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

Tom Callis, PhD
Clinical Science Liaison, Invitae

Presented at ACC.20/WCC Virtual in the
Highlighted Original Research: Heart Failure and Cardiomyopathies and the Year in Review Session
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.

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.

### 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

<table>
<thead>
<tr>
<th>Hypertrophic cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>● &gt;40 disease-causing genes(^1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dilated cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>● &gt;30 disease-causing genes(^2)</td>
</tr>
</tbody>
</table>

Pathogenic and likely pathogenic variants:\(^3\)

| ● MYH7: >300 variants already known |
| ● MYBPC3: >500 variants already known |

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

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

HCM testing referral cohort 5743

Full gene sequencing and CNV analysis of up to 60 genes

Compare to genotyping of 9 variants in MYH7 and MYBPC3

Comprehensive cardiomyopathy referral cohort 8754

Full gene sequencing and CNV analysis of up to 106 genes

Compare to genotyping of 9 variants in MYH7 and MYBPC3
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.
Acknowledgements

Hypertrophic Cardiomyopathy Association (HCMA)
- Lisa Salberg

Invitae
- Rebecca Truty, PhD
- Edward D. Esplin, MD, PhD, FACMG, FACP
- Ana Morales, MS, CGC
- Matteo Vatta, PhD, FACMG
- Robert L. Nussbaum, MD, FACMG, FACP
Thank you