

# Taking Heredity to the Heart : Genetics of Cardiomyopathy

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# Objectives

- ▶ Review the genetic basis of HCM
- ▶ Discuss importance and indicators in the family history
- ▶ Discuss some issues surrounding genetic testing
- ▶ Briefly list other inherited cardiovascular conditions that are on our radar

No conflicts to disclose

# Inheritance Patterns in Cardiac Disease

*All Have a Genetic Basis*



Familial CM  
Familial Arrhythmias  
Familial  
Aortopathies  
Familial  
Hyperlipidemia

Coronary disease  
Hypertension  
Typical hyperlipidemia

## Simple/Mendelian:

### Primary cause:

Single variant with large effect  
(Autosomal Dominant)

### Plus:

Multigenic influences  
Environmental influences

## Complex/Multigenic

### Primary cause:

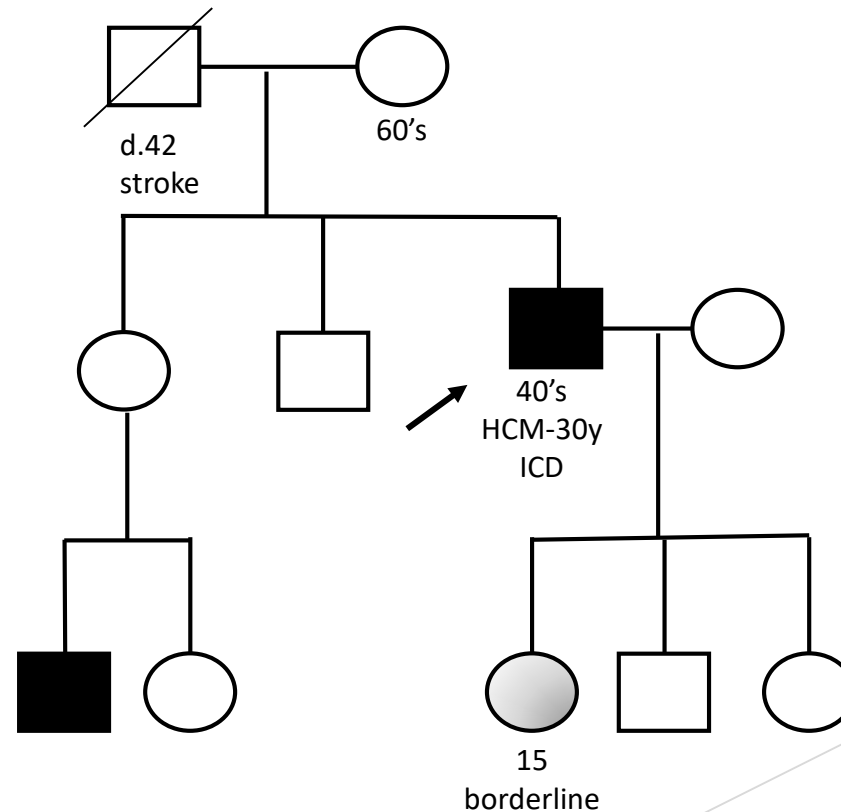
Multiple common variants, each  
with small but additive effects

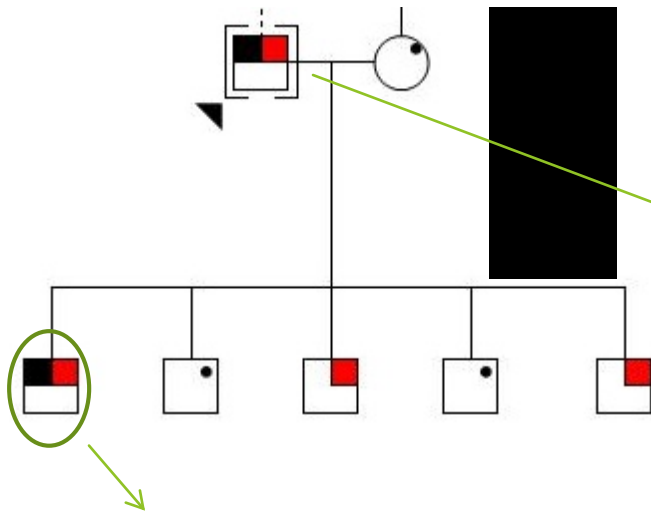
### Occasional:

