of NGS and WGA, the pathology community has a golden opportunity to seize the initiative and capture the value of low cost, high-throughput genome technologies to produce and use genetic data and information in precision diagnosis and individualized predictive care. This initiative changes the clinical paradigm from reaction to prevention. The very concept of the *primary care pathologist* may cause concern among some practitioners in the field but we must recognize the coming promise of personalized medicine and the dramatic implications that WGA will have for the proactive preservation

of health rather than the reactive analysis of disease. The meeting at the Banbury Center raised the possibility of this bold new role for pathologists in the future.

Meeting Agenda and Action Items

The Banbury Conference on “Genome-Era Pathology” brought together representatives from major national pathology organizations (Table 1). We were joined by other major stakeholders in genomics including the Director of the National Human Genome Research Institute of NIH, leaders in personalized medicine initiatives in the Office of the US Air Force Surgeon General, leaders of the Personalized Medicine Coalition, the president-elect of the American Society for Human Genetics, leading figures in the biotechnology industry, and representatives from health insurance and health benefits management organizations. The meeting brought the major pathology organizations together to seriously consider planning for the dramatic changes in our future and to take an affirmative stand to work together to ensure we maintain a leading position. We also sought to inform these pathology community representatives of the diverse perspectives held by other stakeholders from government, the military, personalized medicine advocacy groups and representatives of the technology and health insurance industries.

Two inescapable conclusions emerged. First, if we are to succeed in this bold initiative, the various pathology organizations cannot afford to engage in internecine struggles over jurisdiction. Second, technological advances are moving very rapidly and we must prepare now to meet the coming change. As pathologists, we have many potential allies, but we have no inalienable claim to the future of genomic testing and we must earn the right to participate and be rewarded for our efforts. Establishing our place in genome-era medicine will require the cooperation and interaction of a diverse set of stakeholders. Moreover, to the extent that access to personal genomic information may become more routine, rather than the purview of a privileged few, there will be a great need for teamwork across the medical community. In this context, we engaged our colleagues in pathology and other disciplines to identify six action themes for future efforts (Table 2).

A Call to Action: “Blue Dot” Projects to Ensure the Future of Pathology

The pace of advancement in NGS technologies and WGA was brought into sharp focus in an insightful presentation by Eric Green, MD, PhD, Director of the National Human Genome Research Institute at NIH. Dr. Green, a pathologist by training, presented his vision of the impact of genomics in medicine over the next 10 years and beyond with a “density plot” of hypothetical genomic accomplishments (each represented by a blue dot on the density plot) that advance knowledge about the biology of disease, the science of medicine, and/or the effectiveness of health care. He suggested that while current scientific efforts and those projected for the next 10 years will greatly improve our understanding of the biology of the genome and the genetic basis for human disease, the full impact of genomic-based advances in medical care will not be realized until after 2020. However, Dr. Green asserted that even today, there is the potential for game-changing “blue dot” accomplishments that can significantly advance medicine and improve health care.

Accordingly, it was the consensus of stakeholders at the Banbury Conference that we must define and implement specific “blue dot” pilot projects in the near term to move our national agenda forward to ensure the future of pathology in personalized medicine. Seven such projects were proposed:

Blue Dot Project 1: Establish a nationwide pilot program to ensure that every ACGME-approved residency in pathology in North America includes a mandatory curriculum in genomics and personalized medicine

Such training programs exist in a few residencies. A national committee has been formed including members of the Pathology Program Directors (PRODS) and other key stakeholders to disseminate model curricula and support their widespread implementation. The Pathology RRC must define core competencies in genomics and personalized medicine, and require that all residents in pathology demonstrate proficiency in these areas.

Blue Dot Project 2: Compile and analyze the full range of current testing offered by pathologists in tissue diagnostics and laboratory medicine, and determine which tests might be replaced by NGS or other high-throughput technologies

Establishing the value-proposition of modern high-throughput genomic analysis will require that current testing be replaced by NGS testing that will be more powerful and more cost-effective. Now is the time to inventory our laboratory tests - not only those involving molecular/genetic testing but others such as microbiology or histocompatibility – and determine which might be replaced by NGS technologies. We must also undertake pilot projects to prove the value proposition in this plan.

Blue Dot Project 3: Establish a *clinical grade* variant database

Current sequence variant databases have been built through an ad hoc process designed to support research activities. They fall far short of what is needed for delivery of accurate, safe and effective patient care. Clinical laboratory testing using human genome sequence data requires the creation, ongoing support, and national regulatory oversight of a clinical grade database. Pathologists must take the lead in this essential activity.

