COMMENTS FOR NOVITAS OPEN MEETING

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Novitas LCD Genetic Testing for Cardiovascular Disease (DL39082) Review and Comments:

Our comments are on the proposed covered indications, copied below:

Genetic testing for hereditary cardiovascular disease will be considered medically reasonable and necessary if:

1. The patient has rigorous disease-appropriate phenotyping to establish clinical diagnosis or suspected diagnosis for which the test results would directly impact the management of the patient’s condition, prior to ordering the test  
   AND
2. The evidence for the gene-disease association is evaluated by the evidence-based, transparent, peer-reviewed process of the National Institutes of Health (NIH) sponsored Clinical Genome Resource (ClinGen) and is determined to demonstrate actionability in clinical decision making, meeting all bulleted metrics:

* Disease severity of sudden death, possible death or major morbidity, modest morbidity
* Substantial or moderate evidence of a >40% likelihood of disease
* Substantial or moderate evidence of a highly effective or moderately effective intervention
* The nature of intervention is either low risk/medically acceptable/low intensity intervention or moderately acceptable/risk/intensive interventions,  
  AND

1. Clinical validity and qualitative descriptors from Moderate, Strong & Definitive with contradictory evidence NOT being reported as disputed or refuted.

We recommend that the italicized portions of the above proposed inclusion criteria in bullets #1 and #2 be revised to follow AHA language and remove potentially unclear and restrictive criteria on “>40% likelihood of disease.” We also recommend using broad cardiovascular panels, based on our own and other’s research.

The American Heart Association (AHA) has released a scientific statement (Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement From the American Heart Association. 23 Jul 2020: Genomic and Precision Medicine. 2020;13:e000067) regarding genetic testing which encourages testing for “patients with a confirmed or suspected diagnosis of an inherited cardiovascular disease.” We think this language should be used in bullet #1 to align the policy with the AHA.

We are also including as evidence, two large studies examining genetic testing in cardiovascular diseases, the Invitae CardioDetect program (Data on file at Invitae and abstract submitted to AHA 2021), and a single center 5-year study at Université de Lyon (Janin A, et al. Molecular Diagnosis of Inherited Cardiac Diseases in the Era of Next-Generation Sequencing: A Single Center's Experience Over 5 Years. Mol Diagn Ther. 2021 May;25(3):373-385). CardioDetect is a no-charge cardiomyopathy and arrhythmia genetic testing program made available to cardiologists wishing to test for cardiomyopathies or arrhythmia indications using a comprehensive panel.

In 4,782 tested patients, a positive result (molecular diagnosis) was observed in 19.9% (954). 75.3% (718/954) of the positive results conferred clinical management implications related to diagnosis and prognosis. If testing were restricted to panels associated with the clinician-provided indications for testing, 10.9% (75/689) of positive results would have been missed.

Conclusions: Combined cardiomyopathy and arrhythmia gene panel testing effectively identifies clinically-relevant variants for 1 in 5 suspected cardio rhythm patients. Comprehensive testing captures >10% of patients who would be missed with condition-specific.

The Université de Lyon study enrolled over 4000 probands over five years, including 190 probands who had suffered from sudden cardiac death, 3235 cardiomyopathy probands and 760 probands. All subjects were tested with an expanded panel of 105 genes involved in sudden cardiac death (SCD). 30% of the cardiomyopathy and arrhythmia probands, and 21% of the SCD probands had pathogenic variants. These detected variants had clinical impacts around medical management, identification of heritable causes of SCD, and also resolved misdiagnoses and enabled differential diagnosis in similarly presenting phenotypes with different underlying genetic causes. The authors conclude “Globally, NGS approaches are definitely necessary for patients with cardiomyopathies and/or arrhythmia syndromes but also for victims of sudden unexplained death syndrome.”

These two studies relied on an expanded NGS panel for cardiac related genes and found between 20-30% of the cohort had pathogenic variants, the majority of which were actionable. These studies demonstrate that comprehensive panels provide clinical utility in proper diagnosis and medical management of cardiovascular disease.

In conclusion, we propose the following changes to the proposed inclusion criteria:

Genetic testing for hereditary cardiovascular disease will be considered medically reasonable and necessary if:

1. The patient has a confirmed or suspected diagnosis of an inherited cardiovascular disease [remove verbiage “rigorous disease-appropriate phenotyping to established clinical diagnosis or suspected diagnosis for which the test results would directly impact the management of the patient’s condition, prior to ordering the test”]  
   AND
2. The evidence for the gene-disease association is evaluated by the evidence-based, transparent, peer-reviewed process of the National Institutes of Health (NIH) sponsored Clinical Genome Resource (ClinGen) and is determined to demonstrate actionability in clinical decision making, meeting all bulleted metrics:

* Disease severity of sudden death, possible death or major morbidity, modest morbidity
* [remove bullet “Substantial or moderate evidence of a >40% likelihood of disease”]
* Substantial or moderate evidence of a highly effective or moderately effective intervention [add the word OR]
* The nature of intervention is either low risk/medically acceptable/low intensity intervention or moderately acceptable/risk/intensive interventions,  
  AND

[Revise beginning of sentence with “The ordered panel contains genes”] with [remove verbiage “Clinical validity and qualitative”] descriptors from Moderate, Strong & Definitive with contradictory evidence NOT being reported as disputed or refuted.