

A Call to Action

Training Pathology Residents in Genomics and Personalized Medicine

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Abstract

Genomics and “medical sequencing” will revolutionize clinical laboratory diagnostics as the foundation for the new era of personalized medicine. However, the medical profession lags far behind the technology and business communities in recognizing and preparing for this change. Pathologists must take the lead in the application of genomics technologies, including whole-genome sequencing, to laboratory diagnostics and personalized medicine. As a critical first step in leading this change, we have established a first-in-the-nation resident curriculum in genomics and personalized medicine. Our goal is to catalyze the adoption of similar training modules in every pathology residency in North America. If we succeed in the widespread implementation of this type of training as a core competency in pathology, we will ensure that the discipline of pathology will lead rather than follow in the coming era of personalized medicine.

“Personalized medicine’ refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.”¹

The era of personalized medicine began with the completion of the Human Genome Project in 2003. Sequencing of the first human genome required more than a decade of effort by thousands of scientists and technicians at a cost of \$2.7 billion.² Now, with advances in DNA sequencing technology, biotechnology companies are within a year or two of being able to produce a full human genome sequence in less than a week, in an almost fully automated manner, at a cost of \$1,000.³ Soon a complete human genome sequence will cost no more than various routine imaging studies or other diagnostic tests. At a meeting entitled Personal Genomes,⁴ held at the Cold Spring Harbor Laboratory (Cold Spring Harbor, NY) in September 2009, the main question under debate was not whether “medical sequencing” of individual patients was going to be done, but whether sequencing the whole genome or just the “exome”⁵⁻⁷ would provide the best cost/benefit ratio for clinical usefulness.

Unfortunately, the medical profession lags far behind the technology and business communities in the genomics revolution. Physicians are ill-prepared for the challenges posed when genomic analyses become increasingly routine and genetic data become common components of a patient’s medical record. As the custodians of laboratory diagnostics, pathologists must

embrace these challenges as an opportunity to fulfill a central role in the widespread application of personalized and genomic medicine.⁸ An important first step is educating our residents for this new era in laboratory diagnostics.

The Evolution/Revolution of Molecular Diagnostics

The current model of molecular diagnostics as a stand-alone laboratory service is giving way to a more decentralized, generalized application of molecular approaches across the full spectrum of tissue and clinical laboratory diagnostics. Once sequencing technologies reach a certain price point, they too will find their way into the clinical laboratories. There are many examples in which DNA and RNA sequencing will eventually supplant current methods.⁹⁻¹¹ Perhaps the most obvious is in the field of cytogenetics. Today, we still use 50-year-old technologies of karyotyping and visual examination of chromosome banding patterns to diagnose structural abnormalities in the human genome. Tomorrow, we will simply sequence the genome to learn everything that classical cytogenetics can tell us and so much more. Today, we use a combination of chemical stains, antibodies, and specialized techniques and instrumentation to identify and characterize cells and tissues. Tomorrow, these methods will be augmented, and, in some cases supplanted, by digital gene expression profiling that will elucidate “disease pathways” at the molecular level to provide the high-precision diagnostic information required for exquisitely tailored (ie, individualized) pharmacotherapy.^{8,12} Perhaps the most compelling current example is in oncology where knowledge of germline mutations is used for individualized screening for and prevention of disease and knowledge of somatic mutations in diseased tissue is used for targeted therapy, discovery of new drug targets, and improved clinical trial design.

The future work of clinical pathology laboratories will most likely not be the sequencing itself. As these technologies rapidly become commoditized, clinical laboratories will outsource the production and first-degree annotation of the sequence data. The role of pathologists will be to integrate these data with other pertinent information in the (electronic) medical record and produce clinically actionable recommendations.¹² In the coming decade, the role of clinical laboratories and the pathology community will be to develop and implement the information technologies (“assays”) required to achieve this scope of practice. In the near future, an electronic file of genomic data will be no different from a tube of blood or a throat swab. It is simply another specimen that will come to pathology for analysis and reporting.

An obvious corollary to this increased depth and scope of practice is that pathology will become a medical specialty

that uses computer modeling and simulation, on terabytes of data, as part of its routine practice.¹² This computing will be exposed on the surface for a few years as the new methods are developed. However, pathologists will not have to become computer scientists any more than did our colleagues in radiology. Computing will eventually become imperceptibly embedded in the tools of our profession in exactly the same way that high-performance computing has transparently enabled modern diagnostic imaging.

Pathology and Genomics: Defining the Need for Resident Training

At the present time, no single discipline in medicine has developed a comprehensive approach to train a cadre of physicians who will be prepared to meet the coming challenge. Control of personal genomics has, therefore, shifted into the hands of consumers.¹³ For as little as \$399, and without physician involvement, a person can mail a saliva sample or buccal swab to any of several companies and, within 2 or 3 weeks, receive a report listing more than 100 genetic “risks” for various diseases and conditions based on the results of genome-wide association studies.¹⁴ As an article in the *New England Journal of Medicine* put it,¹⁵ the genome “genie” is out of the bottle, and we concur with Altman¹⁶ that failure of the medical profession to address the resultant challenges is not an option.

We believe that the medical specialty best equipped to meet these challenges is pathology, working in close collaboration with practitioners of genetic counseling. We further believe that the place to start is in the design and implementation of new training programs to address a serious gap in medical education.¹⁷ To this end, we have developed a first-of-its kind resident curriculum in genomics and personalized medicine. Herein we briefly outline the components of this curriculum. (In an online supplement to this article [see www.ajcp.com], we provide a more detailed description of our training program. See also www.GenomicMedicineInitiative.org.)

