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# Progress and Potential:

## Training in Genomic Pathology

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## Abstract

**Context—**Genomic medicine is revolutionizing patient care. Physicians in areas as diverse as oncology, obstetrics, and infectious disease have begun using next-generation sequencing assays as standard diagnostic tools.

**Objective—**To review the role of pathologists in genomic testing as well as current educational programs and future training needs in genomic pathology.

**Data Sources—**Published literature as well as personal experience based on committee membership and genomic pathology curricular design.

**Conclusion—**Pathologists, as the directors of the clinical laboratories, must be prepared to integrate genomic testing into their practice. The pathology community has made significant progress in genomics-related education. A continued coordinated and proactive effort will ensure a future vital role for pathologists in the evolving health care system and also the best possible patient care.

An entire human genome can currently be sequenced for less than $10 000 in several weeks, with further reduction in cost and time anticipated.[1] Multigene panels and next-generation sequencing (NGS) methods are already being applied to detection of germline and somatic variants relevant to clinical care. Pathologists are responsible for directing the laboratories that perform the “traditional” single-gene molecular testing of tumors, and the field is rapidly evolving to include genomic analysis. Similarly, NGS methods are already being used for clinical diagnosis in areas such as microbiology and prenatal testing. In this article,

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we will address the critical need for inclusion of genomics-related topics during pathology training, describe currently available curricula, and present suggestions for building on the significant progress that has already been made in pathology graduate medical education.

## A NEEDS ASSESSMENT: GENOMIC TESTING AND CLINICAL CARE

Pathologists must be trained in genomic methods to keep pace with the rapid developments in medicine and evolving diagnostic modalities. While pathologists with specialty training will direct laboratories performing genomic testing to ensure accurate and precise results, all pathologists will find themselves involved in molecular and genomic testing to some degree. Pathologists will oversee the appropriate collection of samples for genomic testing, a critical first step in the diagnostic process. Selection of a suboptimal sample for testing may lead to incorrect or delayed results or waste of resources. In a 2013 study, *HER2/neu* fluorescence in situ hybridization (FISH) results from hospital-based laboratories did not match those obtained from a company-run gene panel.[2] The discrepant results may have been due to the outside laboratory's method for tumor sampling from the tissue block, leading to inclusion of nontumor tissue in the analysis. Further, the choice of whether to send a sample for such testing, determination of laboratories to which samples may be sent, as well as the postanalytic integration of findings with other aspects of the diagnostic workup will be the responsibility of the pathologist, whether testing is done in-house or sent out. The pathologist is an essential part of the genomic diagnostic process and will play a critical role in many key areas, several of which are summarized below.

### Tumor Analysis

Molecular diagnostic assays detect a range of somatic abnormalities found in tumors and may involve assessment of DNA, RNA, or epigenetic changes. Further, analytic approaches may target a few genes, the exome, or the whole genome, underscoring the complexity and breadth of information to be understood by the pathologist. While sequence-based information encoded in DNA, including point mutations, translocations, and deletions, are often the focus of discussion, it is important to keep in mind that expression changes in genes, detected by expression arrays or transcriptome analysis, are frequently critically altered in tumors.

Gene panels to determine prognosis and guide treatment are already routinely used in cancer care. Testing is commercially available to help determine the need for additional chemotherapy in breast cancer, and a recently developed 167-gene assay can assist in the management of cytologically indeterminate thyroid nodules.[3,4] A 13-oncogene panel is also available to help guide pharmacologic therapy in a variety of tumors. In a prospective study of salivary duct carcinoma cases, this panel influenced treatment decisions in 6 of 8 patients tested.[5]

Several recent examples also illustrate the considerable impact of whole genome and exome approaches in cancer patient care. In a case of treatment-refractory oral adenocarcinoma, whole genome analysis revealed RET expression changes and led to therapy with a RET oncogene inhibitor followed by disease stabilization. When the tumor subsequently progressed, sequencing of a new specimen demonstrated the molecular mechanisms that

enabled drug resistance.[6] Similar methods were also used in a case of a patient with apparent acute promyelocytic leukemia by histology.[7] The typical *PML-RARA* fusion gene could not be detected with a standard FISH assay. In approximately 7 weeks, using NGS, a cytogenetically cryptic PML-RARA fusion protein was identified, leading to appropriate treatment with all-trans retinoic acid.

