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NEXT GENERATION GENETIC COUNSELING

Next Generation Sequencing is the Impetus for the Next Generation of Laboratory-Based Genetic Counselors

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Abstract Next generation sequencing (NGS) is dramatically increasing the number of clinically available genetic tests and thus the number of patients in which such testing may be indicated. The complex nature and volume of the reported results requires professional interpretation of the testing in order to translate and synthesize the meaning and potential benefit to patients, and genetic counselors are uniquely suited to provide this service. The increased need for genetic counselors in this role, coupled with the time required and a limited number of trained and available counselors presents a challenge to current models for making genetic testing available to patients and their healthcare providers effectively and efficiently. The employment of genetic counselors at genetic/genomic laboratories is one model to expand the resources for providing this service. In this article, we briefly review the advent of NGS and its clinical applications, examine the core skills of genetic counselors and delineate the expanding roles and responsibilities of laboratory-based genetic counselors. We also propose changes to the genetic counseling training program curriculum to account for the increasing opportunities for genetic counselors to contribute and thrive within genetic testing laboratories.

Keywords Next generation sequencing · Laboratory-based genetic counselors · Training needs · Genetic counseling curriculum · Genetic counselor core skills

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Background

When the Human Genome Project was completed in 2003, it was well understood that there was still much work to be done before this information could be translated into everyday medical practice. A particular limitation was the time and cost related to traditional sequencing. At the time, all DNA sequencing was performed using the chain-termination method, now commonly referred to as Sanger sequencing (Sanger et al. 1977). Sanger sequencing has been the "gold standard" for over 30 years now. Sanger sequencing is a very accurate method by which to obtain long sequence reads (up to about 200 nucleotides). However, these reads are performed individually resulting in significant restrictions in scale and turn-around time. In the 1990s, a revolutionary but complex technique called massively parallel signature sequencing (MPSS) was developed by Lynx Therapeutics (Brenner et al. 2000). Multiple approaches have since been implemented but the technology, as the name implies, results from running multiple reactions simultaneously to generate large quantities of sequence data in parallel (Bentley et al. 2008; Eid et al. 2009; Shendure et al. 2005; Stoddart et al. 2009). As importantly, sequencers were developed that could run these reactions on a much larger scale. The impact of this technology is clearly seen in the now ubiquitous figure (see Fig. 1) constructed by the National Human Genome Research Institute (NHGRI) Genome Sequencing Program comparing the cost of whole genome sequencing (WGS) to Moore's law (Wetterstrand 2013). Since the introduction of what is now termed next generation sequencing (NGS) into the NHGRI's analysis in January 2008, the cost of sequencing one whole human genome was reduced from almost $10,000,000 to less than $10,000. NGS technologies are now being utilized in various clinical settings and the potential for expansion into a multitude of clinical applications is significant.

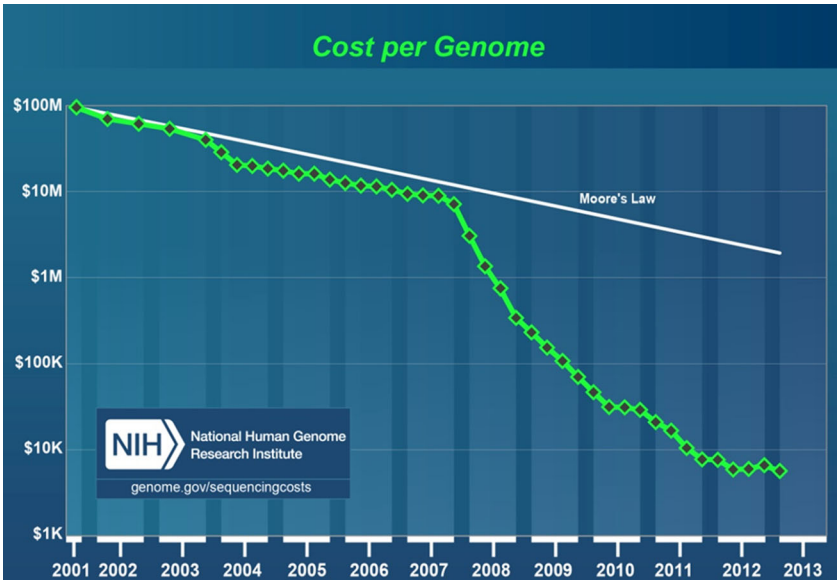

Fig. 1 Reductions in DNA sequencing costs from 2001 to 2012 as compared to hypothetical data reflecting Moore's Law (Wetterstrand 2013). Moore's Law is the observation of a long-standing trend in the computing hardware industry that the 'compute power' doubles every two years. Technology improvements whose pace is on track with Moore's Law are believed to be doing very well. In 2008, genomic sequencing suddenly began to significantly outpace Moore's Law. This represents the time when the sequencing centers transitioned from Sanger sequencing to next generation sequencing technologies. Permission to reprint this figure was obtained from K. Wetterstrand

