Incorporating genetic assessment in the evaluation of cardiomyopathy

Neal K. Lakdawala, MD
Cardiovascular Genetics, Heart Failure, Cardiac Transplantation
Brigham and Women’s Hospital
Harvard Medical School
Disclosures

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• Consulting:
  – BMS/Myokardia
  – Cytokinetiics
  – Tenaya
  – Pfizer/Array
  – Sarepta
Overview

• Core principles
• Who to test
• Why to test
• How to test
Recognizing core principles that apply to genetic cardiomyopathies

- Locus heterogeneity – Multiple loci/disease genes
  - Why panel testing is recommended for probands
- Allelic heterogeneity – Many different disease-causing variants in a particular disease gene
  - Why complete resequencing of disease genes is advised
- Age dependent penetrance – the phenotype does not manifest until later in life
  - Why lifetime longitudinal cardiac testing is advised for at risk family members
- Variable clinical expression – Phenotypic manifestations vary within affected family members
  - Why family history is not uniformly predictive of future clinical events
Who to test

Proband Testing

• Clearly affected individual with unambiguous phenotype (HCM, DCM, ARVC, RCM)

• Rationale:
  – Diagnosis
  – Prognostication
  – Family screening
  – Targeted therapies

Confirmation testing

• After proband testing has been completed and disease-causing variant identified

• With Genetic Counseling!

• Rationale:
  – Risk clarification

Hershberger JCF 2018
Musunuru Circ Genom Precis Med 2020
Case

- 32 year old male
- Previously healthy; no medications
- Progressive palpitations
- Irregularly irregular pulse
- ECG with SR and 1AVB (PR 260 ms)
- Holter with paroxysms of atrial fibrillation
- Echo with mild LV dilation, LVEF 40% (global hypokinesis)
CASE

- Died of "MI" age 38
- Died in MVA age 30
- Age 34
- Age 32
- "Benign palpitations"
- Age 26
- Age 6
- Age 2
Should genetic testing be performed in this patient?

If Yes, why?

• Help clarify risk of family members
• Help predict the patient’s prognosis and guide clinical management
Why Perform Genetic Testing?

• Define the genetic etiology of disease
  – Potential to clarify ambiguous diagnoses
  – Multiple distinct diseases may share a common “low-resolution” phenotype (phenocopies) but have a different genetic basis, disease course, and treatment
    • HCM vs HTN, Athlete’s heart, Storage disease (Fabry, amyloid)

• Determine the probability of disease risk in individuals who may not yet have disease
  – Guide family management: Definitively ID at-risk relatives
    • Pathogenic Mutation Present: At risk for developing disease
    • Pathogenic Mutation Absent: Not at Risk
  – Testing the FAMILY not the individual

• Inform natural history and guide sudden cardiac death risk stratification

• Potential to inform medical therapies
**CLINICAL + GENETIC EVALUATION**

**LMNA Pathogenic Mutation (+)**

- **Genotype (-):**
  - Reassurance
  - Not at risk for developing DCM or related complications
  - Longitudinal follow up not required
    - F/u if clinical change
  - Offspring not at risk

- **Genotype (+):**
  - At risk for developing DCM and related complications
  - 50% risk of transmission to each offspring
  - Longitudinal follow up to monitor for DCM development and stratify risk for SCD
  - Consider other factors
    - Sports/Lifestyle
    - Reproductive planning
    - Life insurance

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**Clarify Ambiguous Diagnoses**

- Focus Longitudinal Family Follow up:
  - From 6 possibly to 1 definitively at risk relative

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**Why to test -Cascade screening**

- At risk for disease
- Longitudinal screening

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**Clinical Care**

- ICD

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**Genotype (+):**

- Pathogenic DCM mutation (+)
  - Died in MVA age 30
  - Likely DCM SCD
  - Died of MI age 38
  - Likely DCM SCD

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**Genotype (-):**

- Not at risk
  - Genotyping not performed
  - No planned follow up

---

**Genotype (+):**

- At risk for disease
  - Longitudinal follow up required
  - Offspring at risk

---

**Longitudinal follow up**

- From 6 possibly to 1 definitively at risk relative

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**Focus Longitudinal Family Follow up:**

