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Developing a genomics rotation: Practical training around variant interpretation for genetic counseling students

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Abstract

With the wide adoption of next-generation sequencing (NGS) based genetic tests, genetic counselors require increased familiarity with NGS technology, variant interpretation concepts, and variant assessment tools. The use of exome and genome sequencing in clinical care has expanded the reach and diversity of genetic testing. Regardless of the setting where genetic counselors are performing variant interpretation or reporting, most have learned these skills from colleagues, while on the job. Though traditional, lecture-based learning around these topics is important, there has been growing need for the inclusion of case-based, experiential training of genomics and

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variant interpretation for genetic counseling students, with the goal of creating a strong foundation in variant interpretation for new genetic counselors, regardless of what area of practice they enter. To address this need, we established a genomics and variant interpretation rotation for Stanford's genetic counseling training program. In response to changes in the genomics landscape, this has now evolved into three unique rotation experiences, each focused on variant interpretation in the context of various genomic settings, including clinical laboratory, research laboratory, and healthy genomic analysis studies. Here, we describe the goals and learning objectives that we have developed for these variant interpretation rotations, and illustrate how these concepts are applied in practice.

Keywords

Variant interpretation; genomics; genetic counseling; rotation; genetics education

Introduction

Since the advent of next-generation sequencing, the quantity and complexity of genetic and genomic tests have surged, and this trend is only expected to continue (Ong, Lin, Das, Grosu, & Fan, 2013; Swanson, Ramos, & Snyder, 2014). In parallel with the rise in testing, an increased number of laboratory-based genetic counselors will be required to support the ordering and interpretation tasks associated with such testing (Christian, Lilley, Hume, Scott, & Somerville, 2012; Waltman et al., 2016). Additionally, the increase in test complexity demands that clinic-based genetic counselors have a broad understanding of the evidence upon which interpretations are made (Facio, Lee, & O'Daniel, 2014).

Clinical laboratory-based genetic counselors are actively involved in interpreting and communicating genomic information, with nearly half of them drafting content for reports, investigating clinical significance of variants, and/or reviewing results data (Waltman et al., 2016). Recent data from National Society of Genetic Counselors (NSGC) Professional Status Survey demonstrate a dramatic increase in the number of laboratory-based genetic counselors over the past sixteen years. In 2002, laboratory-based genetic counselors comprised 6% of employed genetic counselors; this proportion rose to 16.8% by 2014 and to 21.6% in 2018 ("National Society of Genetic Counselors: _S1_Reference12Professional Status Survey 2018 Work Environment," 2018). With this increase in laboratory-based positions, there is a critical need for genetic counselors to receive strong foundational and ongoing training centered around genomics and interpretation of genomic testing (Swanson et al., 2014; Waltman et al., 2016).

While the importance of genomics-trained clinical laboratory-based genetic counselors is evident, there is also a growing need to train clinic-based genetic counselors in genomics and variant interpretation. A solid foundation in genomic test methods and variant interpretation can help clinic-based genetic counselors navigate the ever-increasing complexity of genomic testing options and results and can empower them to serve as even more active participants in the clinical genomic testing process. For example, knowledge of genetic technology enables genetic counselors to think critically about testing options and

select the most appropriate test for a patient (Facio et al., 2014; Swanson et al., 2014). Clinic-based genetic counselors are also well positioned to critically review a genomic test result in the context of their patient, possibly either identifying an inconsistency with the variant classification or recognizing that additional information about this patient's features or family history may impact the classification (Reuter, Grove, Orland, Spoonamore, & Caleshu, 2018; Wain, 2018). In some clinical specialties, such as cardiovascular genetics, the majority of clinic-based genetic counselors are already performing variant interpretation as part of their routine practice (Reuter et al., 2018).

