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Genomic Oncology Education: An Urgent Need, A New Approach

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Abstract

Genomic testing has entered oncology practice. With reduced cost and faster turn-around-times, clinical applications for next-generation sequencing-based assays will only continue to increase. As such, there is an urgent need for health professional education to allow implementation of these new diagnostic tools. However, current medical school, residency and fellowship training has had limited success in educating physicians in the fundamentals of single gene testing let alone genomic methods. In this review, we describe the novel approach the pathology community has taken in genomic education and the potential for application to oncology trainees.

Keywords

Genomics; next-generation sequencing; gene panels; oncology; cancer; molecular pathology; medical education; residency training

The sequencing of the first human genome, completed in 2003, took more than a decade and cost \$3 billion.¹ Today, only 10 years later, similar testing using next-generation technology is available for the cost of a MRI scan and with a turn-around-time measured in weeks.² Genomic assays have entered clinical practice and, while there are applications in almost all areas of medicine, cancer patients will be the first to feel a major impact.³ Given this evolution of practice, oncologists must understand genomic testing. This review will describe the current state of physician knowledge of genomics and how efforts in pathology can be used as a model for genomic education in oncology.

Genomic oncology has entered clinical practice

Standard of care in clinical oncology requires that oncologists be familiar with molecular pathology testing. Single gene mutation assays such as those for JAK2 and KRAS are commonplace. In contrast, for the purpose of this review, “genomics” refers to analysis of a large portion of the genome with a single test. Such assays are being applied to cancer care with increasing frequency.

Commercially available gene expression panels are now routinely used to determine prognosis in breast cancer and the need for chemotherapy.⁴ The SNaPshot assay of greater than 50 mutations in 14 key cancer genes has also entered clinical use. In one study involving non-small-cell lung cancer patients, this test influenced treatment decisions for 78

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of 353 individuals with advanced disease (22%).⁵ In some cases, the results directed entry into available clinical trials and in others, targeted therapy was used off-protocol.

While primarily limited to case reports, there have also been dramatic examples of clinically relevant interventions based on whole-genome, exome and transcriptome sequencing. For example, in a patient with apparent acute promyelocytic leukemia (APML) by morphology, the pathognomonic PML-RAR gene rearrangement could not be detected by standard fluorescence in-situ hybridization (FISH) testing.⁶ Using next-generation sequencing (NGS) methods, a cytogenetically cryptic re-arrangement was identified. After confirmation using novel FISH and polymerase chain reaction (PCR) assays, this information led to treatment with all-trans retinoic acid as opposed to a hematopoietic stem cell transplant. The patient had an appropriate response and the entire diagnostic process took approximately seven weeks.

In another case, a patient was diagnosed with an oral adenocarcinoma.⁷ Despite excision and irradiation, the tumor metastasized to the lung. Based on immunohistochemical (IHC) staining, the patient was then treated with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor but the tumor continued to grow. To potentially discover other treatment options, whole genome and transcriptome sequencing was performed on a lung biopsy specimen. Analysis demonstrated up-regulation of the RET oncogene with confirmation through FISH and IHC assays. Treatment with a RET tyrosine kinase inhibitor led to stabilization of disease for four months. Following disease progression, repeat NGS of a new biopsy specimen revealed mutations that could bypass the RET inhibition.

These cases are representative of increasing clinical applications of genomics in oncology. With decreasing cost and turn-around-time, genomic testing is being utilized to guide the care of cancer patients and not simply at academic medical centers. The use of this testing is poised to greatly expand in the near future. It should also be noted that oncologists will not only be asked to translate the results relevant to treating cancer. Sequencing of large portions of the genome can lead to a host of unrelated incidental findings with potential implications for patients and their families.³

Physicians lack understanding of genetic testing

To effectively apply results to patient care, physicians must grasp the fundamentals of genomic testing and interpretation. Unfortunately, there is evidence that most physicians do not even understand basic molecular diagnostics.

