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SPECIAL ARTICLE

Integration of Genomic Medicine into Pathology Residency Training

The Stanford Open Curriculum

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Next-generation sequencing methods provide an opportunity for molecular pathology laboratories to perform genomic testing that is far more comprehensive than single-gene analyses. Genome-based test results are expected to develop into an integral component of diagnostic clinical medicine and to provide the basis for individually tailored health care. To achieve these goals, rigorous interpretation of high-quality data must be informed by the medical history and the phenotype of the patient. The discipline of pathology is well positioned to implement genome-based testing and to interpret its results, but new knowledge and skills must be included in the training of pathologists to develop expertise in this area. Pathology residents should be trained in emerging technologies to integrate genomic test results appropriately with more traditional testing, to accelerate clinical studies using genomic data, and to help develop appropriate standards of data quality and evidence-based interpretation of these test results. We have created a genomic pathology curriculum as a first step in helping pathology residents build a foundation for the understanding of genomic medicine and its implications for clinical practice. This curriculum is freely accessible online. *(J Mol Diagn 2013, 15: 141—148; http://dx.doi.org/10.1016/j.jmoldx.2012.11.003)*

Data gathering and contextual interpretation of results form the core of the discipline of pathology. As in most areas of diagnostic medicine, expert knowledge in pathology combines the ability to decide what types of investigation should be performed and which findings or results should be prioritized in arriving at an accurate diagnosis. A detailed understanding of the limitations of laboratory testing methods and the significance of results in the clinical context of the patient are equally important. Thus, objective information from diagnostic tests is filtered through a knowledge base of human diseases and their manifestations in a process that is still probably best described as part of the art of medicine.

Good clinical care has always been personalized in the sense of viewing clinical and laboratory data in light of the patient's specific history, current signs and symptoms, habits, behaviors, and family or socioeconomic settings. Genome sequencing for individual patients, particularly if analyzed together with the transcriptome (the collection of RNA species expressed from the genome), proteome (the protein species present in the cells or fluids of the body), and metabolome (the set of small molecules taking part in the metabolic and signaling pathways of the body) of the patient,[1] differs only in the sheer amount of objective, highly detailed new data that will be made available for clinical interpretation. It is likely that large amounts of additional clinically relevant information will become available by performing detailed analyses of the microbiomes of the patient, those populations of microorganisms in residence in various anatomical sites throughout the body that can have a diversity of effects on health and disease.[2,3] In this article, unless otherwise specified, references to genomic testing are meant to include not only the results of analysis of the genome but also the downstream -omes consisting of the transcriptome, proteome, and metabolome. For medical conditions in which genetic

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factors play a significant role, and to the extent that clinically meaningful interpretation of the new genomic and other -omics data, including analyses of microbiomes, will influence the prediction, detection, diagnosis, classification, monitoring, management, or treatment of illness, the approaching era of genomic medicine offers great hope for improvements in patient care.

Initial analyses of whole or partial genome sequences from patients and diseased tissues, such as cancers, have begun to test the scale of the obstacles that must be overcome to enable improved detection, classification, and prognostication of diseases, together with better treatment selection and therapeutic response monitoring. It would be fair to say that genomic analysis of human disease is in its infancy. Published studies have analyzed only a small fraction of the data generated by genome sequencing, typically simplifying analyses by focusing on i) only exonic or splice site mutations in human tumors, ii) correlations with genome-wide association study results or with the relatively small databases of mutations with known phenotypic effects discovered before the genomics era, or iii) medically compelling but relatively uncommon conditions, such as mendelian genetic disorders.

Almost as complicated as the human genome itself is the constellation of scientific, technical, legal, ethical, regulatory, and clinical practice elements that must be appropriately aligned to make the medical use of genome information safe, reliable, and practical (Figure 1). One challenge will be to achieve thoughtful integration of rapidly evolving scientific and bioinformatics technologies with well-designed basic and translational research while keeping in mind the pragmatic concerns of clinical practice. Another will be to succeed in dealing with the larger legal, ethical, and economic frameworks that impact any change in clinical medicine. Meeting these challenges will likely involve partnerships among academic, governmental, private sector, and patient advocacy interests. Targeted federal research funding in these topics, together with appropriate health care legislation and policies that aim to put the interests of the patient first, will be critical in realizing the potential of recent genomic and other -omics technology innovations.

Another important step will be the education of a new generation of pathologists who are familiar with the scientific and medical background and with other aspects of the genomic testing environment (Figure 1) and who are equipped to apply genomic methods in translational research and, eventually, clinical practice. More broadly, to build a foundation in genomic medicine for all practicing physicians, we think that genetics and genomics courses must start early in the medical school curriculum and be incorporated into practice-based learning rather than merely taught in the basic science curriculum.[4] Pilot projects are currently being explored in medical schools [eg, Tufts University School of Medicine[5] and Stanford University School of Medicine (The Dean's Newsletter: September 28, 2009, *http://deansnewsletter.stanford.edu/archive/09_28_09.html#1*, last accessed October 10, 2012)]. Although such education should begin with medical students, it must also be provided at the residency and fellowship training levels. This training is particularly important for current and future pathology trainees, who will be central to the diagnostic process and interpretation of laboratory test results. Ultimately, genomic information also needs to be disseminated and made accessible to other groups, such as policy makers, nonphysician health care providers, and patients and their families.[6]

Pathology training programs need to identify the optimal route for pathology trainees to engage with the subject matter and methods of genomic medicine. The need for such curricula is widely recognized, but they are not yet offered in most pathology residency programs.[7] The need to introduce genomic concepts and knowledge into the curriculum of medical and graduate schools has also been recognized, and innovative approaches are being tried.[8–12] However, we think that the specialty of pathology is where the application of new assay technologies, the interpretation of the new data they provide, and the integration of such data with that derived from the other laboratory diagnostic methods must be implemented in clinical practice. The first pathology residency curriculum in genomics and personalized medicine to be published included a lecture on personal genomics, another on high-throughput sequencing, and a third on interpreting genetic risk.[13,14] This didactic curriculum was supplemented by a voluntary opportunity for residents to obtain limited personal genotyping of single nucleotide polymorphisms by three commercial personalized genomics companies and to perform subsequent interpretation of their own risk factors. In addition, the collaborative intersociety Training Residents in Genomics Working Group has made available four lectures to enhance the education of pathology residents in genomics in the context of an existing curriculum in molecular pathology at individual programs (Intersociety Council for Pathology Information Inc., *http://www.pathologytraining.org/trig_lecture.htm*, last accessed October 10, 2012). These lectures include genomic methods, clinical interpretation of genomic testing, and communicating and reporting genomic test results. Recently at Stanford, we developed a 2-year genomic pathology curriculum based on a core of 10 didactic lectures in the first year and a second-year course of more advanced topics, with opportunities for data interpretation of educational samples.

Recognizing that new genomic methods build on a substantial background of genetic studies and genotype-to–disease phenotype correlations painstakingly accumulated over previous decades, our curriculum reviews the conventional literature so that trainees understand earlier methods and results well, including major disease-associated DNA sequence variants in cancer and inherited disorders. For some trainees, this lecture serves as a refresher of previously acquired information, whereas for others with less molecular background training, this is an essential foundation review. In addition, focused didactic sessions describe new methods for DNA sequencing and sequence data analysis, with