Notably, the majority of genetic counselors who routinely perform variant interpretation in their roles learned this skill from their colleagues while on the job, as opposed to during graduate training (Reuter et al., 2018). In recent years, there has been a push from many corners of the community to incorporate this training more fully in graduate programs. For instance, in a 2014 survey, fifteen of the sixteen surveyed genetic counseling program directors agreed that genomics content should be added to the curricula, and the majority of respondents had already begun to integrate content into their training programs as part of their formal lecture-based and informal curriculum (e.g. journal club, professional meetings, optional guest lectures) (Profato, Gordon, Dixon, & Kwan, 2014). The Accreditation Council for Genetic Counseling (ACGC) implemented updated practice-based guidelines in 2015, which aimed to highlight genomics in the curricula to ensure that graduating genetic counseling students are prepared to tackle current and future genomics-related roles (ACGC Practice Based Competencies; <http://gceducation.org/>). Several groups have advocated for professional training to prepare genetic counselors for roles in variant interpretation and genomic reporting (Swanson et al., 2014; Waltman et al., 2016).

Despite general conceptual agreement that genomics and variant interpretation should be taught in genetic counseling training programs, there are no clear guidelines for how to effectively do so, nor are there measures of competency in this area. Various groups have suggested a combination of lecture-based and practical training is needed (Hooker, Ormond, Sweet, & Biesecker, 2014; Profato et al., 2014; Swanson et al., 2014). Lecture-based training in variant interpretation is currently available to most genetic counseling students, in the form of conceptual lectures, webinars, and conference continuing education experiences (often administered by NSGC). However, structured, practical experience for variant interpretation is less widely available, other than on-the-job training following graduation, conference workshops, or online courses (e.g., American College of Medical Genetics and Genomics (ACMG) or NSGC). To address this need, we created genomics and variant interpretation rotations as part of the MS in Human Genetics and Genetic Counseling Training Program curriculum at Stanford University School of Medicine. Here, we describe the rotations' key learning objectives and our approach to case-based, practical application of core concepts across these rotation settings at Stanford Medicine.

History of Stanford's variant interpretation rotations

The development of a variant interpretation rotation began in 2011, in response to an awareness that future genetic counselors would increasingly require skills to understand, potentially interpret, and discuss genomic test results (Profato et al., 2014). There was a

growing demand for genetic counselors in laboratory and industry settings, and large-scale sequencing technologies were increasing in both research and clinical contexts (Swanson et al., 2014). As clinical testing expanded to larger NGS-based panels and exome testing, more variants were being interpreted per case, and interpretation often involved the additional step of assessing variants in genes that didn't have precise overlap with a patient's clinical features. Additionally, our experience suggested that non-genetics healthcare professionals assumed genetic counselors had variant interpretation skills, which had not previously been part of our lecture-based or rotation training approach. Given that genetic counseling students were already required to complete one "industry" rotation during their training, we began discussions with genetic counselors at Illumina, and designed a 5–10-week remote rotation focused on the emerging field of genomics. The goals of this rotation were to expose students to current genomic sequencing technologies, to provide an opportunity for them develop skills in variant interpretation, and to help them appreciate the roles for genetic counselors in a commercial laboratory setting.

The positive student and supervisor responses to the rotation at Illumina encouraged us to explore other opportunities for variant interpretation training with genetic counselors working in clinical genomics labs and on research projects at Stanford. An initial Stanford variant interpretation rotation was started in combination with a clinic-based rotation in early 2014, and this evolved over time into what are currently three unique rotation experiences at Stanford University, all focused on genomics and variant interpretation. These sites include a clinical genomics laboratory, a clinical research initiative in the setting of undiagnosed disease, and a "healthy" genome research study. The development of multiple rotation settings has enabled us to assign one rotation-based training experience on genomics and variant interpretation to the majority of Stanford genetic counseling students.

Practical application in different rotation settings

While the three rotations provide unique training experiences, the overall structure of each is similar-- currently lasting for 5–10 weeks, 15–20 hours per week, and supervised by genetic counselors, geneticists and/or other faculty associated with the sites. Students may interpret 40–100 variants during the rotation, although the focus of the training is on skill development rather than total number of variants assessed. In general, assigned variants and cases are reviewed and discussed with the supervisor. Across all three sites, students do a combination of in-person and remote work. Although the structure of each rotation is varied (see individual sections, below), the learning objectives are consistent across rotations due to close collaboration among the supervising genetic counselors who work together in the development of rotation curriculums.

Clinical Laboratory Setting

Students have the opportunity to complete a variant interpretation rotation within the Stanford Medicine Clinical Genomics Program, a clinical laboratory performing exome sequencing. This rotation focuses on variant interpretation in the context of clinical exome sequencing for rare inherited disease. The main objectives include utilizing American College of Medical Genetics and Genomics and the Association for Molecular Pathology

(ACMG/AMP) criteria for variant assessment and classification (Richards et al., 2015), and reporting findings relative to a primary indication versus incidental or secondary findings.