Rare variants with larger effect  
size

# Autosomal Dominant Inheritance

- ▶ A single altered gene is passed on in a family
- ▶ 50% independent probability of gene being passed on (regardless of sex)
- ▶ Reduced penetrance and variable expressivity
- ▶ Nothing skips generations





46 y/o father,  
Asymptomatic

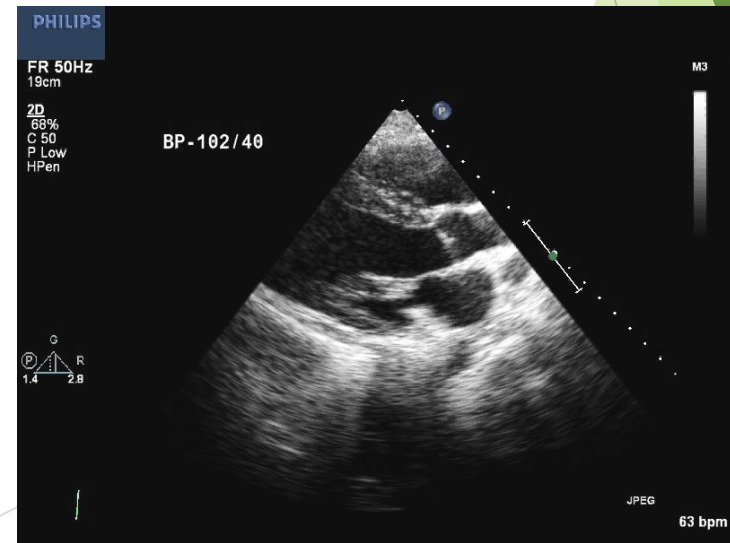
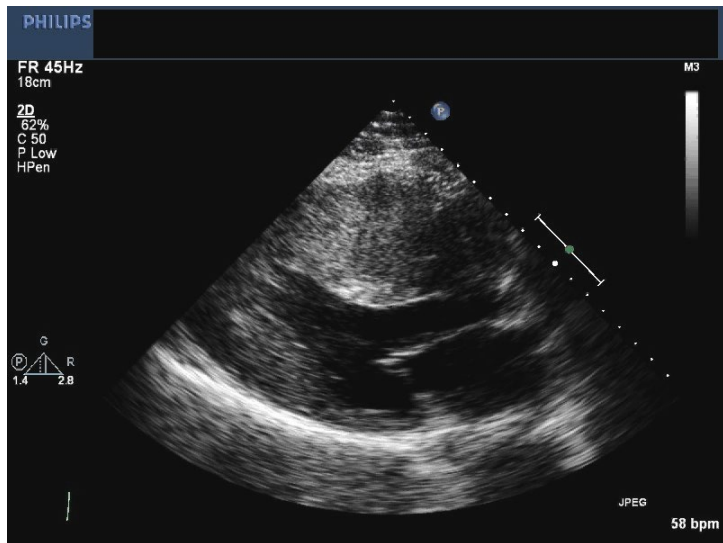
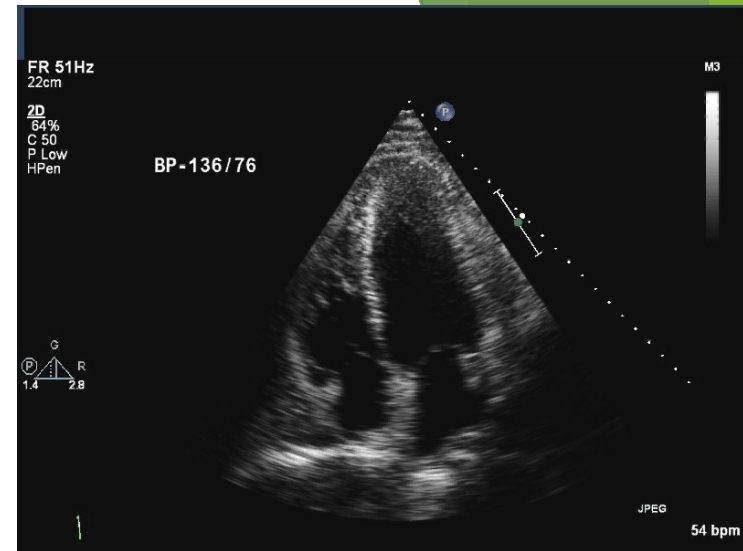
**TNNT2 Arg286Cys**

