Cardiologists beware: clinical limitations of genotyping- versus sequencing-based strategies for cardiomyopathy evaluation

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Disclosures

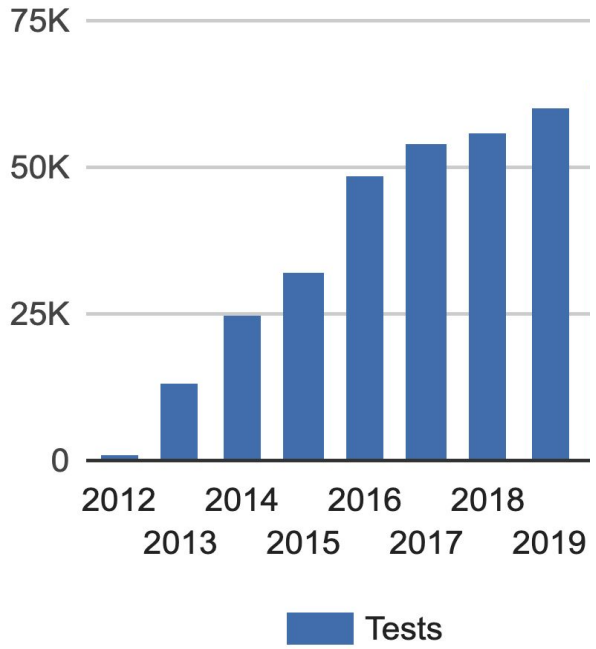
Employee and stockholder of Invitae Corporation

Objectives

- Recognize the spectrum of genetic tests available to clinicians and consumers today
- Determine how often individuals with genotype positive cardiomyopathy could be falsely reassured by partial screening tests
- Describe the importance of understanding the limitations of different testing methodologies

The number of genetic tests is growing rapidly and includes FDA-authorized direct-to-consumer (DTC) tests and hybrid models where consumers order laboratory-developed tests (LDTs) with physician support.

Number of tests submitted to the NIH Genetic Testing Registry[1]



References: 1) Genetic Testing Registry (GTR) - NCBI. [cited 19 Mar 2020]. Available: https://www.ncbi.nlm.nih.gov/gtr/

Across the spectrum of testing available, methods vary and different testing modalities are most appropriate for different types of variants.

The clinical limitations each modality are not always well-understood by non-specialists nor precisely defined among specialists.

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Molecular DNA testing methods include:

- DNA chip analysis
- Sanger sequencing
- Allele-specific PCR
- MLPA
- Chromosomal microarray analysis
- Next-generation sequencing
  - Gene panels
  - Exome sequencing
  - Genome sequencing
  - Copy number variants

Different testing modalities have inherent strengths and weaknesses, and may include the detection of:

- Known or novel variants
- Single, few or many variants
- Small or large variants
- Simple or complex variants

Recently, a limited variant screening strategy for 9 pathogenic or likely pathogenic (P/LP) cardiomyopathy variants in *MYH7* and *MYBPC3* was made available to consumers as a LDT through a **hybrid ordering model.**

Cardiomyopathies are genetically heterogeneous involving many genes and thousands of variants

Hypertrophic cardiomyopathy
- >40 disease-causing genes[1]

Dilated cardiomyopathy
- >30 disease-causing genes[2]

Pathogenic and likely pathogenic variants:[3]
- *MYH7*: >300 variants already known
- *MYBPC3*: >500 variants already known

References: 1) Cirino AL, Ho C. Hypertrophic Cardiomyopathy Overview. GeneReviews. University of Washington, Seattle; 2008. Last Update: June 6, 2019. **2)** Hershberger RE, Morales A. Dilated Cardiomyopathy Overview. GeneReviews. University of Washington, Seattle; 2007. Last Update: August 23, 2018. **3)** Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018;46: D1062–D1067.