At the beginning of the rotation, students are assigned key readings (table I), followed by a weekly set of variants where they are expected to identify and utilize the appropriate databases to perform the variant and gene-level assessment. As the rotation progresses, assigned variants increase in difficulty, and students are expected to synthesize increasingly complex and sometimes conflicting information into an ultimate interpretation and variant classification. Towards the end of the rotation, multiple variants are assigned in the context of a case and patient phenotype. Students must curate each of the variants individually, then holistically review all the variants in the context of the patient's clinical features and family history, to determine if and how the variants should be reported clinically.

During their rotation, students attend weekly meetings with the interpretation team in the lab, consisting of genetic counselors, biocurators, lab directors, geneticists, and pathologists. In these meetings, ongoing variant assessments are discussed, and students have the opportunity to observe how a clinical lab approaches variant interpretation and reporting. Observing experienced individuals discuss variant interpretation enables exposure to a greater breadth and depth of variants, and normalizes that variant interpretation is a complex, and often collaborative process.

Clinical Research Setting

The second setting for a genomic variant interpretation rotation is with the genomic curation team of the Stanford Center for Undiagnosed Diseases (CUD), a clinical site of the Undiagnosed Diseases Network (UDN) (Gahl, Wise, & Ashley, 2015; Ramoni et al., 2017). This rotation focuses on variant interpretation for a specific patient with a rare, undiagnosed disease who has had uninformative clinical exome and/or genome sequencing. The main objectives are that the students identify candidate variants, and sometimes candidate genes, by re-analyzing the patient's raw genomic data (typically the variant call file (vcf) and aligned sequencing reads) and that students recognize the benefits and limitations of applying ACMG/AMP criteria in the context of rare diseases.

The students begin the rotation by re-reviewing variants reported on the patient's prior clinical genetic testing reports. Next, students perform a detailed chart review to clarify phenotype and family history, abstract Human Phenotype Ontology (HPO) terms (Köhler et al., 2017), and create a patient-specific candidate gene list. Based on the patient's clinical history and disease area, students learn to develop and apply manual filtration trees to raw genomic data. This process facilitates understanding of allele frequency cut-offs, as well as the benefits and limitations of using gene lists and inheritance patterns in narrowing the candidate variant list. Variants which pass the filtration steps (approx. 30–100) are then prioritized using the concepts achieved in the stated learning objectives below, with particular attention to patient phenotype, segregation, gene-disease association, and gene function. On average, the top five variants are selected for in-depth review for students to practice synthesizing and incorporating the principles of variant interpretation. The rotation culminates in a presentation of relevant variant findings and assessments to a multi-disciplinary team of physicians, genetic counselors, bioinformaticians, and data scientists.

Patients enrolled in the UDN represent the most challenging diagnostic dilemmas; many patients have already had exhaustive clinical and genetic workups, meaning their underlying diagnosis is usually not obvious. Because of that, students are encouraged to think outside of the box and consider the molecular underpinnings of patient phenotypes and the molecular pathogenesis of candidate variants. It requires students to go beyond ACMG/AMP classification criteria and entertain hypotheses for new candidate genes, gene-disease mechanisms and follow up testing or experiments. They may also gain familiarity with handling and visualizing sequencing reads (e.g., [viewing.bam](#) files via Integrative Genomics Viewer (IGV)) (Robinson et al., 2011), providing the opportunity to identify sequence artifacts and false positives. Students also have the opportunity to apply their variant interpretation skill-set in the setting of a particular patient and consider what type of information should be reported and how it should be delivered to the family.

“Healthy” genome study setting

Students have the opportunity to learn variant interpretation in the context of a research setting in which they gain experience working on exome data derived from generally healthy participants enrolled in a genomics research study. The objectives for this rotation overlap considerably with the other two rotations, including learning to identify variants with potential medical significance and classifying those variants according to ACMG/AMP criteria, utilizing participants’ personal and family medical history to prioritize and classify variants, and explaining the significance of rare disease-causing variants to participants, including describing necessary follow-up steps.