A common phrase used when discussing the accuracy of NGS is "sequencing depth". Sequencing depth refers to the average number of times that a specific base/nucleotide is sequenced. The greater the number of times the genome is sequenced, the greater the "sequencing depth" and the more accurate the individual base calls. Whole genome sequencing using NGS can routinely call variants (base changes) with greater than 99.9 % sensitivity and specificity at a depth of 30-fold and greater than 95 % of the genome is covered at an average sequencing depth of 30-fold (Kingsmore and Saunders 2011). Currently, the detection of structural variants and trinucleotide repeats is not possible, although the improvement of long-read technologies (the ability to sequence kilobases in a single read) and improvements to alignment and variant calling algorithms are underway to address these shortcomings.

As a result of this technology, the landscape of genetic testing options for pediatric and adult clinical care has expanded. Rather than offering single gene tests using Sanger sequencing, clinical laboratories are now able to test many genes as a part of a single testing platform. These panels include testing for disorders ranging from hereditary cardiomyopathies, deafness and cancer syndromes to large pan-ethnic carrier screens (Ambry Genetics 2013; Bell et al. 2011; Lombardi 2013; Smith 2013). Equally significant is the availability of exome- and genome-level sequencing. In 2009, the Illumina Clinical Services Laboratory (San Diego, CA) became the first Clinical Laboratory Improvement Amendments (CLIA)-certified, College of American Pathologists (CAP)-accredited laboratory to offer whole genome sequencing. In May 2013, the Medical College of Wisconsin's Developmental and Neurogenetics Laboratory (Milwaukee, WI) followed suit. In September 2011, Ambry Genetics (Aliso Viejo, CA) became the first lab in the United States to offer whole exome sequencing with clinical interpretation. Currently, at least five other laboratories are offering this testing. An online review of the websites for these laboratories indicates they all employ genetic counselors. The number of tests offered per year is growing rapidly.

The majority of the labs offering whole exome sequencing perform singleton and trio analysis (individual plus parents) and quote a turn-around time of 90+ days. The turn-around time of whole genome sequencing has shortened considerably by combining improvements in the sequencing technology with bioinformatics tools for variant classification and phenotype filtering. Turn-around time is now shorter than that of most multi-gene panels and whole exome sequencing, facilitating clinical use in the intensive care setting. Such rapid molecular diagnosis has shortened the time from initial evaluation to genetic and prognostic counseling and treatment (Saunders et al. 2012).

NGS has also dramatically altered the prenatal genetic testing sphere. In October 2011, non-invasive prenatal testing (NIPT) became clinically available via massively parallel sequencing of fetal cell-free DNA (cfDNA). Currently, four laboratories in the United States offer NIPT; all use NGS-based technologies. Detection rates range from 99.1 to 100 % for Down syndrome (trisomy 21), 97.2–100 % for trisomy 18, and 78.6–100 % for trisomy 13 (Bianchi et al. 2012; Norton et al. 2012; Palomaki et al. 2012). The demand for such testing

has been overwhelming and in under two short years, the number of tests performed in the United States is estimated at over 88,000 (Futch et al. 2013; Saldivar et al. 2013; Wang et al. 2013). Increasingly, pregnant women are opting for NIPT first instead of choosing the standard invasive prenatal procedures: chorionic villus sampling (CVS) and amniocentesis. Clinics are reporting decreased rates of invasive testing, a finding that has been attributed directly to the clinical implementation of NIPT. For example, a recent study from Stanford University found a decrease in diagnostic testing rates, from 52.8 % to 39.2 %, in patients with positive aneuploidy screening after the introduction of NIPT (Chetty et al. 2013). And, a study by Rosenthal et al., reported a 40 % reduction of amniocentesis procedures since the implementation of NIPT (Rosenthal et al. 2013). Initially NIPT was offered to detect trisomies 21, 18 and 13. The number of conditions that can be identified by NIPT has already increased since its inception (e.g., testing for sex chromosome aneuploidies), and will likely continue as recent publications have shown the ability of NIPT using NGS to detect subchromosomal aberrations and single-gene mutations (Fan et al. 2012; Kitzman et al. 2012; Li et al. 2005; Srinivasan et al. 2013).