## Germline Analysis

While somatic tumor sequencing will likely be the largest initial area for clinically actionable genomic testing, human disease related to germline abnormalities will also be affected by these new techniques. For example, the causative variants of several inherited genetic disorders have been determined by using NGS.[8] In one particularly dramatic case, a 15-month-old child presented with intractable inflammatory bowel disease.[9] Whole-exome sequencing demonstrated a variant in the X-linked inhibitor of apoptosis gene (*XIAP*) which, although not typically associated with colitis, can lead to hemophagocytic lymphohistiocytosis (HLH). Given the poor prognosis of HLH, the patient underwent a bone marrow transplant with an apparent cure of his inflammatory bowel disease. For the diagnosis of heritable cardiomyopathies and other constitutional disorders, the use of targeted gene panels has become a routine and effective approach to simultaneously assess multiple potentially causative genes.[10] Similarly, multigene panels for the assessment of familial cancer syndromes are becoming more common.[11]

Preconception and prenatal diagnostic capabilities will be expanded with new genomic methods. A single carrier screening test for more than 100 genetic diseases is now available for preconception planning.[12] Another commercially available test uses NGS methods to quantify the amount of fetal DNA circulating in the mother's blood, with an imbalance indicative of the possibility of trisomy 13, 18, or 21.[13] For cytogenetic testing, chromosomal microarrays are being increasingly used, and several studies[14,15] indicate good performance in comparison to karyotyping for prenatal diagnosis and investigation of stillbirth.

There are multiple additional areas that will incorporate germline genomic testing, such as transfusion medicine and pharmacogenomics. For the former, testing platforms now enable genotyping at multiple blood group loci, allowing for easier matching of recipient and donor as well as identifying individuals with rare blood groups antigens.[16] Pharmacogenomics offers the promise of reducing adverse drug reactions, which are a major cause of morbidity and mortality. Genomic analysis will drive drug selection and dosing based on an individual's ability to metabolize the drug.[17]

## Microbial Testing

In parallel with human genomic testing, advances in NGS technologies will have great impact on the analysis of microbes. The first bacterial genome to be sequenced, *Haemophilus influenzae* strain Rd, took more than 1 year and $1 million to complete.[18] Less than 20 years later, a single instrument can generate 768 bacterial genomes per week for approximately $50 per strain.[19] If this trend continues, a $10 bacterial genome, far less than the cost of a conventional microbiology laboratory workup, will become a reality.

To demonstrate the feasibility of integrating whole genome sequencing into the routine workflow of a clinical microbiology laboratory, Long et al[19] recently sequenced the genome of every organism recovered at their institution on a single day. Most organisms were successfully identified, and several potential clinical improvements were illustrated, including detection of uncultured organisms and earlier time to detection. For example, sequencing identified 2 *Mycobacterium* species more than 10 days before conventional methods.

Other clinical applications of whole genome sequencing include investigation of outbreaks and unusual infections. For example, whole genome sequencing was used to define the index case and subsequent transmission events underlying a nosocomial outbreak of multidrug resistant *Klebsiella pneumoniae* infections at the National Institutes of Health (NIH) Clinical Center (Bethesda, Maryland).[20] Wright et al[21] recently used whole genome sequencing to characterize the organism recovered from a patient with a fatal anthraxlike infection. The genomic data demonstrated that this *Bacillus cereus* strain had acquired the genes encoding the tripartite anthrax toxin and quickly ruled out the possibility of bioterrorism. These data immediately guided the emergency public health response.

