Title: **Rising to the Level of Clinical Importance: Challenges to adjudicating and reporting variants discovered with genomic analysis**

Description:

Interpretation of individual gene variants identified through massively parallel sequencing (MPS) modalities is in principle no different than interpretation of variants identified using Sanger sequencing. However, traditional genetic testing has been performed predominantly in genes considered to have a high a priori likelihood of harboring a disease causing pathogenic variant in a given patient. The complexities of interpreting large-scale genomic analysis arise from the sheer number of variants to analyze, including variants within genes with no known disease association and variants within known disease-causing genes for which the patient has a low a priori risk of having a pathogenic variant. For genomic tests, the considerable number of rare nonsynonymous variants demands the utilization of a threshold to determine which findings to report and interpret in the context of an individual’s phenotype and which findings should not be reported due to their lack of clinical relevance and/or uncertain pathogenicity. The laboratory’s dilemma is therefore determining which variants warrant reporting back to the clinician and thereby the patient. This session explores the challenges and reasoning employed by clinical laboratory geneticists to determine which variants should be included in genomic sequencing reports and the impact of these decisions on clinical care. Presenters from multiple genetics subspecialties will explore the impact of MPS-based test results in diverse practice settings. Molecular cases will be reviewed to highlight challenging decisions where variants were on the threshold of rising to the level of clinical importance but were ultimately not reported. As such, this session will focus, not on the overall diagnostic yield of genomic sequencing, but on the decision process for adjudicating and reporting sequence variants, highlighting when individual sequence variants may not be reported, and why. We will also introduce the process and future plans of ClinGen expert consensus panels to assist and improve on variant interpretation and clinical validity of gene-disease associations.

Target Audience:

This session is relevant to a diverse audience of genetics professionals, including clinical genetic counselors, clinical geneticists, genetics fellows, laboratory directors, laboratory genetic counselors, genetic researchers, bioinformaticians, and any professional utilizing genetic test results or interpreting genetic variants.

**Learning Objectives**

* Describe technical challenges and limitations in variant interpretation arising from use of MPS-based clinical molecular sequencing.
* Analyze difficult cases where identified variants were ultimately not returned by a laboratory due to lack of evidence supporting pathogenicity.
* Assess whether the interpretation of variants should differ in the setting of a potential diagnostic result versus an incidental finding.
* Evaluate the decision process used to determine whether a variant should be reported by a laboratory.
* Provide an update on ClinGen efforts to improve and streamline variant interpretation.

**Speakers**

Michael Friez, PhD, FACMG

Speaker Topic: (343) Beyond the known phenotype: considering variants that would require expansion of the classic phenotype.

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Lora Bean, PhD, FACMG

Speaker Topic: (344) Interpreting data without having all of the data: handling off target copy number variants and single variants in genes associated with autosomal recessive disease

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Kristy Lee, MS, CGC

Speaker Topic: (345) Sorting through variants related to phenotypes associated with extreme genetic heterogeneity

University of North Carolina at Chapel Hill

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Birgit Funke, PhD, FACMG  
  
Speaker Topic: (362) Facilitating clinical molecular diagnostic analysis: ClinGen frameworks for curating variant pathogenicity and gene-disease associations

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**Kate Foreman, MS, CGC**

Speaker Topic: (285) Genetic counseling after an exome: making meaning of diagnostic results and incidental findings.

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Moderators

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