With such appealing characteristics as high test accuracy, number of conditions tested, rapid turn-around time, and positive coverage decisions by third party payers, genomic sequencing is "expected to become a central piece of routine healthcare management which can be practiced regularly by physicians from their offices" (Ong et al. 2013). That being said, there is uncertainty about how the genetic information provided by NGS technologies should be effectively integrated into current medical practices. When there were a limited number of genetic tests available and thus a limited number of patients for whom these tests were indicated, healthcare providers relied on genetic professionals, especially certified genetic counselors (CGCs), to facilitate genetic test ordering, informed consent, and results disclosure/interpretation. With the introduction of NGS, the number of available genetic tests has already soared from a few hundred in 2003 to currently over 3,000 (Nagy and Sturm 2013). As such, many more patients will now be candidates for genetic testing. The number of CGCs (3,193 according to the American Board of Genetic Counseling, Inc.) pales in comparison to the number of potential patients in need of counseling and testing (American Board of Genetic Counseling 2013). There is approximately one genetic counselor for every 135,000 individuals in the United States (Brunham and Hayden 2012). Thus, the traditional practice of providers referring relevant patients to genetic counselors is not sustainable and alternative models must be considered if genetic testing is going to be effectively integrated into routine medical practice.

The Genetic Counselor Roles and Responsibilities

The roles and responsibilities of a genetic counselor must broaden to meet the needs of healthcare professionals and patients as genetic testing becomes applicable to a much larger patient population. Historically, genetic counselors have worked primarily in a clinical setting, "providing information and support to families who have members with birth defects or genetic disorders and to families who may be at risk for a variety of inherited conditions…and review[ing] available options with the family" (National Society of Genetic Counselors 1983). While the majority of genetic counselors currently counsel patients as part of their regular job responsibilities, the number of genetic counselors who do not directly counsel patients is increasing. In 2004, the Professional Status Survey (PSS), which is administered bi-annually to NSGC members to document the working environment and professional activities of its members, began to account for changes in the professional roles of genetic counselors (Parrott and Manley 2004). In the 2004 PSS, 7 % of respondents indicated that their primary work setting was a diagnostic laboratory and in the 2012 PSS there was a greater than 50 % increase for a total of 11.2 % (National Society of Genetic Counselors 2012; Parrott and Manley 2004). It is not coincidental that the increasing number of genetic counselors working primarily in a diagnostic laboratory occurred during the same time as the development and implementation of next generation sequencing technologies.

The typical roles and responsibilities that CGCs have had in the core areas of clinical pediatrics, prenatal and cancer genetics will continue to be of great importance. However, the growth of laboratory-based genetic counselors is one way in which our field can adjust to the expansion of genetic testing into routine healthcare. But, what do laboratory-based genetic counselors do if they do not directly counsel patients in clinic? Review of the genetic counseling literature provides little information about genetic counselors in laboratory-based roles. In 2010, Christian et al. administered a survey to laboratory-based genetic counselors in order to define their most common roles (Christian et al. 2012). Forty-three laboratory genetic counselors completed the survey. The results of this survey showed that 95 % of respondents reported serving as a customer liaison and 88.4 % indicated calling out results as part of their job responsibilities. Additionally, over 60 % of respondents reported one or more of the following as routine tasks: laboratory support, writing policies and procedures, and administrative duties (Christian et al. 2012). These roles cover a broad spectrum of responsibilities involving both an external element (the ordering providers) as well as an internal element (the laboratory itself). These roles have not been described in detail, particularly as they pertain to NGS technologies.

Roles of a Diagnostic Laboratory-Based Genetic Counselor

External Roles

Patient-Independent Provider Education

In our experience, the laboratory-based genetic counselor role of "customer liaison" can be best described as educating providers. While clinic-based counselors educate patients and less often providers, laboratory-based counselors educate providers and less often patients. Provider education includes patient-independent education (general information about the risks, benefits and limitations of genomic testing technologies) and patient-specific education (pertaining to a particular patient's medical and family histories and test results/interpretation). Patient-independent provider education typically takes place in traditional settings such as grand-rounds, departmental, regional, and national meetings and articles published in peer-reviewed medical journals. Additionally, since NGS technologies differ significantly from the traditional sequencing technologies, provider education is increasingly being conducted via more lengthy educational seminars.

