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Opportunities for the Genetic Counseling Profession through Genomic Variant Interpretation: Reflections from an Ex-Lab Rat

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Abstract

The genetic counseling profession continues to expand and respond to the changing landscape of genomic medicine. “Non-traditional” genetic counseling roles have become more commonplace and the transferability of the genetic counselor skill set has been widely acknowledged, particularly in genetic laboratory settings. As these expanding roles continue to mature, all genetic counselors can benefit by learning and adopting clinically-relevant skills, such as genomic variant interpretation, which can be applied to direct patient care. These skills can enrich our patients’ understanding of their test results, help ensure quality patient care, and could be useful in positioning genetic counselors as critical members in the medical team as we continue to fully transition into the genomic medicine era.

Keywords

variant evaluation; variant interpretation; clinical genetic counseling skills; laboratory genetic counseling skills

In 2007, when I entered the genetic counseling workforce as a new graduate in a clinical genetic testing laboratory, about 7–8% of genetic counselors reported holding laboratory positions (NSGC PSS 2004; NSGC PSS 2006) and the term “non-traditional” was still clearly stamped across these positions. It was an exciting time, as the number of genetic counselor laboratory positions rose to 20.9% of primary work settings by 2016 (NSGC PSS 2016). Literature documenting the transferability of clinical genetic counseling skills into “non-traditional” settings and the emergence of roles due to the acquisition of new skills has also begun to grow (Christian, et al. 2012; Goodenberger, et al. 2015; Everett, et al. 2014; Waltman, et al. 2016). This remarkable evolution has been acknowledged at recent National Society of Genetic Counselors (NSGC) Annual Conferences where leadership actively argued against using the term “non-traditional” at all. This is a welcomed acceptance of the current state of the genetic counseling profession and its broad, promising future.

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After nine years primarily in a laboratory-based position, I have transitioned into a clinical and research-based setting, where I lead a team of genetic counselors in a multi-disciplinary neurodevelopmental medicine institute and contribute to several research initiatives. This transition has provided an opportunity to reflect on how laboratory genetic counseling experience can strengthen direct patient care and can allow the genetic counselor to fulfill important healthcare needs in the era of genomic medicine. By documenting these professional reflections, I hope to outline key arguments for the active incorporation of variant interpretation principles and tools into clinical genetic counseling practice, comment on the need for on-going educational efforts to grow these skills, and promote research and discourse about the flow of newly-acquired, relevant skills across specialties within the genetic counseling profession.

Genetic counselors are all aware that, while we may be in a radiant age of genomic technology and data acquisition, the clinical genetics profession is not quite as illustrious at interpreting genomic data. Only a small proportion of identified genomic variants have completely understood functional consequences. The medical literature contains many published variants whose pathogenicity is assumed based on a single association with a clinical phenotype and which lack robust control population data, convincing functional studies, or basic familial segregation data. The potential for rare, benign variation in humans was not appreciated and, historically, if a variant was identified in a patient it was often assumed that it must be disruptive.

Many laboratory genetic counselors have had unique exposure to these interpretive challenges. They are often involved in genomic variant interpretation and curation activities and have expertise using genomic databases and resources that are critical to the difficult mission of unraveling the health implications of the human genome (Waltman, et al. 2016). These skills have not been extensively taught in most graduate programs; the current guidelines for sequence variant interpretation and many of the current genomic resources did not even exist until a few years ago, and they have only very recently been considered potential tools for a clinician. Therefore, laboratory-based positions have provided learning opportunities for a subset of the genetic counseling profession that are only recently being discussed as beneficial in clinical settings.