## WHAT WILL PATHOLOGISTS NEED TO KNOW?

With the multiple applications to patient care, pathologists will clearly need to be trained in genomics-related diagnostic tools. The level of knowledge required will differ between the genomic pathology specialist who directs the laboratories performing the testing and the nonspecialist who will help in sample acquisition, integration of findings into reports, and communication with clinical colleagues. This training will build on the already existing molecular pathology rotations incorporated into residency program curricula; this knowledge base itself must be combined with an understanding of the technical issues surrounding NGS approaches, assay design and validation, and bioinformatics. The ultimate goal is for the pathologist to make a contextual interpretation of the data, based on a clinical question and taking into account patient phenotype, and effectively report the results to other clinicians.

While an in-depth description of required competencies is not the intent of this review, below are several important considerations for genomic pathology training.

### Targeted Versus Whole Genome Approaches

Trainees need to understand the fundamental NGS approaches used in clinical genomics. Currently, there are 2 major methods in widespread clinical use for targeted sequencing, namely, amplification based (which rely on multiplex polymerase chain reaction, often using an emulsion-based technique) and hybrid capture based (which are usually solution based, but can also be performed by solid phase techniques).[22–24] The number of genes, classes of mutations that can be detected, and depth of coverage differ between amplification-based and capture-based approaches for targeted sequencing, and targeted approaches likewise differ from whole genome methods.[25,26] It is likely that no single targeted or whole genome technique will, in the end, be used to perform all clinical sequencing, but rather that various approaches will find niches within the spectrum of clinical genomic DNA sequencing.

### Platforms, Assay Design, and Validation

Given the pace of scientific advancement, there is an increasingly short cycle time between discovery of a genotype associated with either a clinically relevant phenotype or response to a particular therapy and constant evolution of commercial sequencing platforms.[27] As such, it is unlikely that the US Food and Drug Administration will be able to keep pace with review and approval of associated NGS in vitro diagnostics, and most clinical NGS testing (at least in the foreseeable future) will be performed via laboratory-developed tests.[28] The pathology specialists who will be responsible for the design, development, and validation of most clinical genomic tests will need more than a passing knowledge of the various NGS approaches and platforms and all pathologists will still need a fundamental understanding of core principles.[29]

### Bioinformatics

The clinical utility of the genomic sequencing is absolutely dependent on the bioinformatic approaches used to evaluate the large data sets produced by NGS techniques. It has become increasingly clear during the last several years that the bioinformatic pipelines for analysis of single-nucleotide variants, small insertions and deletions (indels), copy number variants, and structural variants differ in fundamental ways. Trainees will need some understanding of the different bioinformatics pipelines for detection of these 4 major classes of DNA variation in order to assure that clinical genomic tests have optimal performance.

### Reporting

Clinical genomics requires interpretation of sequence variants in the context of the specific disease under analysis, since the same mutation can have different diagnostic, therapeutic, and prognostic implications in different clinical settings. Thus, training in clinical genomics requires acquisition of the facts related to the way the different variants contribute to diagnosis and patient care. Trainees must gain facility in the use of various internet Web sites that catalogue sequence variants and learn efficient search strategies to quickly uncover recent clinically relevant discoveries regarding specific genes in specific tumor types. Owing to the many ethical, legal, social, and reimbursement issues associated with genomic testing, pathologists will also need significant knowledge of these areas as well. Ultimately, trainees must learn how to integrate results with other clinical and laboratory data and effectively report findings to other health care providers.

## A NEEDS ASSESSMENT: PHYSICIAN GENOMIC MEDICINE KNOWLEDGE

Given their important role in result reporting and communication, pathologists must also take the lead in educating clinical colleagues. There is evidence that most physicians do not understand single-gene, let alone, genomic testing. Recently, at a large reference laboratory, approximately 30% of orders placed for 36 molecular tests were inappropriate. In many of these cases (68%), the wrong test was ordered.[30] Increasingly, pathologists are expected to be the “gatekeepers” of the laboratory to ensure appropriate test utilization and cost-effective ordering patterns.[31]