However, given the research context and the fact that most participants are generally healthy, students focus on some unique aspects of variant interpretation. For example, students in this rotation classify variants in genes associated with diseases for which the participant often has no known personal or family history—much as clinical labs do when assessing incidental/secondary findings in exome cases. In this context, additional caution has to be exercised in applying ACMG/AMP classification criteria to these variants, as the criteria were developed for the primary purpose of assessing genetic variants in known Mendelian disease genes, in reference to a specific disease (Richards et al., 2015). Students also learn how to identify and interpret pharmacogenomic variants and describe them to participants. Participants in the research study are also given polygenic risk assessments for complex diseases such as coronary artery disease (comparable to the types of information provided by many direct-to-consumer genetic testing companies), and students learn how these risk assessments are performed, how to describe them to participants, and how they differ from risk conveyed by highly penetrant variants.

In the first several weeks of this rotation, the trajectory overlaps significantly with the other rotations, including reviewing lectures and coursework on variant interpretation, reading foundational literature, reviewing relevant resources and databases, and going through practice variants together (see table I for examples). Students are then introduced to the variant filtering process in healthy participants, and assigned further practice variants meant to illustrate various teaching points. For these variants, students utilize a template for gathering relevant evidence and classifying the variant. They are expected to fill out more of

the template as the rotation progresses and they gain more exposure to various resources. Midway through the rotation students are assigned to curate the exome data of a generally healthy research participant. They contact the participant to take a detailed personal and family medical history, which is incorporated into the analysis. The student is then responsible for classifying the filtered variants according to the ACMG/AMP classification guidelines (Richards et al., 2015). Students also research information about well-established pharmacogenomic variants identified in their participant. Students ultimately meet with the research participant under the supervision of the rotation lead to discuss medically relevant findings in Mendelian disease genes, pharmacogenomic variants, and the results of complex disease risk assessments performed for several common conditions.

Overarching Learning Objectives

Many of the key concepts and skills required for variant interpretation will be the same regardless of whether the team is focused on clinical variant assessment, research analysis, or “healthy” genomic sequencing. As such, all three Stanford rotations share six major learning objectives, each of which has been developed iteratively over the past seven years via discussion with course lecturers, rotation supervisors, and students. These objectives include: (1) application of genomic technology concepts, (2) critical use and evaluation of genomics resources, (3) assessment of phenotypes, (4) evaluation of gene-disease associations, (5) review and classification of variants, and (6) standards and diversity in reporting criteria. In practice, many of these objectives overlap significantly (e.g. critical analysis of medical literature is always important). Overall learning objectives, associated concepts and skills, and the core competencies students are to achieve throughout the rotations are listed in Table I and detailed in the sections below.

Learning objective 1: Application of genomic technology concepts

These rotations focus on reinforcing three key genomic technology concepts that are typically introduced in prerequisite coursework: variant nomenclature, benefits and limitations of genomic tests and technologies (including how to determine the most appropriate test for a patient), and variant prioritization and filtering.

Variant nomenclature is the bedrock of variant interpretation, and a thorough understanding is essential in developing proficiency. Students are taught HGVS-nomenclature (Human Gene Variation Society; <http://varnomen.hgvs.org/>), the standard utilized by the field to describe sequencing variants. Students will discuss a diverse set of variants with their supervisor and lab team members, and will look up these variants in a variety of online databases. Special effort is made to include variants that emphasize a diverse range of concepts including legacy names, impact of different transcripts, and different variant types. As in coursework and clinical rotations, students are taught to critically assess the tests they intend to order from a laboratory, by identifying the strengths, benefits, and limitations. The detection of different variant types and coverage of test regions within the context of a patient case is emphasized. Relevant questions include: What are the limitations of the analysis as they apply to this case? What information is missed by this test and technology method? Is an orthogonal method needed to confirm this result?

Bioinformatics pipelines, variant filtration, and variant prioritization are often considered a “black box” to many genetic counselors. Students are exposed to the framework of variant filtration and prioritization, wherein a genomic analysis begins with millions of variants (this will vary depending on the test type), and is then systematically reduced to variants most likely to cause disease and therefore warrant variant assessment and classification. By grounding this experience in the context of a patient, students are able to recognize how individual types of information such as phenotypes, disease prevalence, allele frequency, and suspected inheritance pattern all have an impact on determining which variants are ultimately reviewed.