With clinically-available genomic testing, clinicians can be inundated with data, from lists of reported genomic variants with corresponding, and perhaps conflicting, literature to various bits and pieces of evidence derived from population databases and computational predictions. Which types of data are most powerful? Which sources are most reliable? How do we put it all together? These questions are not just difficult for the clinician; laboratories and genomic medicine leaders are currently wrestling with these problems, and their work has resulted in major improvements and Herculean collaborative efforts. The 2015 American College of Medical Genetics and Genomics (ACMG)-Association for Molecular Pathology (AMP) joint guidelines for the interpretation of sequence variants have moved us toward increased objectivity (Richards, et al. 2015). Publicly available patient and population databases, such as ClinVar, the Exome Aggregation Consortium, and the Genome Aggregation Database, can allow for more transparent and constructive deliberation of genomic variants (Harrison, et al., 2016; Lek, et al., 2016). However, these efforts have

required an impressive amount of humility and cooperation, acknowledging that no single laboratory can perfectly interpret all genomic variants and that some previous interpretations may be erroneous or out of date (Amendola, et al., 2016; Harrison, et al., 2017). Even our current population databases, which have been so important in informing recent variant interpretation improvements, have limitations and should continue to be developed and curated. Despite admirable attempts, clinical variant interpretation is not yet a perfect, automatable algorithm, making the clinical perspective a vital component of variant interpretation.

Genetic counselors' clinical perspectives are important in variant interpretation efforts and we should embrace the opportunities to contribute to large-scale efforts and to fine-tune our clinical practice. This involves thinking critically beyond the laboratory's report, ensuring that we understand why the variant classification was made, adding clinical nuances that are difficult for laboratories to appreciate, and critically reviewing the data important to a variant's interpretation. This can be as natural a process in patient care as pulling together the pieces of a patient's clinical history or interpreting a pedigree. But, it requires two things: 1) acknowledgement that laboratory interpretations are limited by subjective perspectives and data available at a single point in history, and 2) familiarization with genomic tools and resources in order to actively engage in the variant interpretation process. Incorporating variant interpretation processes can enhance genetic counseling practice and is a critical skill for genetic counselors to embrace as they are increasingly incorporated as genetics experts in non-genetics medical settings. Furthermore, genetic counselors can engage with laboratories, research efforts, and collaborative curation efforts with their clinical assessments and contribute to the greater body of genomic medicine in ways that are potentially dramatic.

Although there is very little literature available about clinical genetic counselor variant interpretation activities, genetic counselors are trained to critically review scientific data and many may already perform many of these types of activities to some extent (Bland, et al. 2017; Scherr, et al. 2015; Wain, et al. 2017; Yashar, et al. 2016; Zirkelbach, et al. 2017). We consider key concepts like segregation, variable expressivity, penetrance, and phenocopies in an evaluation. We recognize ascertainment bias in the literature and the importance of documenting the source of clinical or family history information. We understand genetic mechanisms of disease, types of genomic variants, population genetics principles, and how to discuss these concepts in a meaningful way with our patients. Our educational foundation is strong and can certainly support the adaptations that genomic medicine requires.

It is not easy to adapt to change and to acquire new skills. With demanding patient loads, administrative support limitations, and billing restrictions, it can be difficult to keep up (McPherson, et al. 2008). But, if genetics professionals get overwhelmed and confused by variant interpretation, how much more difficult is it for our patients? It is our job to mediate ambiguity and translate laboratory interpretations in a way that patients can understand so they can incorporate genetic test results into health decisions. Therefore, the more confidently and accurately we understand a variant's interpretation, the more able we will be to discuss it and answer questions that could arise from a variety of unique responses, needs, or perspectives. The impact of this practice goes beyond patient education. In my

experience, rapport and trust are deeply strengthened when the genetic counselor clearly understands the underlying rationale for a variant's classification and has assessed information beyond the laboratory report. Not all counseling encounters involve detailed discussions of variant interpretation, but a genetic counselor should be equipped for such discussions. The genetic counselor's job is not simply to read the report to a patient, but to help them understand the take-home messages that result from it. When I need to tell a patient that the "mutation" they have been living with for years is now considered a "variant of uncertain significance," the last message I want them to take away is that the healthcare system is unreliable or cannot be trusted. A comfortable understanding of current variant interpretation practice is a powerful asset in maintaining patients' trust and helping them adjust to a reclassified variant.