Our program consists of several components. First is a series of didactic presentations focused on the following: (1) the current state of genomic analysis in personalized medicine, (2) basic aspects of next-generation sequencing technologies and their potential diagnostic applications, and (3) how genetic counselors use genetic information to guide and counsel patients and their physicians. The second component of the curriculum uses the time-honored tradition in medicine of practicing on oneself in exactly the same way students in medical school practice physical examination techniques on each other or type their own blood. In our case, we provide a *strictly voluntary* opportunity for our residents to have their own genomes analyzed for potential disease-gene

associations. The final component of the curriculum is a rigorous, literature-based, in-depth analysis of the underlying scientific evidence regarding the significance of current disease-gene associations. As current genotyping platforms are supplanted by next-generation sequencing technologies, we expect to offer our trainees the opportunity to have their complete genomes and/or transcripts sequenced as a (voluntary) part of the future curriculum.

The overall focus of our new curriculum is not on the technologies because these are changing rapidly and many current methods are likely to be obsolete even before the current residents' training ends. Rather, our main goal is to ensure that our residents understand the potential power of DNA and RNA sequence data and analysis in clinical laboratory diagnosis. We also strongly encourage the residents to engage in translational research activities designed to facilitate applications of sequencing technologies in next-generation molecular diagnostics.

To our knowledge, no other residency program in any medical specialty has conducted or developed a similar type of training module for their house staff. However, given the certain role that sequencing technologies and applications will play in the future of laboratory medicine, it is imperative that we prepare our residents for the practice of pathology in the era of personalized medicine. *Accordingly, our goal is to help ensure that by July 2012, every pathology residency program in the United States and Canada will implement a personal genomics curriculum into its training such that every resident graduating from an Accreditation Council for Graduate Medical Education–approved program will have developed core competencies in this field.* We are also working with the College of American Pathologists to advance this agenda and partner with them to encourage the discipline of pathology to take the lead in the future applications of genomics in medicine. If we succeed, pathology will not only maintain, but also expand its traditional function and scope of practice as the diagnostic enabler of clinical medicine. We will also ensure that pathologists are regarded as the “go-to” medical experts in the application of modern genomics to personalized health care. If, however, pathologists fail to seize this opportunity, genomic medicine will be fragmented across a dozen other medical specialties, undoubtedly increasing the complexity and cost of health care for patients, providers, and payers.

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References

1. President's Council of Advisors on Science and Technology. Priorities for Personalized Medicine. September 2008. http://www.ostp.gov/galleries/PCAST/pcast_report_v2.pdf. Accessed April 14, 2009. Quoted by: Personalized Medicine Coalition. The case for personalized medicine. May 2009. <http://www.ageofpersonalizedmedicine.org/objects/pdfs/theCase.pdf>. Accessed February 23, 2010.
2. National Human Genome Research Institute, National Institutes of Health. The Human Genome Project Completion: Frequently Asked Questions. <http://www.genome.gov/11006943>. Accessed February 23, 2010.
3. Mardis ER. Anticipating the \$1,000 genome. *Genome Biol.* 2006;7:112. doi:10.1186/gb-2006-7-7-112.
4. Cold Spring Harbor Meetings and Course Program. Personal genomes. <http://meetings.cshl.edu/meetings/person09.shtml4>. Accessed February 23, 2010.
5. Biesecker LG. Exome sequencing makes medical genomics a reality. *Nat Genet.* 2010;42:13-14.
6. Choi M, Scholl UI, Ji W, et al. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. *Proc Natl Acad Sci U S A.* 2009;106:19096-19101.
7. Maher B. Exome sequencing takes centre stage in cancer profiling. *Nature.* 2009;459:146-147.
8. Walk EE. The role of pathologists in the era of personalized medicine. *Arch Pathol Lab Med.* 2009;133:605-610.
9. Kahvejian A, Quackenbush J, Thompson JF. What would you do if you could sequence everything? *Nat Biotechnol.* 2008;26:1125-1133.
10. Shendure J, Ji H. Next-generation DNA sequencing. *Nat Biotechnol.* 2008;26:1135-1145.
11. ten Bosch JR, Grody WW. Keeping up with the next generation: massively parallel sequencing in clinical diagnostics. *J Mol Diagn.* 2008;10:484-492.
12. Boguski MS, Arnaout R, Hill C. Customized care 2020: how medical sequencing and network biology will enable personalized medicine. *F1000 Biol Rep.* 2009;1:73. doi:10.3410/B1-73.
13. Kaye J. The regulation of direct-to-consumer genetic tests. *Hum Mol Genet.* 2008;17:R180-R183.
14. Hardy J, Singleton A. Genomewide association studies and human disease. *N Engl J Med.* 2009;360:1759-1768.
15. Hunter DJ, Khoury MJ, Drazen JM. Letting the genome out of the bottle: will we get our wish? *N Engl J Med.* 2008;358:105-107.
16. Altman RB. Direct-to-consumer genetic testing: failure is not an option. *Clin Pharmacol Ther.* 2009;86:15-17.
17. Salari K. The dawning era of personalized medicine exposes a gap in medical education. *PLoS Med.* 2009;6:e1000138. doi:10.1371/journal.pmed.1000138.