Learning objective 2: Critical use of genomics resources

The resources which inform variant and gene interpretation vary widely in their strengths and weaknesses. To ensure accurate variant classification, we teach students to use and critically assess these resources, including recognizing their limitations and weighing evidence in light of those limitations; to identify, properly read and evaluate biomedical literature; and to identify key pieces of evidence relevant to variant interpretation.

In all three rotations, students are trained to navigate resource databases and tools, and also to recognize instances where a resource cannot be applied, or where the data those resources provide are unreliable or inconclusive. This includes widely-used population databases (which may have small population sizes, include patients with known diseases, or lack coverage for a variant of interest), *in-silico* predictors (which have limited accuracy), gene-phenotype and variant databases (which may be outdated, infrequently updated, or include unreliable information).

Of all the resources that genetics professionals utilize for gene and variant interpretation, one of the most important, and most challenging for students, is the primary literature. Evidence provided by primary literature is often crucial for accurately assessing a variant’s pathogenicity, but the task of understanding and applying that evidence to a specific patient is studded with pitfalls. Students are taught to critically assess medical literature for the purposes of variant classification, with a special focus on learning to question whether the conclusion is supported by the evidence presented. If a paper claims to have identified a variant that is causative of disease, does it back that claim with evidence? If so, how substantial is that evidence? Does it provide functional studies? If so, were they well designed? Is there segregation data? Is the phenotype in question specific, and were the patients well-phenotyped? The answers to questions such as these can impact how the ACMG/AMP classification criteria are applied, and therefore, the final classification.

While lecture-based learning can provide foundational knowledge that can be useful in this context, this skill is best learned by experience. Students are given both practice variants designed to illustrate specific teaching points and case-based variants identified in real patients or research participants.

Learning objective 3: Assessment of phenotypes

A critical role for both laboratory- and clinic-based genetic counselors is interpreting genetic results in the context of a specific patient’s clinical phenotype. A deep understanding of

phenotype is not only crucial for clinical correlation of genetic findings, but also for informing likely disease mechanisms, which in turn guides both the testing strategy and the possible evaluation of genes of uncertain significance (GUS). Furthermore, careful phenotype assessment followed by assignment of HPO terms is a powerful tool for creating gene lists to prioritize variants in genomic analysis, and is key for case matching via online databases such as MatchMaker Exchange (Philippakis et al., 2015). In a variety of ways, integrating deep phenotype assessment skills into genetic counseling practice enhances testing strategies, diagnostic abilities, and ultimately improves patient care.

We highlight three specific concepts to develop critical phenotype assessment skills: (1) building a comprehensive, focused disease narrative for a case, and using it as a tool for clinical correlation; (2) distinguishing “primary” clinical features from “secondary” features (i.e. those secondary to the disease process of other features), and systematically describing these features using HPO terms; and (3) learning to identify key phenotypic features that are most objective and specific (“pertinent positives”), and how to differentiate features that a patient had specifically been evaluated for and does not have (“pertinent negatives”- e.g., a normal kidney ultrasound in the setting of a syndromic presentation), from a mere absence of data.

Students are taught the basic theory and methods behind phenotype assessment in a short lecture, and quickly dive into practicing these skills in the context of an assigned case. Use of real cases enhances student interest and ownership over the assignments, and facilitates the application of these learned skills to their own cases in the future.

Learning objective 4: Evaluation of gene-disease associations

Before evaluating whether a variant of interest may be contributing to a specific disease or phenotype, it is of crucial importance to have sufficient confidence that the gene itself causes disease. Even genes available for testing through commercial clinical genetic testing may not have robust evidence supporting disease causality (Grant et al., 2018; Hosseini et al., 2018; Renard et al., 2018). We teach rotation students to critically evaluate the evidence for a gene-disease association and identify when the evidence is sufficient. Students must understand the limitations of interpreting variants in genes with insufficient evidence (genes of uncertain significance (GUS)).

