The evaluation of the molecular basis of disease (EMBoDy) in clinical reporting: What genetic counselors need to know for counseling and return of novel genetic etiology results identified via diagnostic exome sequencing

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BACKGROUND
- Exome sequencing serves a dual role as a diagnostic and a discovery tool.1-3 and case reports of patients in whom a novel genetic etiology is identified on a clinical basis are becoming abundant.2,4-7
- A novel genetic etiology is a newly described gene-disease relationship.
- In our laboratory, a novel genetic etiology is reported in roughly 1/10 patients.
- The analysis and assessment criteria used to evaluate novel genetic etiologies for clinical reporting are markedly different than those used for a clinically characterized gene.
- Given the implications for genetic counseling, it is important for genetic counselors to be aware of these differences.

TERMINOLOGY
- **Characterized Genetic diseases**: A gene that has been linked to a disease or phenotype.
- **Novel Mendelian disease genes**: Genes that are not currently known to underlie a Mendelian genetic condition.
- **Evaluation of the Molecular Basis of Disease (EMBoDy)**: The analysis of new gene-disease relationships.
- **Clinical Validity**: The determination that a particular disease is truly caused by a specific genetic variant.
- **Novel genetic etiology**: A gene-disease relationship and/or mechanism not previously reported or with limited evidence based on ClinGen clinical validity assessment criteria (http://www.clinicalgenome.org/knowledge-curation/clinical-validity-classifications/).
- **Characterized Disease**: A disease or phenotype whose underlying molecular etiology is established with at least moderate level of evidence based on ClinGen clinical validity assessment criteria (http://www.clinicalgenome.org/knowledge-curation/clinical-validity-classifications/).
- **Idiopathic Disease**: A disease or phenotype whose underlying molecular etiology or etiologies have not been established. For heterogeneous conditions, there may be multiple etiologies.

RESULTS
- For alterations in characterized genes in which the patient’s phenotype is consistent with the known clinical and molecular spectrum, the reportable findings are categorized as positive, likely positive, or uncertain (Figure 1).
- Because no previous patients have been reported for novel genetic etiologies, a unique set of scientific criteria are used to make the case for the gene’s potential implication in the patient’s phenotype (Figure 2).
- Evaluated evidence includes relevant human microdeletion syndromes, gene function and expression profiles, co-localization/interaction with gene products known to cause similar presentations, animal models, gene family/pathway information, and possible mutational mechanism inferred from distribution of variants in control populations (Figure 2).
- The analysis of alterations among novel genes involves first filtering out genes with insufficient knowledge of gene function (Figure 3).
- These gene findings with insufficient available evidence are provided in a supplemental list in the patient’s report. These are not negative findings, and the possibility exists for sufficient scientific evidence to emerge in the future (Figure 4).

TAKE-HOME POINTS
- Negative characterized gene findings are fundamentally different than negative novel gene findings in that most alterations in novel genes cannot be ruled out.
- As new information becomes available about the function of genes, it is possible for a once novel gene to become relevant for a patient.
- Genetic counselors should remain in contact with the laboratory to gain new information, to perhaps find additional patients with alterations in the same gene, and obtain re-analysis.

REFERENCES