For example, the genetic counselors at Verinata Health, an Illumina company, developed a one-day, interactive course titled "Advanced Training for Genetic Counselors (ATGC) on NIPT." This course is intended to provide an understanding of the nuances of NGS-based NIPT for practicing prenatal genetic counselors. Facilitated by the laboratory genetic counselors, this course focuses on critical analysis of clinical validation studies, clinical implementation and ethical challenges associated with the introduction of NIPT. Positive feedback from participants of the pilot course led to establishment of ongoing CEU-approved regional courses which have been attended by over 180 genetic counselors in the United States and Canada.

Another example of laboratory-directed educational events led by and including genetic counselors is Illumina's Understand Your Genome (UYG) symposium which was first offered in 2012. UYG is a two-day event featuring didactic lectures and interactive workshops focusing on the clinical application of whole genome analysis and includes the offering of whole genome sequencing to the participants.

Patient-Specific Provider Education

Genetic counselors routinely educate patients in the clinic about inheritance patterns, genetic testing strategies, test logistics and test results. This skill is transferrable to a laboratory setting where genetic counselors can assist providers with questions related to genetic testing for specific patients. This patient-specific education can include pre-test conversations with providers on test appropriateness, testing strategies, and test logistics. It can also include discussion about alternative testing options for patients who may not meet criteria for a particular test.

A 2003 survey of genetic counselors demonstrated that greater than 50 % of counselors in the clinical setting relied on laboratory personnel for assistance with various aspects of the genetic testing process (McGovern et al. 2003). If more than half of clinic-based genetic counselors were in need of assistance from genetic laboratories, one can assume that this need is even greater for those clinicians who do not specialize in genetic medicine.

Patient-specific education is also necessary post-testing. A majority of laboratory-based genetic counselors report one of their roles is to call abnormal/unusual test results to ordering providers (Christian et al. 2012). Although some physicians may be able to order genetic tests appropriately, they may not have the ability to appropriately understand the interpretation and counsel patients about their test results. For example, in an evaluation of 177 patients at risk for Familial Adenomatous Polyposis who underwent genetic testing of the APC gene, 83 % of patients were tested based on appropriate indications. However, 31.6 % of the time the result was interpreted incorrectly by the ordering provider. In particular, there was a lack of understanding about possible false negative results (Giardiello et al. 1997). It is essential for laboratories to assist providers with understanding test results and their clinical significance to avoid potential harm that may be caused by incorrect interpretation and management. The core skills of genetic counselors make them excellent candidates to help providers correctly interpret patient-specific results (NSGC 2009).

While the aforementioned provider education roles do not involve direct patient contact, it should be noted that some laboratory-employed genetic counselors are contracted by clinical practices to provide direct patient counseling. The latter scenario has been the subject of much debate due to the potential conflict of interest presented by this arrangement. Such arrangements exist because many clinical practices cannot afford to employ their own genetic counselors and patients at such clinics may not otherwise be receiving appropriate pre- and post-test genetic counseling. However, concerns have been raised that these counselors may encourage their patients to undergo certain genetic tests offered by their employer over other available options (Harris et al. 2013; Pollack 2012).

One might expect that the non-directive approach upon which the field of genetic counseling is based would prevail regardless of one's employer. However, the appearance of a conflict of interest remains as indicated by one insurance company's recently drafted policy on coverage for specific genetic tests. Cigna's new policy requires patients to undergo genetic counseling, by a non-laboratory employed genetic counselor, prior to genetic testing for hereditary breast cancer, hereditary colorectal cancer and/or Long QT syndrome (Cigna

2013). While this new policy has reinforced the importance of pre-test counseling by a geneticist or genetic counselor, it has also reinforced the perceived conflict of interest by excluding laboratory-employed counselors from being considered "in network" providers.