Blue Dot Project 4: Identify and validate operational models for WGA

In a multi-institutional fashion, we propose to conduct 4 projects each involving analysis of 10 whole human genomes in major clinical areas such as cancer or pediatric developmental disorders. The purpose of these short range (12 – 18 months) projects is to test operational models, produce clinical variant database entries, and assess different whole genome sequencing technologies and mapping analyses. These pilots will set the stage for future developments in WGA in human diagnostics and preventive medicine. The central hypothesis to be tested is, *does performance of WGA ad initio improve patient management, outcomes, and cost avoidance when compared to current standard practices?*

Blue Dot Project 5: Formulate regulatory guidelines to conduct whole genome test accreditation

Genomic testing is fundamentally no different than other types of laboratory testing, albeit at an unprecedented level of data complexity. The performance and interpretation of human genome sequence data as a clinical laboratory activity must fall under the same type of regulatory oversight as other clinical testing. The CAP, with the support of other national pathology organizations, must seize the initiative here and develop national standards and regulations governing genome testing.

Blue Dot Project 6: Define the concept of the primary care pathologist in genome-era medicine

A survey conducted by the CAP indicates that 50% of pathologists desire more direct patient interactions in their clinical practice.[8] The number of ostensibly healthy individuals undergoing genome analysis will increase dramatically in the next several years. A substantial opportunity exists in analyzing this information and advising primary care physicians in risk management and health preservation strategies. Pathologists must decide how to participate in this activity and how to partner with other health care professionals such as genetic counsellors to develop direct patient interactions as part of the new practice of primary care pathology.

Blue Dot Project 7: Address reimbursement issues

Pathologists and their national organizations working in a coordinated fashion should analyze the current landscape of reimbursement, identify barriers and recommended specific actions required to develop a national plan for reimbursement for genome-era testing, curation, and interpretation.

Conclusions and Next Steps

The Banbury participants recognize that there has been and continues to be considerable activity by the molecular/genetic pathology community and many others on many of these issues. It is imperative that we now coalesce our efforts into convergent pathways. This “call to action” report is only a first step in mobilizing the pathology community and engaging diverse stakeholders in the future of personalized medicine. Going forward, the Banbury participants committed to working together in specified task groups to reach out to a broader stakeholder community, develop actions plans and monitor progress on the “blue dot” projects against milestones at 3 month intervals, and reconvene in the Spring/Summer of 2011 to further refine and reinforce this national agenda. We welcome your comments and participation.

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Table 1

Participants in the 2010 Banbury Conference on Genome-Era Pathology

Representing: Employer or Organization	Name	Position (if applicable)
National Human Genome Research Institute	Eric Green	Director
Aetna	Joanne Armstrong	Director, Personalized Medicine Coalition
Office of the Air Force Surgeon General	Ray Jeter	
	Heather Halvorson	
Illumina Technologies	Tina Hambuch	
	David Bentley	
Affymetrix	Rick Hockett	
Next Generation Informatics	Ronald Ranauro	
MedCo Health Solutions	Bryan Dechairo	
American Society of Clinical Pathology	John Tomaszewski	President-Elect
American Society for Human Genetics	Lynn Jorde	President-Elect
Association for Molecular Pathology	Karen Mann	President
	Mary Williams	Chief Operating Officer and Director of Scientific Programs
Association of Pathology Chairs	James Crawford	Past-President
College of American Pathologists	Jay Schamberg	Member, Board of Governors
	Tom Malone	Director, Transformation of Pathology Program
	Jill Kaufman	
	Nazneed Aziz	
Personalized Medicine Coalition	Wayne Rosenkraus	President and Chief Executive Officer
United States and Canadian Academy of Pathology	Stuart Schnitt	President
	Frederic Barr	
	Ron DeLellis	
	Scott Tomlins	
Beth Israel Deaconess Medical Center (meeting organizers)	Mark Boguski	
	Peter Tonellato	
	Jeffrey Saffitz	
	Richard Haspel	

Table 2

Action themes for future efforts by pathologists in personalized medicine.

1	Define genome-era pathology
2	Educate pathologists in the use of genetic data and information.
3	Define the role of clinical laboratories in the genome-era and review the implications of pathology-wide analysis and reporting of whole genome data.
4	Partner with national and international pathology associations to promote the development and review of operational and regulatory issues.
5	Address insurance and reimbursement issues.
6	Initiate a set of pilot projects to identify the practical aspects and challenges in implementing this vision.