Genetic evaluation is recommended by **all major cardiology professional societies** to improve the diagnosis and management of cardiomyopathy patients and family members.[1-4]

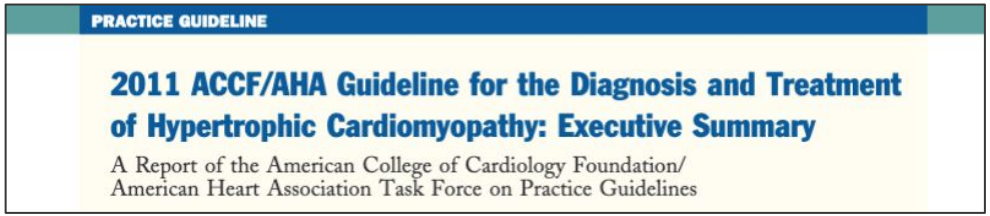
HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

Genetic Evaluation of Cardiomyopathy—A Heart Failure Society of America Practice Guideline

2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society



References: 1) Gersh BJ et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: Executive summary. J Am. Coll Cardiol. 2011;58:2703-38. **2)** Ackerman MJ et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Heart Rhythm. 2011;8;1308-39.
3) Al-Khatib SM et al. 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2018;72:e91-e220. **4)** Hershberger, RE et al. Genetic Evaluation of Cardiomyopathy-A Heart Failure Society of America Practice Guideline. J. Card. Fail. 2018;24,281-302.

Objective of this study

- Determine how often screening for only the 9 specific variants in just two genes, *MYH7* and *MYBPC3,* would miss other P/LP variants and falsely reassure individuals at risk for cardiomyopathy

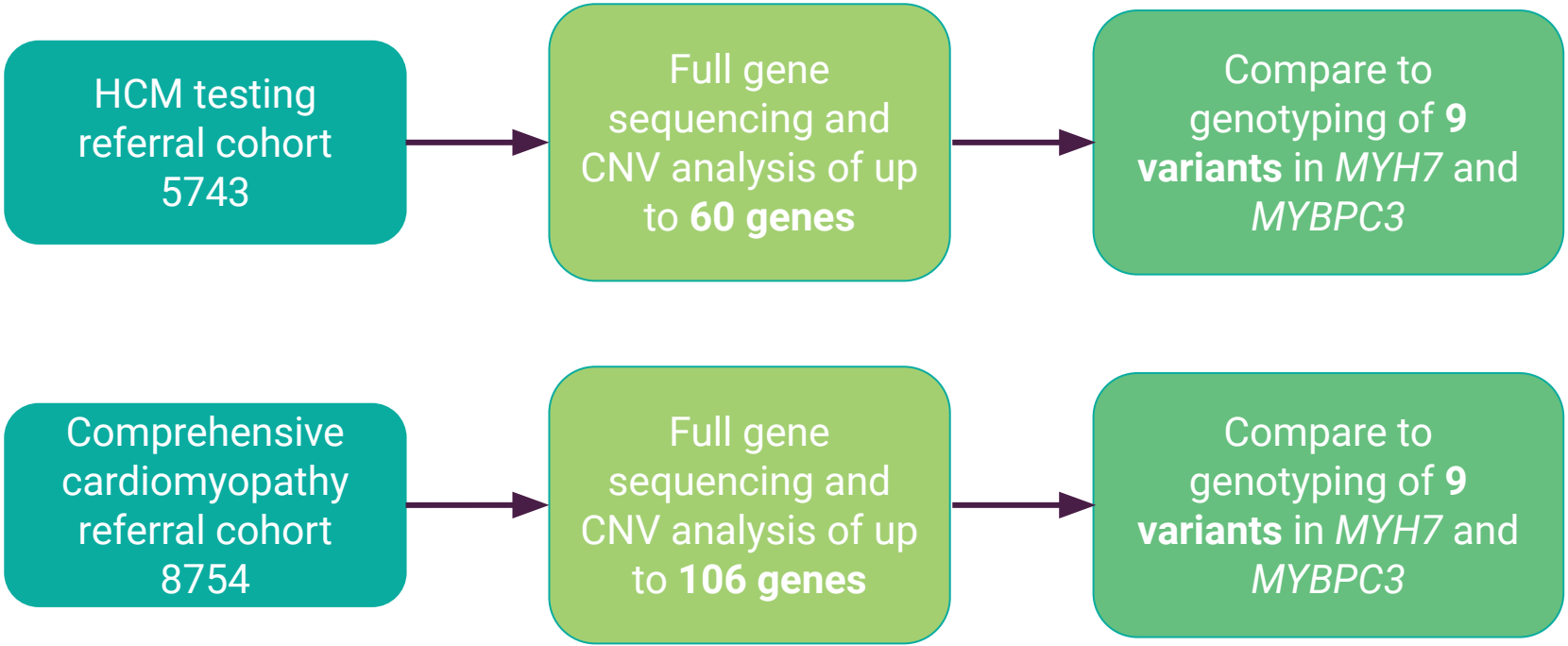
Methods

Analyzed de-identified data from two indication-based cohorts:

- 5,743 patients of multiple ethnicities referred by healthcare providers referred for **HCM testing of up to 60 genes**

- 8,754 patients of multiple ethnicities referred by healthcare providers referred for **comprehensive cardiomyopathy testing of up to 106 genes**

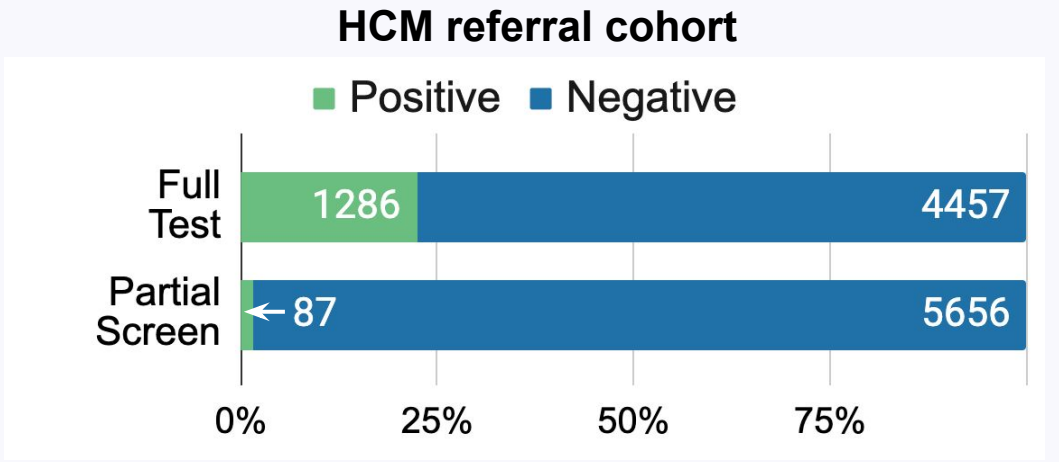
Methods

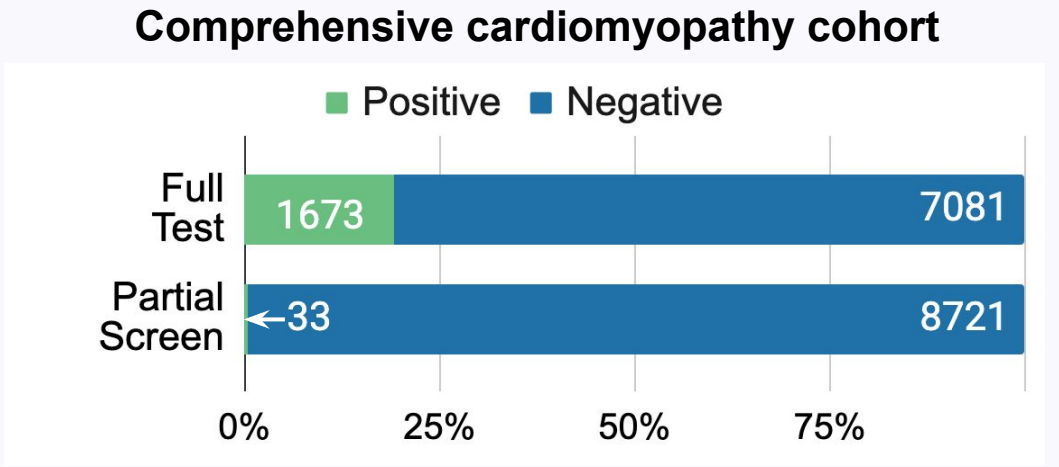


Results

The yield of clinical testing by sequencing was 22.4% (1286/5743) in the HCM group and 19.1% (1673/8754) in the comprehensive cardiomyopathy group for P/LP variants within the genes analyzed.

In contrast, the calculated yield of a genotyping screen reporting 9 specific variants in these same groups was, respectively, 1.5% (87/5743) and 0.4% (33/8754).





Conclusions

- These results predict that 96% of individuals with genetically-positive cardiomyopathy would be falsely reassured by a negative result through a limited genotyping testing strategy.

- It is paramount for clinicians to avoid interpreting such uninformative results as an “all-clear” that would preclude patients and at-risk family members from receiving appropriate care and monitoring based on their true risk.

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Thank you