Such exclusions of laboratory-employed counselors will not have a negative impact on the laboratory genetic counseling roles we have highlighted in this paper as they do not involve direct patient contact. However, we recognize that such conflict of interest concerns may exist around laboratory genetic counselors educating healthcare providers about various genetic tests. Of the 144 ATGC on NIPT attendees who completed course evaluations, 89 % agreed that the information was presented without commercial bias, suggesting that laboratory-employed counselors may be able to offer responsible provider education with minimal conflict of interest (Swanson and Snyder 2013). We hypothesize that paying genetic counselors employed by laboratories by salary, rather than by commission, may help minimize any direct personal conflicts of interest.

Internal Roles

Results and Interpretation

Just as laboratory-based genetic counselors are well-suited to help ordering providers navigate through the genetic/genomic testing process, they are equally able to assist their laboratory colleagues in both the pre- and post-analytic stages of testing. Once a sample is received by a laboratory, the genetic counselor may review the patient's medical and family histories to ensure that the correct test has been ordered. In some cases, he/she will need to obtain additional information from the ordering provider to facilitate determination of test appropriateness. In a review of molecular tests ordered at ARUP Laboratories, Miller et al. reported that on average, one-third of molecular tests are ordered incorrectly (Miller et al. 2011).

Following the completion of sample analysis, the genetic counselor may assist laboratory directors with the interpretation of the results. "Interpretation" of the genomic variants detected by NGS technologies is widely recognized as a bottleneck to service delivery, as referenced by the phrase the "$1000 genome with the million dollar interpretation" (Davies 2010). Once a variant is called, it is annotated in an automated fashion. However, variants of interest must then be evaluated for possible clinical significance. This includes an assessment of the annotation data—allele frequency, predicted impact on the function of the protein, the degree of evolutionary conservation, etc.—and a review of available peer-reviewed literature. These data must then be incorporated into the clinical context of the individual patient, whether related to a known diagnosis, predisposition and risk assessment, carrier screening, pharmacogenomics or other indications for testing. Given the volume of variants identified by whole exome or whole genome sequencing, the phenotypic presentation of the patient must be considered so filters can be applied to narrow the focus of testing and optimize the interpretation of the variants (American College of Medical Genetics and Genomics 2012). Genetic counselors have a deep knowledge and understanding of genetics along with clinical expertise, making them a particularly valuable resource for variant interpretation.

Other Roles

Genetic counselors can use their core skills (designated by quotation marks) in a variety of additional ways to support laboratories. Their "ability to tailor, translate and communicate complex information in a simple, relevant way for a broad range of audiences" makes genetic counselors ideal candidates to aid in the design of provider and patient marketing materials. Genetic counselors' "in-depth knowledge of healthcare delivery" helps bring the voice of the customer to laboratory employees, who may not be familiar with the significance of what the test results mean for patients and what the needs are of the clinicians ordering such testing. This knowledge of healthcare delivery, along with a "deep and broad knowledge of genetics" makes genetic counselors invaluable in laboratory discussions pertaining to the development of new or improved test offerings. And, the "ability to dissect and analyze a complex problem", enables genetic counselors to be part of research and development teams, allowing for a more interdisciplinary approach to research studies (National Society of Genetic Counselors 2009).

Expected Training Needs for the Genetic Counseling Profession

While the unique skill-set of genetic counselors already allows for placement of graduates into laboratory-based roles, as these roles continue to expand, certain aspects of the genetic counseling graduate curriculum could benefit from specific changes. Drawing from our experience working with genetic counseling students, we found that a comprehensive understanding of NGS technology is essential, as well as training that will help prepare counselors for the variety of unique challenges that may arise as a result of this technology.

As genetic counselors take on more variant curation responsibilities in laboratories performing whole exome/whole genome sequencing, they will need a baseline understanding of what this entails. Genetic counseling students should be introduced to molecular databases such as ClinVar, HGMD, and 1000 Genomes. They will need to know how to search these databases and once the necessary information is located, be able to review this information to determine its credibility

and significance as it relates to patient-specific scenarios. Additionally, they will need to critically analyze the literature and combine documented information like allele frequency, protein impact and functional data with family studies to assess the clinical significance of a variant. These skills are also valuable for the clinical counselor as they will be faced with increasing numbers of rare variants and must communicate the limitations of the available data to their patients.