A study published in 1997 demonstrated poor physician understanding of testing for the APC gene variant associated with familial adenomatous polyposis.⁸ Approximately 20% of the time an inappropriate testing strategy was used and 32% of results were misinterpreted. Over a decade later, there does not appear to have been much improvement. A 2010 study examined test ordering practice at a large reference laboratory for 36 molecular tests.⁹ Review by genetic counselors uncovered problems with 30% of orders (almost 1200 test requests). The majority of cases (68%) involved selection of the wrong test. NF1 deletion/duplication testing and alpha globin sequencing were the most frequently mis-ordered tests (68% and 80% respectively).

Physicians admit to their lack of knowledge. In a 2013 study of over 200 internists, 74% rated their knowledge of genetics as “somewhat poor” or “very poor” and approximately 80% indicated a need for additional training.¹⁰ Particularly concerning, 65% of these physicians had counseled a patient on a genetic issues and 44% had ordered a genetic test in the past six months. In another study of 401 family doctors, 55% reported they had no knowledge of the Genetic Information and Non-Discrimination Act (GINA).¹¹ This

information is critical in helping patients understand genomic testing-related insurance and employment issues.

Current physician training in genetics is inadequate

A decade since the completion of the human genome project, it appears many physicians still have difficulty interpreting single gene testing. This finding is perhaps not surprising given the content of current medical school genetics courses. In a study from 2007, genetics course directors from 112 medical schools in the United States and Canada were surveyed on course content.¹² Only 11% of courses included “practical” training in medical genetics. Similarly, in a focus-group based study involving family medicine residents, participants believed that medical school genetics training “dealt with rare disorders and was not clinically relevant.”¹³

This deficiency in medical school education is widely recognized and there have been numerous publications promoting the need for improved training in genetics and genomics.^{14–17} In contrast, there have been few actual published practical programs to improve health professional knowledge. The rare examples include several novel medical student electives such as the effort at Stanford University to incorporate student genotyping into the classroom and the “genes-to-society” curriculum at Johns Hopkins University which integrates genomics as a “horizontal strand” during the first 15 months of medical school.^{18–21}

There are even fewer examples of training beyond undergraduate medical education. In 2010, a set of core competencies was published by the European Society of Medical Genetics.²² This list, however, is not detailed and includes only basic goals such “identify individuals with or at risk for a genetic condition.” In the United States, a plan has been described to create teaching modules for physicians in genomic biology, disease susceptibility and pharmacogenomics but no further details have been published.²³

Pathologists must play a key role in genomic testing

Pathologists are trained in test validation and quality control and already direct the laboratories that perform single gene assays. In addition, all patient samples pass through the pathology department. Whether diagnostic testing involves analysis of tissue sent to the grossing room or blood samples to the clinical laboratories, pathologists have the access and opportunity to coordinate molecular testing.

Molecular genetics is embedded in pathology residency training and year-long molecular genetic pathology fellowships.²⁴ This training, however, does not necessarily include concepts in genomic medicine. A 2010 survey distributed to members of the Pathology Residency Directors Section (PRODS) of the Association of Pathology Chairs (APC) suggests most residency programs do not have a genomic pathology curriculum. Of the 42 programs responding (23%) only 31% had any training in genomic pathology-related topics.²⁵

Still, with the background in molecular pathology and assay design, pathologists are ideally positioned to play an important role in translating genomic technology to patient care. In 2010, representatives from major pathology organizations, insurers, industry and the National Institutes of Health (NIH) met at the Banbury Conference Center at Cold Spring Harbor laboratory to discuss the future of genomic pathology. Seven projects, crucial for ensuring the role of pathologists in genomic medicine, were proposed.²⁶ Project #1 had the goal “to ensure that every ACGME-approved residency in pathology in North America includes a mandatory curriculum in genomics and personalized medicine.” When a report of

the Banbury Conference proceedings was published in the *American Journal of Clinical Pathology*, an accompanying editorial stated “although all seven projects certainly have merit and are important to pathologists...project 1 is, without doubt, a “no-brainer” and the need to introduce NGS and whole-genome technology topics into medical student and pathology resident education is mandatory.”²⁷

