GENES TO GENOMES: EVOLUTION OF MOLECULAR TESTING FOR INHERITED CARDIOMYOPATHY

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FROM GENES TO GENOMES - EVOLUTION OF MOLECULAR TESTING FOR INHERITED CARDIOMYOPATHIES

Heart Failure Update 2018 - Toronto

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WHAT WILL BE COVERED?

• Brief overview of inherited cardiomyopathies

• A decade of clinical genetic testing – lessons learned

• Ensuring clinical validity: which genes should be tested?

• From reaction to prevention – are we ready for predictive testing?
THE MAIN INHERITED CARDIOMYOPATHIES

- **DCM**: Dilated
- **HCM**: Hypertrophic
- **ARVC**: Arrhythmogenic right ventricular

- Collective incidence (idiopathic): > 1/500
- Can lead to SCD

- Substantial genetic component
- Incentive for predictive testing

Maron et al. Circulation. 2007: Causes of SCD in 1435 young competitive athletes
AFFECTED CELLULAR STRUCTURES

Most commonly affected structure: SARCOMERE
(contractile unit of the muscle)

Dunn 2013: Circ Cardiovasc Genet.
WHEN AND WHY TEST FOR GENETIC VARIANTS?

When symptomatic
• Establish/confirm clinical Dx
• Family testing: release mutation NEG members from clinical screening
• Treatment (e.g. Fabry disease as phenocopy, ERT exists)

Before the onset of symptoms
• Reduce adverse outcomes or prevent disease
HISTORY OF GENETIC TESTING FOR CARDIOMYOPATHY

Adapted from: Maron 2012, JACC 60:715
A DECADE OF GENETIC TESTING
WHAT HAVE WE LEARNED?
GENETIC HETEROGENEITY + MODERATE DETECTION RATES

**HCM**
- 32% POS (n~3,000)
- 2 genes (MYBPC3, MYH7) = ~80%

Alfares 2015, Genet in Med

**DCM**
- ~37% POS (n~800)
- 1 predominant gene (TTN): 14%
- No other gene >5%

Pugh 2014, Genet in Med
MANY VARIANTS ARE UNIQUE

Hypertrophic Cardiomyopathy
~3,000 probands tested at the laboratory for Molecular Medicine

63% seen only once

Very few recurring variants...
Proband with clinical Dx + FHx of DCM

DCM testing inconclusive

Dx revised to ARVC

ARVC panel: positive

~3% of DCM patients carry a pathogenic variant in an ARVC gene

Traditional testing does not make sense for disorders with clinical overlap
MULTI DISEASE TESTING FACILITATES DIAGNOSIS

• Original clinical definition based on most severe cases

• Too narrow, full range of clinical variability emerged over time
INCREASING NUMBERS OF PUBLISHED DISEASE GENES

- >60 DCM genes
- >50 HCM genes
LARGE GENE PANELS – TROJAN HORSES

% inconclusive
~10 % ➔ ~60%

% positive
~10 % ➔ ~37%

Pugh et al. 2014
MORE = BETTER?

Use in clinical practice

PANELS

EXOME

GENOME

2018
CLINICAL VALIDITY

WHICH GENES SHOULD BE ON A PANEL?
CLINICALLY OFFERED GENE PANELS ARE EXTREMELY VARIABLE

Hypertrophic Cardiomyopathy

Which one should one order??

Genetic Testing Registry (Jan 2016), representative HCM panels

- Other
- Other syndromic (RASopathy)
- Storage cardiomyopathy
- Sarcomere (≥ 1% detection rate*)
THE CLINICAL GENOME RESOURCE (ClinGen) STANDARDS FOR ASSESSING CLINICAL VALIDITY

ClinGen’s Critical Questions:
- Is this gene associated with a disease? Clinical Validity
- Is this variant causative? Pathogenicity
- Is this actionable? Clinical Utility

Curated & Medically Relevant Knowledge
- ClinVar & Other Resources

Improved Patient Care Through Genomic Medicine

MANY PUBLISHED GENE-DISEASE ASSOCIATIONS ARE INSUFFICIENTLY SUPPORTED

Jodie Ingles..... Birgit Funke (HCM gene curation expert panel): in preparation
EVIDENCE BASED TEST CONTENT SELECTION

- Currently, labs choose content
- Need professional society guidance
- Need regulatory enforcement
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Today

Future

Not as easy as it seems
The promise and peril of genomic screening in the general population

Michael C. Adams, MS¹, James P. Evans, MD, PhD¹, Gail E. Henderson, PhD², Jonathan S. Berg, MD, PhD¹; GeneScreen Investigators
SUMMARY

• Inherited cardiomyopathies have a strong genetic etiology

• Potentially severe outcomes (SCD) provide a strong incentive for genetic testing of presymptomatic family members

• All cardiomyopathies are genetically and clinically heterogeneous

• Multi-disease (“pan-cardiomyopathy”) testing is useful and feasible, moving quickly towards exome/genome testing as a first line test

• More is not better: Literature contaminated with many insufficiently supported gene-disease association claims

• Clinical testing gene panels are not standardized, expert guidance needed!

• Predictive testing in healthy populations starting to be discussed – but insufficient understanding of the penetrance of cardiomyopathy variants in unaffected individuals…
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Cardiomyopathy Variant Curation Expert Panel

Laboratory for Molecular Medicine
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