Physicians are aware of their lack of genomic medicine knowledge. In a 2013 study of more than 200 internists, although 65% had counseled a patient on a genetic issue in the past 6 months, 74% rated their knowledge of genetics as “somewhat poor” or “very poor” and approximately 80% indicated a need for additional training.[32] These findings are not surprising given that genomics education in medical school is not yet emphasized. Whereas numerous editorials and commentaries have been written on the need for training health professionals in genomics, there is limited information on curricular content during core courses or rotations.[33–36] Furthermore, there is evidence that genetics instruction in medical school is not focused on clinical care. In a 2007 survey of more than 100 medical school genetics courses, only 11% included “practical training” in medical genetics.[37] Supporting this finding, a focus-group–based study involving family medicine residents concluded that medical school genetics training “dealt with rare disorders and was not clinically relevant.”[38] Clearly, improvements in genomics training of medical students are needed, and several institutions have begun to undertake revision of undergraduate medical curricula to prepare their students to practice medicine in the new genomic era that lies ahead.[39–42]

Of course, specialists other than pathologists, in particular geneticists and genetic counselors, will play an important role in genomics-related patient care and medical education. However, there are, currently fewer than 3000 molecular geneticists and genetic counselors but approximately 20 000 board-certified pathologists.[43,44] Pathologists clearly need to take a leading role in translating genomics to patient care.

## CURRENT TRAINING IN GENOMIC PATHOLOGY

Given the above, there is a strong case for training pathologists in genomics. This conclusion was also reached at a 2010 meeting at the Banbury Conference Center at Cold Spring Harbor Laboratory (Cold Spring Harbor, New York) to discuss the future of genomic pathology. Representatives from major pathology organizations, insurance consortiums, industry, the NIH, and the military agreed that a major goal should be “to ensure that every Accreditation Council for Graduate Medical Education (ACGME)–approved residency in pathology in North America includes training in genomics and personalized medicine.”[45] An editorial accompanying the conference recommendations reiterated that “the need to introduce NGS and whole-genome technology topics into medical student and pathology resident education is mandatory.”[46] A 2010 survey conducted through the Pathology Residency Directors Section (PRODS) of the Association of Pathology Chairs (APC), however, revealed that of the 42 programs responding (23% of the total), 93% provided training in molecular pathology, while only 31% included any training in genomic pathology–related topics such as NGS.[47]

With the rapid evolution of clinical genomics, we must work together to ensure that pathology residents receive the basic training needed to be ready for the demands of practice in this new era. Relatively few programs are routinely performing genomic testing in-house, and many programs lack the in-house expertise needed to teach trainees. Further educational tools and support are needed.

### Single-Center Curricula

Several programs have developed and published curricula in genomics to facilitate training of pathology residents. In 2009, Beth Israel Deaconess Medical Center (BIDMC; Boston, Massachusetts) implemented genomics training for all residents; the curriculum included knowledge, affective, and performance-based objectives.[48–50] To provide a strong factual foundation, 3 lectures were created. The first provided a general overview of genomic testing and the role of pathologists; the second reviewed NGS methods; and the third, delivered by genetic counselors, covered communicating results with patients. To foster understanding of the emotional impact genomic testing can have on patients (ie, "affective" objectives), residents were offered free-of-charge direct-to-consumer genomic testing, on a voluntary basis, using chip-based single-nucleotide polymorphism analysis to determine "risk" for 40 conditions. The company also provided genetic counselors to help with consent and questions regarding the analysis. Subsequently, residents presented a journal article on a condition of their choice that used genomic methods. As evidence of the degree of critical appraisal, 2 residents discovered an error in a direct-to-consumer testing site in listing the risk for multiple sclerosis associated with a specific single-nucleotide polymorphism.[51]

There has been some debate on the utility and ethics of educational genetic testing.[39,41,52] In an anonymous survey, no BIDMC residents felt coerced into participating and several commented that the testing added to their understanding of genomic pathology. Given the factors that drive adult learning, self-testing is not a new concept in pathology training as some programs allow residents to use their own blood for analysis (eg, for a type and screen).[53,54]

Information on the BIDMC curriculum, including the lectures, is available online.[55] Major revisions are being planned, including the integration of the curriculum into the month-long molecular pathology and cytogenetics rotation. Exercises related to genomic data analysis and communication of results to patients are also being created.