All clinicians rely on laboratory specialists to provide relevant interpretations of clinical data, which will give useful, reliable clinical guidance. While variants of uncertain significance (VUS) are largely considered not useful for clinical guidance, genetic counselors are sophisticated enough to admit that not all VUSs are created equal. Some are unconvincing and clog up the medical record and the counseling session. But with some, a patient's phenotype or family history may fit well with reported literature, and there may be a strong argument for potential pathogenicity based on supplemental clinical evidence. Are we serving our patients well by rigidly insisting that both types of results be treated equally? I don't think so. Genetic counselors can be the key to gathering relevant clinical data, even over the course of years, that could tip the interpretive scales toward benign or pathogenic classifications. We can mark variants for re-evaluation in 6 or 12 months in case another publication comes out. We can help our patients and families understand how to focus their energy, especially if they are inclined to participate in patient registries or social media groups. And we can contribute to public knowledge through thoughtfully selected case reports, collaborating with one another, and by submitting variants with up to date clinical data to publicly available curated databases, like ClinVar, as clinicians (Wain, et al. 2017).

Importantly, the genetic counselor might be the one medical professional involved in a patient's care who will recognize when there is a problem with how a variant has been classified. Patients will present with genetic test reports from years ago. How valid are those interpretations? Non-genetics professionals are far less likely to understand how genomic variants are interpreted, how our understanding of genomic variation has changed, or how variant classification terminology has changed. They may have no cause to question an interpretation, resulting in potential harm if medical recommendations are based on inaccurate or outdated laboratory reports. The genetic counselor within the medical team would recognize when to contact the laboratory about re-interpretation and could assess newly available evidence relevant to current variant interpretation practice. Genomic medicine will be applied in all areas of healthcare and the genetic counselor workforce is envisioned to find professional niches just as broadly. Genetic counselors can fulfill the role of validating the clinical interpretation of genomic data that a patient's clinical team is using to implement changes in medical care. It is an incredibly vital role that requires our scientific rigor, our communication skills, and our ability to work as part of a healthcare team.

For many genetic counselors, embracing variant interpretation in the clinical setting will mean actively pursuing educational opportunities. Seek out opportunities to attend sessions and short courses on genomic resources or variant interpretation at national or regional conferences. The Clinical Genome Resource (ClinGen), NSGC, ACMG, and other organizations have created webinars and YouTube videos to help answer questions and build familiarity. Many of these, such as those provided by ClinGen at <https://www.clinicalgenome.org/genomeconnect/educational-resources-webinars/>, are freely available. These resources can provide big-picture overviews of the types of evidence used in variant interpretation, current sources of this information, and an understanding of the relative strength of different types of evidence. This can be a helpful starting point to identify specific tools and resources to research further. Getting comfortable with one genomic resource or component of variant interpretation at a time can be a less overwhelming way to incorporate new skills into clinical practice. Additionally, continue driving the fulfillment of genetic counselor educational needs by reaching out to one another, NSGC, and other professional networks. Consider how variant interpretation practices can be incorporated into clinically-oriented education sessions, start conversations with genetic counselor colleagues about challenges and successes related to variant interpretation, and include elements of variant interpretation in case conferences.

Finally, engaging with one's laboratory and acting as a clinical partner can forge a stronger professional relationship, leading to a more nuanced understanding of the laboratory processes, perspectives, strengths, and weaknesses. Get to know laboratory genetic counselors, ask them to explain their interpretation processes, and contact them with questions about reports. Laboratories should welcome discussions with clinical providers about how variants are classified and appreciate feedback on how they can improve the utility of a laboratory report so that this process is transparent. These skills may also be useful in choosing between genetic laboratories and navigating potential interpretation discrepancies between laboratories.

The traditional components of a counseling session have withstood history, yet we continue to innovate by adapting to the needs of patients and medical colleagues in diverse settings. Our conception of pre-test informed consent is evolving with the breadth of genomic test options (Bernhardt, et al. 2015). We are discussing how to identify the patients and clinical scenarios which most require a genetic counselor's expertise to maximize time and impact (Yashar, et al. 2016). And, with additional research and education, variant interpretation processes can be more consistently incorporated into direct patient care and genetic counseling program curricula. In this time of massive genomic data acquisition and fluid understanding, genetic counselors have an opportunity to borrow from the broader professional range that "non-traditional" roles have created, by embracing a strong understanding of genomic variant interpretation. What better way to celebrate the broadening of our profession than to actively adopt the best of what we can teach each other.

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