Until recently, the process of assessing a gene-disease relationship was largely variable between groups; however, international efforts are working to make the approach more explicit and systematic (Strande et al., 2017). Such frameworks describe a spectrum of evidence levels for defining gene-disease relationships. Applying these current standards involves not only reading and critically evaluating the medical literature (see critical resource review section, above), but also understanding how to weigh different types of evidence (e.g. experiments demonstrating phenotype in an animal model are stronger than *in vitro* functional studies). It also requires comparison and combination of evidence from different publications and authors. Along those same lines, students are taught how to collate evidence supporting a phenotypic spectrum of disease, as well as the possible conclusion that multiple distinct diseases can be caused by different variants within the same gene. A third essential element is the ability to inspect past publications that claim gene-disease

associations, with the lens of contemporary standard of evidence. For example, a published disease gene based on one variant that appeared rare when compared to a cohort of 300 “ethnically-matched” controls may actually be relatively common in the large population databases available today; therefore, calling into question the gene-disease relationship. The main teaching points regarding gene-disease associations are achieved through example readings, followed by practical application. The principles at the core of evaluating gene-disease associations are not confined by context, which make it an objective easily integrated into any rotation or training module on genomic variant interpretation. To gain experience applying the published frameworks and operationalizing the concepts learned in selected readings, students may be assigned to gather information on specific gene-disease associations and prepare a written report that summarizes their findings and assessment of gene causality.

Learning objective 5: Review and classification of variants

The process of variant review involves all the skills detailed above, but we give students an opportunity to apply those skills explicitly and within context, while reviewing prioritized variants for a patient. For example, students are taught to assess variants not only by checking the allele frequency data available in public databases, but also by considering how a patient’s specific ethnic background, or the specific details of the associated disease (such as disease prevalence and penetrance) may impact evaluation of allele frequency. Students learn that proper assessment of a variant includes a critical review of the disease associations for that gene, followed by assessment of the match between gene-disease association, and the specific phenotypes seen in this patient.

After reviewing available variant data, students will learn to classify variants using a structured framework. Students are trained on the details and application of the ACMG/AMP guidelines (e.g. different rules apply to missense and loss-of-function alleles), as well as on the recently proposed recommendations for adaptation of those guidelines (Amendola et al., 2016; Biesecker & Harrison, 2018). These classifications are done specifically within the context of patient analysis - students are asked to classify each variant as pathogenic, likely pathogenic, uncertain significance, likely benign, or benign for a patient’s indication. Although particular emphasis is given to the ACMG/AMP guidelines, students are also exposed to other structured approaches of variant evaluation, such as evaluation of research candidate genes, complex disease risk assessments, or pharmacogenomic variants (e.g. Clinical Pharmacogenetics Implementation Consortium; <https://cpicpgx.org/>).

Learning objective 6: Standards and diversity in reporting criteria

Integral to variant interpretation is the concept of “reportability.” Although millions of variants are present in any individual genome, only tens or hundreds are manually reviewed and even fewer are formally classified. We teach students how the context in which genomic testing is performed impacts decisions about which variants will be reported, and how those are reported to the ordering provider or research participant.

With clinical testing, rules and recommendations from ACMG, College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) govern what should and should not be on a clinical report and how variants should be described. Clinical reports are intended for the patient's medical chart and will be available to medical providers for assistance in that patient and their family's medical care. In a clinical setting, variants are typically only reported if they are in genes related to the patient's phenotype, i.e. the clinical indication for testing (Rehm et al., 2013). Toward this goal, students are trained in writing clear, concise reports focused on variants that have been classified according to ACMG/AMP criteria regarding pathogenicity relative to the patient's primary phenotype. By writing these reports, students learn to appreciate how clinical laboratories are generally limited by the current state of knowledge of the field.

In contrast with clinical testing, research settings may enable more flexibility in terms of which variants can be further investigated and reported. For instance, research settings focusing on undiagnosed disease can allow assessments of genes that are not currently implicated in human disease, or regions of the genome that are not yet generally clinically interpretable (e.g., promoters or UTRs). Thus, students in these settings will learn how to follow up novel gene candidates, such as with animal models, or through familial genomic studies without limiting on patient phenotype, with the goal of identifying new gene-disease associations.

Finally, students are taught how reporting strategies regarding secondary or incidental findings can also vary depending on the context. In a clinical laboratory setting, reported variants are generally limited to those that are high confidence and medically actionable in accordance with guidelines from the ACMG (Kalia et al., 2017). In a research setting focusing on healthy genome analyses, reported variants may include a broader set of variants, including high confidence variants as observed in clinical lab settings, as well as lower penetrance variants or pharmacogenetic variants.