In addition to variant curation, laboratory-based genetic counselors collaborate with other laboratory staff to review clinical histories and help integrate this information into individualized result interpretation and recommendations. Christian et al. found that nearly half of laboratory genetic counselors sign laboratory reports as part of their responsibilities (Christian et al. 2012). This is not an area currently included in the NSGC Scope of Practice. Therefore, many graduate programs may be unprepared to introduce students to these types of responsibilities that can expose laboratory genetic counselors to medical-legal consequences. In order to ensure protection of genetic counselors, graduate programs may consider providing additional training in the areas of medical malpractice and relevant state and federal CLIA regulations.

Hands-on experience is the cornerstone of genetic counseling training programs. The Accreditation Council for Genetic Counseling (ACGC) adopted a "Standards of Accreditation for Graduate Programs in Genetic Counseling" in February 2013 (Accreditation Council for Genetic Counseling 2013). The program standards for instructional content set-forth in this document include clinical training and fieldwork experience. Section B3.2.1 of the standards addresses the specific requirements for "core cases", of which students need at least 50 cases. To be considered a "core case", the clinical interaction must occur face-to-face and students must actively participate in at least one role in each of the three Fundamental Counseling Roles categories (Management, Education, and Counseling). While we recognize the importance of all of these roles, as laboratory positions continue to evolve for genetic counselors, we encourage the ACGC to consider adapting their requirements to include skills learned during laboratory rotations.

Laboratory rotations will not provide the face-to-face clinical interaction with patients that is required for the "core cases"; however, these rotations will arm students with a better understanding of the roles and responsibilities of the laboratory-based genetic counselor. In reviewing the skills listed in the Fundamental Counseling Roles categories, it is apparent that there is much overlap between these skills in the clinical and laboratory settings (see Table 1) (Accreditation Council for Genetic Counseling 2013). Given the significant overlap, the ACGC might simply modify the three Fundamental Counseling Roles category requirements for core cases by removing the face-to-face requirement. Many of these actions are carried out with healthcare providers over the phone, rather than patients in person, in a laboratory setting. The ACGC would also need to consider whether it would be acceptable for certain counseling roles to not be met.

Table 1 ACGC-defined fundamental clinical counseling role requirements: achievability in a clinical setting versus a laboratory setting

Fundamental clinical counseling roles	Clinical setting	Laboratory setting
Management Roles:		
Case preparation	√	√
Collection/documentation of medical, developmental, and/or pregnancy history	√	√
Collection/documentation of family history/ pedigree	√	√
Risk assessment	√	√
Evaluation/coordination of genetic testing	√	√
Clinical documentation	√	√
Other follow-up	√	√
Education Roles:		
Inheritance pattern	√	√
Risk counseling	√	√
Diagnosis/prognosis/natural history	√	√
Medical management/prevention/treatment	√	√
Genetic and/or prenatal testing options and possible results/benefits/limitations	√	√
Results disclosure	√	√
Research options/consenting	√	√
Counseling Roles:		
Establishing rapport/contracting	√	√
Psychosocial assessment	√	–
Psychosocial support/counseling	√	–
Resource identification/referral	√	√
Case processing/self-assessment/self-reflection	√	√

Alternatively, a separate laboratory experience component could be added while recognizing that many of the skills are cross-functional. Such a separate component could include laboratory responsibilities such as variant curation, results interpretation, discussion of test results with ordering providers, collection of follow-up information pertaining to test results, developing patient/provider information sheets on new technologies, participating in laboratory-sponsored clinical research studies, and writing case reports and research papers. As laboratory rotations are being developed, participating laboratories may wish to confirm with their insurance brokers that their policies cover liability for student involvement with patient samples and ordering providers.

Conclusion

Laboratory-based genetic counselors can assist healthcare providers with a general understanding of the benefits and limitations of various genetic tests as well as with the

interpretation of patient-specific test results. They can also support their laboratory colleagues in many ways including ensuring the correct test has been ordered, clinical test interpretation, designing clinically-sound marketing materials, and participating on research study and product development teams. The need for laboratory-based genetic counselors will likely grow as there are not enough clinical genetic counselors to counsel every patient who may benefit from the increasing number of available genetic tests. This responsibility is falling on other healthcare providers who are not trained in genetics, and who in turn will rely on the expertise of laboratory-based genetic counselors. Modifications to the genetic counseling training program curriculum to include laboratory-based rotations will better prepare future genetic counselors to meet the needs of genetic testing laboratories and healthcare providers, in addition to the needs of the patients.

Conflict of Interest Amy Swanson and Holly Snyder are both employed by Verinata Health, an Illumina company. Erica Ramos is employed by Illumina, Inc.

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