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 Mendelian disease gene****:* A gene known to underlie at least one Mendelian genetic condition.
- ***Novel Mendelian disease gene***: A gene that is 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 pathogenic variants in a particular gene.
- ***Novel genetic etiology:*** A gene-disease relationship and/or mechanism not previously proposed or with limited evidence based on ClinGen clinical validity assessment criterion (http://www.clinicalgenome.org/knowledge-curation/gene-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 criterion (http://www.clinicalgenome.org/knowledge-curation/gene-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.

Figure 1: Results categories for characterized versus novel genetic etiology results

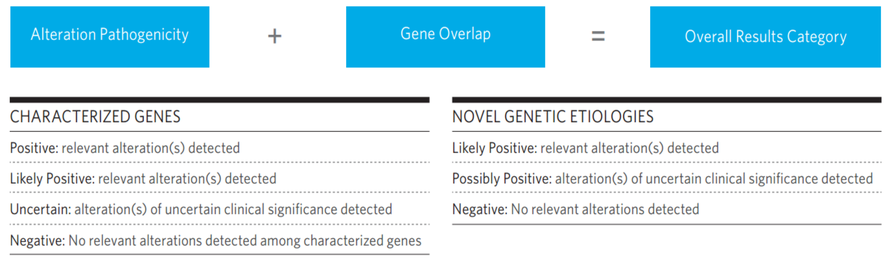


Figure 2: Flow diagram outlining the process of the Evaluation of the Molecular Basis of Disease (EMBoDy)

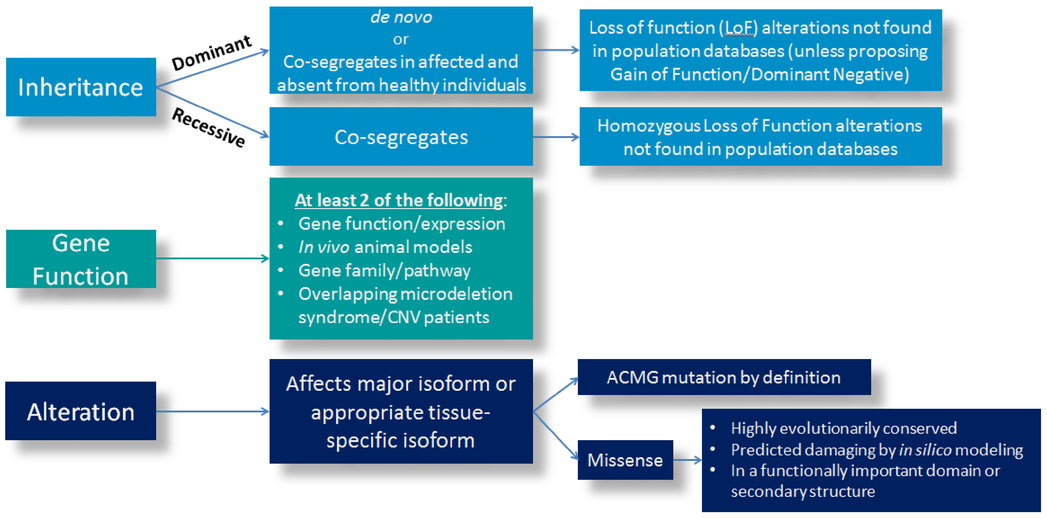
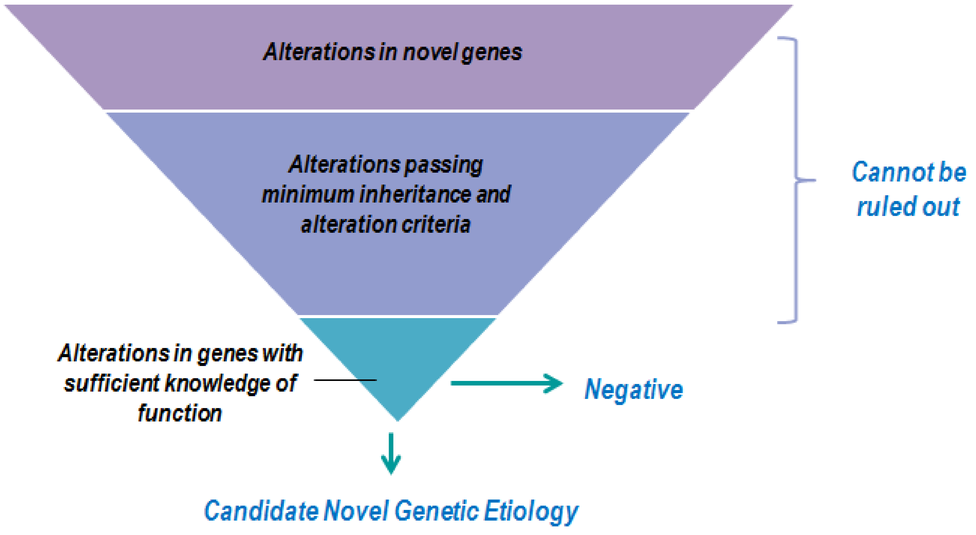


Figure 3: Analysis and manual filtering of alterations in novel genes



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**).

Figure 4: Comparison of analysis of characterized vs novel genes

Analysis of Novel Genetic Etiologies

- **Rule out alterations likely benign**
- Genes with insufficient knowledge of function cannot be ruled out – ***Provided in supplemental section of report***
- Rule out alterations in genes unlikely to explain the patient's phenotype *from among genes with sufficient knowledge of function*

Analysis of Characterized Genes

- **Rule out alterations likely benign**
- Rule out alterations in genes in which the clinical association is inconsistent with the current patient

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.

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