Stanford University (Stanford, California) has also developed a resident genomics curriculum that has been taught since 2010 and was reported in the *Journal of Molecular Diagnostics*.[56] It is offered annually and includes basic and advanced courses. The basic course is a series of 10 lectures that comprise a mandatory genomics curriculum for all anatomic and clinical pathology residents and molecular genetic pathology fellows. Other fellows and interested faculty use these lectures to augment their genomics knowledge as well. This lecture series includes a review of the principles of molecular biology, human variation, genetics and genomics, and delves into current and emerging methodologies for research-based and clinical diagnostic applications of genomics. Following these fundamental aspects, the lectures focus on different practice areas and cover genomic medicine as related to solid tumors, hematopoietic cancers, inherited genetic disease, human leukocyte antigen genetics, and pharmacogenomics. A session on regulatory, economic, and ethical facets, as well as on the potential impact of genomic analyses on lifestyle and medical care decisions, concludes the series. A foundation for the analysis of complex genome data is also provided and bioinformatics concepts are interwoven throughout the series. In addition, the course was designed to address and integrate each of the core

competencies of the ACGME: patient care, practice-based learning and improvement, interpersonal and communication skills, professionalism, medical knowledge, and systems-based practice. Each lecture has specific stated learning objectives.[56]

An advanced genomic medicine elective is offered each year for residents, fellows, and faculty who "plan to work actively with genomic data, use genomic sequence interpretation tools, and participate in genomic testing for research and clinical purposes."[56] Taught in a small-group interactive environment, the elective includes additional instruction in NGS and genetic variation, with a greater focus on the algorithms for aligning nucleic acid sequences, genomic sequence analysis tools, the limitations and artifacts or errors inherent to the various approaches, as well as bioinformatics and statistical methods.

The Department of Pathology at Stanford University developed this comprehensive 2-tiered curriculum because the integration of genomic pathology into residency training was recognized as an urgent need and a critical component to well-rounded pathology training. Understanding that other residency programs may not have the resources or the expertise among their faculty to develop a genomics course, the decision was made to make the lectures publicly available online.[57] Since they became available online in late September 2012, there have been 7030 lecture views (accessed May 10, 2013), with the greatest number of hits for the human leukocyte antigen, microarray, introductory, and methods lectures.

## Beyond Single-Center Initiatives

Whereas dissemination of single-center curricula is helpful, more needs to be done to assist residency programs in implementing genomic pathology training. In the aforementioned 2010 survey of pathology residency directors, 91% of programs without training wanted to include a genomics curriculum but were precluded by the lack of faculty expertise and resident training time. Respondents believed online modules would be the most helpful tool in implementing a new curriculum.[47]

The survey results prompted the creation of a PRODS working group to assist pathology residency programs in developing genomics training. Made up of experts in medical education, clinical molecular genetics, and molecular genetic pathology, the Training Residents in Genomics (TRIG) Working Group represents a truly collaborative approach. In addition to members from major pathology organizations, the National Society of Genetic Counselors (NSGC), the American College of Medical Genetics and Genomics, and the National Coalition for Health Professional Education in Genetics (NCHPEG) have appointed representatives, with the American Society for Clinical Pathology (ASCP) providing administrative support. In 2012, the TRIG Working Group released a series of PowerPoint (Microsoft, Redmond, Washington) lectures with notes, initially posted with free access on the Intersociety Council for Pathology Information Web site, and now also available on a separate TRIG Web site.[58,59] Topics include a review of genomic methods, applying genomic technology to clinical care, and communicating with patients.

To further promote training of pathology residents in genomics, working group members have given presentations at the annual meetings of many major pathology organizations

including the Academy of Clinical Laboratory Physicians and Scientists, ASCP, and the United States and Canadian Academy of Pathology. Abstracts have also been presented at the annual meetings of NSGC and NCHPEG and articles describing the progress of the TRIG Working Group have been published.[47,60,61]

The TRIG Working Group also has provided survey and knowledge questions for the Pathology Resident In-Service Examination (RISE). Administered by the ASCP, this examination is taken by almost all residents in the United States. Scores allow residents to gauge their educational progress and have been correlated with board examination performance.[62] Using the RISE allows a yearly national assessment of the current state of resident training in genomic pathology.

