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PERSPECTIVES

The Evolving Role of the Laboratory Professional in the Age of Genome Sequencing

A Vision of the Association for Molecular Pathology

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Molecular pathology encompasses disciplines of oncology (somatic variations), inherited disease (germline variations), infectious disease (microbial/viral variations), and histocompatibility and red cell genotyping. Specialized training is available for M.D.s and Ph.D.s in clinical molecular laboratory medicine. Accredited training programs include molecular genetic pathology, available for M.D.s/D.O.s (pathologists and clinical geneticists) through the American Board of Pathology and the American Board of Medical Genetics and Genomics, and Clinical Molecular Genetics available for persons with an M.D./D.O. and/or Ph.D. degree through the American Board of Medical Genetics and Genomics. Other credentials of Ph.D.-level molecular laboratory directors are also available. Training focuses on laboratory processes and regulations, technology, and result interpretation in the context of patients' clinical and family histories. In this era of genomic medicine, technology and our understanding of genomic data are rapidly advancing. With ongoing advancements, the role of molecular laboratory directors continues to evolve. Here, we describe these roles as they exist and expect to evolve as genomic sequence analysis becomes an increasingly important tool in diagnostic medicine.

Genome Sequencing and the Practice of Precision Medicine

The massively parallel nature of next-generation sequencing (NGS) enables comprehensive characterization of a patient's genome and represents an important milestone for precision medicine, which is defined as the tailoring of medical treatment to the individual characteristics of each patient.[1] Correlation of sequence information with other laboratory, clinical, and structural characteristic findings amplifies the power of other diagnostic methods. Data generated by NGS may inform, at an unprecedented level, diagnosis and prognosis, drug response predictions, and efficacy and safety of treatments. In addition, it enables evaluation of prenatal conditions, microbial pathogenesis, disease susceptibility, and disease progression monitoring. It is also likely to guide lifestyle decisions, including reproductive considerations for carriers of clinically important genomic variants. This potential, however, has not been fully realized. It can be reached only when evidence-based classification systems, validated databases of clinically actionable variants, streamlined bioinformatics pipelines, and advances in technology are available to support advances in knowledge, which will take time and resources.[2,3]

Genome sequencing is currently offered in a limited but growing number of diagnostic laboratories. The selection of appropriate patients for exome and genome testing requires

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The 2013–2014 Executive Committee of the Association for Molecular Pathology consisted of Lynne Abruzzo, Vivianna M. Van Deerlin, Helen Fernandes, Jennifer L. Hunt (2013 President), Elaine Lyon (2014 President), Iris Schrijver (2012 President), and Steven Schichman.

Standard of practice is not being defined by this article, and there may be alternatives.

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careful consideration of clinical presentation, test rationale, patient population, and clinical and family histories. Clinical evaluation of a given patient for testing, therefore, requires a consideration of the overall health benefits and the potential risks of genome results. For example, the possibility of the discovery of incidental or unexpected findings may present important dilemmas to patient management, and the potential for patient anxiety and uncertainty subsequent to such findings is of concern.[4] Informed patient consent and appropriate genetic counseling, therefore, are essential elements of an NGS-based testing approach and must include strategies to create patient awareness and understanding of risks versus benefits.[5] Genetic counselors are now increasingly used directly in molecular laboratories to help with test selection and guidance. In many practice settings, targeted mutation panels in a limited number of carefully selected genes may be the practical interim step in the application of massively parallel genome sequencing until more evidence-driven, comprehensive, reliable tools for interpretive comparison become available.

Clinical Integration of Genome Sequencing Requires a New Patient Care Model

Medical practitioners must collaborate to most effectively harness the power of NGS technology for patient care decision making. The Association for Molecular Pathology (AMP), through its Whole Genome Analysis working group, together with other organizations such as the College of American Pathologists, the American College of Medical Genetics, and the Centers for Disease Control and Prevention, is addressing these issues[2,6–8] to accomplish and maintain the goals of excellence in genomic medicine. Development of evidence-based standards to evaluate clinical utility among various patient populations and establishment of regularly updated consensus practice guidelines cooperatively synthesized among professional organizations are the foundation for successful integration of NGS into clinical practice. In addition, professional societies have a growing role in providing education in genomics to current and future clinicians, who will apply the information derived from this testing in their practices.[9]

The need for excellence however, achievable in part through synergistic efforts among experts, extends further. Optimal interpretation and integration of genomic test results for clinical management requires a team approach through which molecular laboratory directors function cooperatively with the other clinical caregivers to bridge inevitable gaps in knowledge and differences in expertise. Such a team approach, through, for example, *genome boards* that are akin to traditional tumor board meetings, permits those who generate genomic data and the associated interpretations to better understand the medical concerns for a given patient (ie, the clinical context for ordering the test).[10] It also encourages effective interactions with other health care providers who seek to build and maintain a knowledge base of genomic developments but cannot be expected to distill and use the vast amount of data alone. Thus, easily accessible expert consultation with laboratory directors such as molecular pathologists and appropriately certified Ph.D. laboratory directors enhances effective communication to the patient and, as part of an increasing trend, communication directly with patients. These approaches enable optimal use of the results, serving the goal of improving patient care. Now, more than ever, patients and their health records must be front and center to accomplish the coordinated, high-quality, and tailored health care that is essential to improving patient care through contemporary precision medicine.

The Role of the Laboratory Professional in the Clinical Use of Genome Sequencing

In contrast to a strict separation of disciplines and independent practice models, what emerges from an integrated patient care model is coordinated care. The foundation for precision medicine is built through coordinated application of various areas of clinical expertise. The value of the molecular laboratory director in this process is not simply in data generation but also as a provider of the analytic and postanalytic interpretation thereof, as it does for conventional molecular diagnostic testing. Genomic interpretation ideally should include reporting that is integrated with findings from other laboratory services and interactive knowledge sharing and participation in the integration of the information into a patient management plan.

In the media and scientific literature, there is a sustained focus on cost-effective, faster, and better genome sequences for clinical decision making (*http://www.genome.gov/sequencingcosts*, last accessed February 28, 2014).[11] Although the areas of technical development are indeed where the most rapid advances are made, the focus has resulted in a limited public understanding of the clinical testing process. The perception of those external to laboratory medicine is often that the role of molecular laboratory directors is limited to overseeing the handling of patient samples and the running of the assays. The expertise of molecular laboratory directors extends well beyond analytic and clinical validation of laboratory tests, and the pre-analytic and analytic phases of this testing. Importantly, it also includes the post-analytic phase of clinical interpretation. Molecular laboratory directors are trained to perform genome tests in their Clinical Laboratory Improvement Amendments—certified and (most commonly) College of American Pathologists—accredited laboratories, adhering to the regulatory requirements for such testing. The interpretation of analytic results was always a part of the scope of work for molecular laboratory directors, but in the context of genome sequencing, this part of laboratory testing has become much more extensive, because of large amounts of data to be analyzed and because of the labor-intensive assessment of pathogenicity for individual variants.