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**Why to test -Cascade screening**

- At risk for disease
- Longitudinal screening
**REPRODUCTIVE OPTIONS:**

**PREIMPLANTATION GENETIC DIAGNOSIS (PGD)**

**Requirements:**
1. Pathogenic mutation identified in the family
2. *In Vitro* Fertilization

- Mutation positive
- Transfer mutation negative embryos to initiate pregnancy
- Confirm results with amniocentesis or CVS during pregnancy

- Mutation negative
- Not Implanted
Why to test – *Prognosis and Clinical management*

**LMNA Cardiomyopathy**

*Higher frequency of ventricular arrhythmias*

- Predictors of sustained VT or VF (VA)
  - **Risk Factor**
  - **HR**
  - **HR**
  - LVEF≤50%* 3.4 (1.5-8.1) 4.4 (1.7-11.0)
  - Male gender 3.2 (1.3-8.0) 2.9 (1.2-7.0)
  - Structural mut. 2.5 (1.1-6.0) NS
  - NSVT NS NS 4.4

- 2017 ACC/AHA/HRS guidelines provide different threshold for primary prevention ICD placement
- Because VA are so common, ICD advised for patients referred for PPM for HB³

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2. Van Rinsingen JACC 2012
3. Meune NEJM 2006
Why to test  
**Targeted therapies**

- Current therapeutic implications:
  - TTR cardiomyopathy - Multiple  
  - Fabry disease – Enzyme replacement/chaparone therapy

- Ongoing trials
  - Array 797 in LMNA DCM (ph 3)  
  - Danicamтив in MYH7/TTN related DCM (ph 2)  
  - RP-A501 (gene therapy) in LAMP2 HCM (ph 1)
  - Many more to come . . .
### Picking a Genetic Test in CMP

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phenotype negative, with FH of CMP</strong></td>
<td>Confirmation testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Classic CMP phenotype (e.g. ARVC, HCM, DCM)</strong></td>
<td>Disease Specific Panel</td>
<td>1. Broad CMP Panel</td>
<td>Research referral</td>
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<tr>
<td><strong>Atypical CMP</strong></td>
<td>1. Broad CMP Panel</td>
<td>Chromosomal microarray*</td>
<td>Research referral</td>
</tr>
<tr>
<td><strong>Atypical CMP Motivated Family Recessive Inheritance</strong></td>
<td>1. Broad CMP Panel</td>
<td></td>
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<tr>
<td></td>
<td>2. Expanded Phenotyping</td>
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*Green = refer to cardiac genetics clinic; WGS/WES = whole genome/exome sequencing; microarray can enable detection of CNV; genetic counseling for all*
How to test – Interpreting and applying results

Proband Testing

- Only pathogenic or likely pathogenic variants are actionable
- Variants can be further adjudicated with cosegregation testing
- Interpretation can be reviewed in clinvar and gnomAD

Confirmation testing

- Should be generally restricted to pathogenic or likely pathogenic variants
- With Genetic Counseling!

Hershberger JCF 2018
Musunuru Circ Genom Precis Med 2020
Cirino JAMA Cardiology 2017
Key takeaways

- **Who** – unambiguously affected patients with hypertrophic, dilated, restrictive and arrhythmogenic cardiomyopathy (LOE “A” recommendation, except restrictive “B”)

- **Why** – clarify diagnosis, inform cascade screening, impact clinical management

- **How** –
  - Panel testing for probands
  - Mutation confirmation testing for at-risk family members
  - With genetic counseling (LOE “A”)

Hershberger JCF 2018
Resources

- “Role of Genetic Testing in Inherited Cardiovascular Disease”
  – Cirino AL et al. JAMA Cardiology 2017; 2:1153
- “Genetic Evaluation of Cardiomyopathy – A Heart Failure Society of America Practice Guideline”
  – Hershberger RE et al. J Card Fail 2018;24:281
- “Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement from the American Heart Association”
- Clinical Genomics Bootcamp
  – American Heart Associations Scientific Sessions; November 2022
- gnomAD https://gnomad.broadinstitute.org/
Thank You!

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