Of course, pathologists must also collaborate with other groups with genomic medicine expertise; however, there are currently <3000 molecular geneticists and genetic counselors in the United States as opposed to approximately 18,000 pathologists.^{23,28}

Single program approaches to genomic pathology training

Several residency programs have recognized the need for genomic pathology training and have designed curricula. In 2009, faculty at Beth Israel Deaconess Medical Center (BIDMC) established a mandatory genomic pathology curriculum for residents.^{29,30} The design was based on three major classes of teaching objectives: knowledge, affective and performance-based.³¹ The knowledge-based objectives were achieved through a series of three lectures. An introductory lecture provided a basic overview of genomics and the important role of the pathologist in genomic testing. The second lecture described genomic testing methods including NGS. The final lecture, given by genetic counselors, focused on communication of genomic testing results to patients.

To provide an even greater appreciation for affective issues related to the patient experience, residents were offered free-of-charge direct-to-consumer (DTC) genomic testing. Participation was completely voluntary, not required to participate in the curriculum and results were only seen by the ordering resident. The company utilized SNP testing to determine “risk” for 40 conditions and provided genetic counselors to answer any questions residents might have regarding results. While there has been some debate on the ethics and utility of offering genetic testing students and trainees, such an approach is not unique in pathology.^{18,20,32} At some programs, residents may perform laboratory testing on their own blood samples (e.g., a type and screen).³³ In addition, a key incentive for adult learners is the “need to know.”³⁴ Consistent with this idea, several residents selected the topic for their end-of-curriculum presentation based on the results of testing.

This final component of the curriculum, a presentation to their colleagues on a paper related to genomic testing of a disease of their choice, allowed the residents to directly apply the knowledge and experience from the other two components of the curriculum. These 15 minute presentations covered a wide variety of both malignant and non-malignant diseases. Suggesting the success of this portion of the curriculum, two residents actually found an error on a DTC website.³⁵ For a variant associated with multiple sclerosis, after reviewing the relevant literature, the residents determined that the incorrect odds ratio was listed.

Stanford University has also taken the lead in resident training in genomic pathology.³⁶ A mandatory series of 10 lectures was started in 2010 and is now available online.³⁷ Lecture topics include methods in measuring and manipulating nucleic acids, types of genetic variation, application to specific diseases (e.g., inherited disorders, solid tumors, pharmacogenomics) and ethical and regulatory issues. In 2011, the department began offering an advanced genomic elective which is taught in a small group interactive format.

The TRIG Working Group: A model for training in novel technologies

While single institution programs are an important start, they provide training for only a small number of residents. Based on the aforementioned survey suggesting minimal genomic pathology resident training, a PRODS committee was created in 2010.²⁵ The

Training Residents in Genomics (TRIG) Working Group is made up of experts in molecular pathology, medical education, medical genetics and genetic counseling. Most educational initiatives in pathology have been through single organizations limiting the breadth of expertise.^{38,39} From its inception, the TRIG Working Group has taken a novel approach by including members of all major pathology organizations as well as non-pathologists with genetics expertise. Founding members included not only past presidents of the Association for Molecular Pathology (AMP) and a past editor-in-chief of *The Journal of Molecular Diagnostics* but, also the Executive Director of the National Coalition of Health Provider Education in Genetics and a representative from the National Society of Genetic Counselors.

The initial goals of the TRIG Working Group were also unique. Many groups have published curricula consisting of lists of topics for trainee instruction but often, this list is the final output.^{38,39} In contrast, the TRIG Working Group made creating a curriculum only the first step. Goals also included plans to implement the curriculum and evaluate dissemination and efficacy.