The accomplishments of the TRIG Working Group were used as the basis for an R25 grant application aimed at further development of a genomic pathology curriculum. The National Cancer Institute is now providing funding of $1.3 million during a 5-year period to allow the creation of online modules, resident workshops, and assessment tools, with the ASCP providing design support. Educational resources will be evaluated at 4 residency sites, and national trends in genomics training will be assessed with the RISE. The ultimate goal is to ensure genomics training in more than 90% of pathology residency programs in the United States by the end of the grant-funding period.

While the TRIG Working Group represents an effective collaborative approach to developing a genomic pathology curriculum, several individual pathology organizations have also taken important steps in developing genomics training resources. The College of American Pathologists has initiatives involving improvement of graduate and continuing medical education. Work groups have been formed to identify core competencies and skills related to informatics and genomics. The output from these groups will be used to develop curricula and teaching tools.

The Association for Molecular Pathology (AMP) has also previously published curricula for molecular pathology training in pathology residency programs and is in the process of revising guidelines to include genomics training.[63] The AMP Molecular Curriculum Task Force has been charged by the Training and Education Committee of AMP with integrating guidance for training in genomics into a curriculum in molecular pathology. This group will be publishing curriculum recommendations later in 2013.

For fellowship training, the Molecular Genetic Pathology (MGP) Directors Council, in association with AMP, has formed a task force to address genomics training for MGP fellows. MGP fellowships train pathologists to serve as directors of molecular diagnostic laboratories. Increasingly, the most needed new expertise for these positions is a thorough knowledge of genomics. With this in mind, this task force is updating previously published guidelines for fellow training in genomics to address all aspects of NGS and other clinically oriented genomics technology including specimen acquisition and processing, technical considerations, data analysis and interpretation, effective use of online resources, reporting of results, communication with the clinical team, and medicolegal and social issues.[64] The

resulting guidelines, also expected to be published in late 2013, will be linked to clinical competencies that can be directly used by training programs.

## FUTURE DIRECTIONS

The pathology community has taken a robust approach to incorporation of genomics training. The growth of genomic medicine, however, provides numerous challenges for pathology training programs. The amount of time required for pathology residency training is expected to remain 4 years, though the volume of information that must be mastered before entering practice is growing rapidly. Molecular pathology and genomic medicine must be integrated in a way that complements the basic diagnostic and laboratory skills that make up the bulk of pathology residency training. The knowledge expected of an anatomic pathology/clinical pathology–trained pathologist must be further defined and differentiated from the competency level expected of a board-certified molecular-genetic pathologist and the additional expertise that might be the purview of individuals with even further subspecialty training. To accomplish these goals, groups focusing on pathology residency and fellowship training, including program directors, ACGME, ABP, and others, will need to work together to ensure that curricular expectations, capabilities, and assessment efforts in genomics are aligned.

Besides residents and fellows, by necessity, other groups must receive training in genomic medicine. Medical students entering pathology residency will be expected to understand basic concepts of molecular diagnostics and genomics. As noted above, several medical schools have taken steps in providing instruction in these areas; however, as directors of courses in the preclinical curriculum, pathologists are well situated to help ensure that physicians are prepared to practice genomic medicine. As an important first step, the Undergraduate Medical Educators Section of the APC has recently surveyed members on current incorporation of genomic topics into their pathology courses.

Finally, the education of practicing physicians, particularly pathologists, in genomic medicine is critical. Professional organizations, scholarly journals, and credentialing organizations must provide continuing education activities, self-assessment modules, and educational courses to practicing pathologists so that they, too, can be kept abreast of the most current information related to genomic medicine and molecular pathology. Many educational resources developed for residents and fellows can also be used in continuing medical education.

## CONCLUSIONS

The pathology community has made significant progress in educating trainees in genomic medicine. Single institutions and organizations have made important contributions, while the collaborative and comprehensive approach of the TRIG Working Group can be a model for future initiatives in pathology education. This proactive and coordinated effort will ensure not only a future vital role for pathologists in the evolving health care system but also the best possible patient care.

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