Practical considerations

Developing a variant interpretation rotation has many elements in common with setting up any other hands-on learning activity or rotation. The general structure should be carefully considered (length of the rotation, model of supervision, whether the rotation is remote or in-person). Each program will need to develop learning objectives consistent with the activities the rotation site can offer and take into consideration the lecture-based training that students will already have around molecular genetics concepts, sequencing and genetic testing technology, analytic methods, *in silico* models, bioinformatic approaches and functional testing of variants. We found it most effective for students entering the rotation to have already completed lecture-based coursework and students are encouraged to look back at notes, recorded lectures, and other online resources at the beginning of the rotation. If it is not practically possible to provide this foundational knowledge prior to the rotation, pairing the rotation with learning via readings, coursework, or webinars should be considered. Additionally, regular meetings between students and supervisors to discuss student variant assessments and underlying thought processes greatly improved their skills, and enabled more individually tailored, iterative learning opportunities. Finally, it may be necessary to

develop new methods of evaluating student progress using evaluation forms or metrics distinct from those used to evaluate clinical skills.

A more challenging aspect of setting up a variant interpretation rotation may be incorporating it into the overall student rotation schedule. The variant interpretation rotations at our institution are the same length as clinical rotations (5–10 weeks, 10–15 hours per week). Our students are able to complete one variant interpretation rotation in addition to at least four traditional clinical rotations. In part because they begin rotations in their first year of training, we do not feel that the variant interpretation rotations interfere with clinical training or case log book completion. Additionally, the clinical and variant interpretation rotations are designed to enhance one another: clinical rotations allow students to appreciate the need for and apply variant interpretation skills, and variant interpretation rotations equip students with skills to function more effectively in clinical settings. To date, 17 students have participated in one of the three variant interpretation rotations at our institution. Students were asked to provide evaluation of the three sites, and 8 responded. Seven of the eight “significantly agreed” and one “agreed” that “the rotation taught me skills I will need as a practicing genetic counselor.” Seven of the eight also “significantly agreed” and one “agreed” that “overall, the rotation was a valuable experience.”

The evaluation of students in these rotations should also be considered, and metrics to measure progress as well as evaluation forms will need to be developed. Students at our institution are evaluated on their ability to achieve the learning objectives outlined in Table I. We assess students using a rotation evaluation form that assesses genetic counseling competencies as they apply to variant interpretation skills. While a minimum number of cases worked on and/or variants interpreted is not required for the student logbook, we encourage students to include their work in their portfolio of clinical experiences.

Discussion

Regardless of specialty, genetic counselors are increasingly expected to be proficient in variant interpretation and genomics concepts in the era of genomic testing. One approach to teaching and developing such skills is to supplement conceptual or lecture-based education within genetic counseling training programs with experiential rotation experiences. Our experience has been that these hands-on experiences provide opportunities to develop very different skills that can complement the knowledge students obtain from lectures. Students gain exposure to real genomics cases, have the opportunity to experience the “art” of variant interpretation in greater depth, and recognize the potential reasons for disparities between variant interpretations across clinical laboratories. They may also have the opportunity to focus within a single relevant clinical area, which benefits those who choose either a clinic or a laboratory-based genetic counseling position. Finally, the experience of curating variants, discussing them with a laboratory or research-based team, and justifying their interpretations provides genetic counseling students the opportunity to further develop critical thinking skills that can be applied across all genetic counseling settings.

While the three Stanford rotation sites we have described are distinct, we believe that there are core learning objectives in variant interpretation, tailored for genetic counselors, that

span any context. Application of these learning objectives can happen in clinical, laboratory or research settings. Our anecdotal feedback from students suggests that these rotations are received positively, and have been critically useful in their diverse clinical, research or lab-based genetic counseling roles following graduation.

