Ambry Genetics

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Human Mutation
OFFICIAL JOURNAL
HGVS
HUMAN GENOME VARIATION SOCIETY
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RESEARCH FOR YOUR PRACTICE

Best Practices for Clinical Validity

WHICH GENES MATTER, WHY AND WHEN

Ambry Genetics and Washington University team up to develop a systematic method for translating which genes cause which diseases. Published in *Human Mutation*, this approach aims to improve consistency of genetic test results across the industry leading to more clinically relevant results.

WHY THIS MATTERS TO YOU

When it comes to clinical validity (scoring how well a gene is associated with a disease), experience is critical. One challenge of diagnostic exome sequencing (DES) is keeping up with newly published gene discoveries and translating the information into accurate patient results. Here we describe a comprehensive clinical validity process which has led to the reclassification of 6% of results overall and 35% of novel Candidate gene results.[1]

BACKGROUND

DES analyzes virtually all genes in the genome and can identify an underlying diagnosis to adjust a patient's medical management, benefiting patients, payors, and the healthcare system.[2,3] However, only about 1/3 of disease-causing genes have been established as clinically relevant.[4] Specifically, it is important to determine what evidence is "enough" to make a diagnosis, as inadequate data can lead false negative results, incorrect diagnoses and missed opportunities for timely treatment.

Clinical validity leads to
6%
reclassification

POINTS FOR YOUR PRACTICE

- This scoring system offers a new method for evaluating the clinical validity of gene-disease relationships, allowing for consistent results across the industry.[1]
- In the absence of an industry-wide consensus, this study offers suggested methods for reanalysis of negative/uncertain DES cases.[4] These methods led to overall reclassification of 6%.[1]
- This system enables reclassification of up to 35% results from Candidate to Characterized based on the most current data and newly published gene discoveries.
- Public data sharing is imperative to help patients and families gain a diagnosis informed by new gene discoveries and rapidly evolving knowledge.[6]

SIGNIFICANT FINDINGS

Established Scoring System:
Clinical validity based on weighted evidence of the following criteria

Number of unrelated patients	1-4 pts
Other statistical evidence	0-1 pt
Number of publications	0-3 pts
Gene function	0-4 pts
Gene disruption *(in vitro)*	0-2 pts
Model organism *(in vivo)*	0-2 pts
	SUM

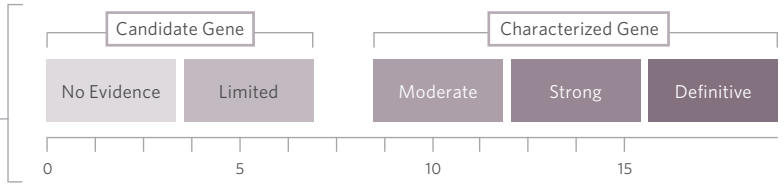
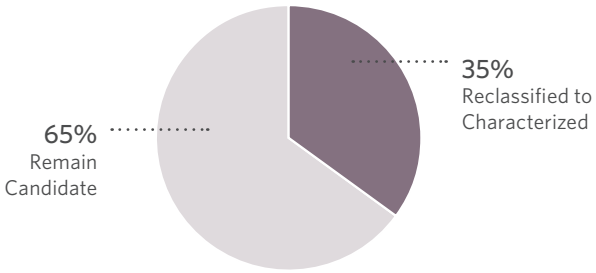


Figure 1. Smith *et al.*, 2017.

Reclassification increases diagnostic yield:
This scoring system, led to overall reclassification of 6% of all results and 35% of Candidate findings.

Reclassification of Candidate findings



Candidate genes are examined only in qualifying cases.
Figure 1. Smith *et al.*, 2017.

LEARN MORE ABOUT OUR RESEARCH
Smith ED *et al.* Classification of Genes: Standardized clinical validity assessment of gene-disease associations aids diagnostic exome analysis and reclassifications. Human Mutation, 2017, 38(5):600-08.

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