The members of the TRIG Working Group chose to start with a structured evaluation of the BIDMC curriculum. By March 2012, after developing more extensive objectives, lectures with notes were posted with free access on the Intersociety Council for Pathology Information website and are now posted on a separate TRIG website.⁴⁰ This initial curriculum included an introductory lecture followed by lectures on genomic methods, applying genomic technology to clinical care and communicating with patients.

To disseminate the curriculum and promote training of pathology residents in genomics, TRIG Working Group members have given presentations at major pathology meetings. Portions of the lectures have been presented at the annual meetings of the United States and Canadian Academy of Pathology (USCAP) and American Society for Clinical Pathology (ASCP). A number of articles have also been published describing the progress of the TRIG Working Group.^{25,41,42}

The TRIG Working Group is also evaluating the degree of resident training and knowledge in genomic pathology. Since 2012, members of the TRIG Working Group have provided knowledge and survey questions for the pathology Resident In-Service Exam (RISE). This exam is taken by nearly all pathology residents in the United States, and these questions can assess attitudes as well as perceived and actual ability related to genomic pathology.⁴³ The exam can also determine the number of programs that are offering training. The use of the RISE allows a comprehensive assessment, at a level rarely seen in medical education, of the current state of resident training in genomic pathology.

Based on the unique approach and progress to date, in 2012 the chair of the TRIG Working Group received a \$1.3 million R25 grant from the National Cancer Institute/NIH. With the ASCP providing educational design support, this grant has already been used to further refine the original TRIG curriculum to create day-long resident genomic pathology workshops. Using a team-based learning approach, these workshops allow hands-on training with online genomics resources. Workshops have been scheduled for the 2013 ASCP Annual Meeting and the 2014 USCAP and Academy of Clinical Laboratory Physicians and Scientists (ACLPS) Annual Meetings. A three-hour course based on the TRIG Curriculum will also take place at the 2013 College of American Pathologists (CAP) Annual Meeting. Plans also include creating online modules to be tested at four residency program sites and continuing to nationally assess genomic pathology training using the RISE. The ultimate goal, at the end of the 5 year funding period, is to ensure genomics training in >90% of the pathology residency programs in the United States.

More effort is needed

The TRIG Working Group has made significant progress in genomic pathology education but more assistance is required. Recognizing this need, other pathology organizations have started to provide additional support. CAP has recognized the potential of genomic technology to transform health care and has started developing curricula and teaching programs for practicing pathologists. AMP is in the process of creating updated syllabi for pathology residents and molecular genetic pathology fellows that include genomic medicine.

However, for genomic medicine to truly become a standard part of pathology residency and fellowship training, accreditation and certification bodies must include related requirements. The ACGME is undergoing a sweeping reform in its process of accrediting residency programs. Each specialty has developed “milestones” for residents and fellows to achieve during their training. That one pathology milestone requires proficiency in “advanced precision diagnostics and personalized medicine” is a positive sign of progress in genomic pathology education.⁴⁴ To provide further incentives, the American Board of Pathology should consider including genomic pathology on the list of topics covered on certification exams.⁴⁵ Such knowledge as a requirement to become a board certified pathologist would surely invigorate genomic pathology education.

Beyond pathology: Implications for oncology

Given the rapid integration of genomics into clinical medicine, all health care providers and not just pathologists must have training in genomic medicine. As noted above, oncology is the specialty in which this technology is first being applied to patient care on a large scale thereby making training an especially urgent need. The TRIG Working Group model can be applied across specialties with educational initiatives promoting inter-society and inter-specialty collaboration. The focus should not just be on creating lists of competencies but also teaching and evaluation tools. To assist in this effort, the TRIG Working Group materials are freely available on their website.⁴⁰

In 2011, the director of the National Human Genome Research Institute wrote, “it is time to get serious about genomics education for all health care professionals.”¹⁷ The pathology community has taken major innovative steps to carry out this mission. It is time for other specialties to be proactive in educating their trainees in principles of genomic medicine.

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