Limitations

While presenting overarching learning objectives for variant interpretation, we report on the experience of one institution. Practical application may be challenging in the absence of onsite genomics projects or laboratories that involve variant interpretation. Additionally, genetic counselors or experts currently doing variant interpretation, or those who feel comfortable developing a rotation and/or teaching these skills, may not be available at all institutions. One way to address this particular challenge could be to create a remote rotation experience, in collaboration with supervisors from other institutions or labs who have this specific expertise. Time limitations due to students having an already full rotation schedule could interfere with the feasibility of implementing a variant interpretation rotation. Finally, the long-term effectiveness of providing variant interpretation rotations has not been assessed.

Practice Implications and Future Research

These experiences can serve as a useful foundation upon which to develop further genetic counseling variant interpretation rotations, as well as guidelines and competencies for genetic counselors in variant interpretation. Additionally, we aim to stimulate further dialogue and collaboration in development and iteration of these types of rotation experiences. Finally, we suggest that future research should aim to assess outcomes and identify best practices for these rotation experiences.

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Table 1:**Overarching Learning Objectives of a Variant Interpretation Rotation**

Learning Objective	Key Concepts	Skill building activities
Application of genomic technology concepts	(1) HGVS variant nomenclature standards	- Look up variants in reference databases, considering different naming conventions and/or legacy names when applicable - Use HGVS nomenclature to properly describe variants in written summaries and reports
	(2) Benefits and limitations of genomic tests and technologies	- Practice examples illustrating these points, and discuss with supervisor
	(3) Technical aspects of variant calling, filtering, and prioritization steps of genomic sequencing analyses	- Utilize a patient case to demonstrate how and when filtration criteria are applied
Critical use of genomics resources	(1) Critical use of databases and tools	- Look up variants in reference databases, including examples that demonstrate limitations of such databases and tools, discuss examples with supervisor
	(2) Critical evaluation of relevant medical literature	- Practice examples and discussion with supervisor - Read and assess biomedical literature relevant to patient variants
	(3) Identification and assessment of relevant evidence supporting/refuting variant pathogenicity	- Practice examples and discussion with supervisor - Identify and discuss key supporting/refuting evidence from both literature and database resources
Assessment of phenotypes	(1) Construction of a comprehensive disease narrative for a patient	- Review patient medical records and family history - Summarize patient narrative for supervisor
	(2) Identification of primary and secondary clinical features	- Practice examples and discussion with supervisor - Translate relevant clinical features to HPO terms using HPO browser
	(3) Identification of pertinent positive findings, and differentiation between pertinent negative findings and the absence of data	- Practice examples and discussion with supervisor - Translate relevant clinical features to HPO terms using HPO browser
Evaluation of gene-disease associations	(1) Weighting of a combination of different data types	- Read seminal readings on gene-level evidence evaluation (e.g. MacArthur et al., 2014; Strande et al., 2017)
	(2) Variants in the same gene can cause different diseases, and the same disease may present on a phenotypic spectrum	- Practice examples and discussion with supervisor
	(3) Evaluation of genes for their potential role in human disease, and assessment of the strength of available evidence	- Perform and write a literature review of gene-level evidence for a given gene, applying the conceptual framework, starting with selected training examples - Evaluate gene-disease associations and assign strength of evidence from patient cases
Review and classification of variants	(1) Variant interpretation uses a framework of explicit rules (e.g. ACMG/AMP guidelines)	- Read seminal papers on ACMG/AMP guidelines (Richards et al., 2015; Amendola et al., 2016; Biesecker & Harrison, 2018)
	(2) Variants must be interpreted within patient and disease context	- Practice variant assessment and assign classifications of example variants - Perform variant assessment and assign classification of patient variants - Summarize variant information in written and verbal formats
	(3) Different guidelines are applicable to different types of variants	- Practice assigning guidelines for example variants, and discuss with supervisor - Assess and classify an entire set of prioritized patient variants for at least one patient, under supervision and write up or present results
Standards and diversity in reporting criteria	(1) Reportability standards and deliverables vary according to test	- Read a variety of example reports

Learning Objective	Key Concepts	Skill building activities
	type, analysis setting, and finding type (primary, secondary, incidental)	
	(2) Communicate complex variant interpretation decisions, and underlying evidence, to genetics professionals	- Practice examples and discussion with supervisor - Write variant summaries for review by supervisor - Discuss variant summaries with rotation team members
	(3) Summarize complex genetics concepts to patients and study participants	- Report variants to genetics professionals and patients and/or study participants, under supervisor guidance