20 y/o male diagnosed HCM age 4 mo  
Myectomy age 11, Class II CHF, primary  
prevention ICD age 16, appropriate  
shock age 19

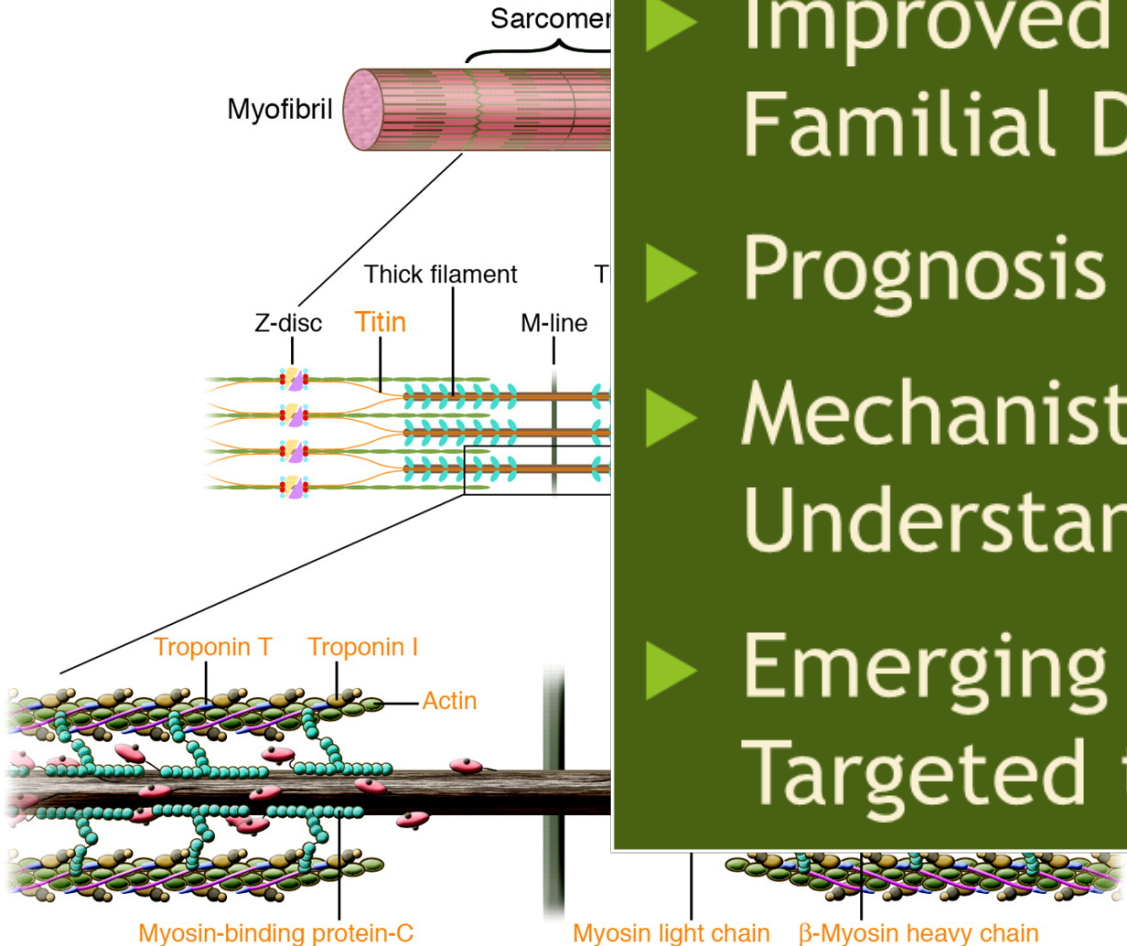
**TNNT2 Arg286Cys**

16 y/o brother  
Asymptomatic

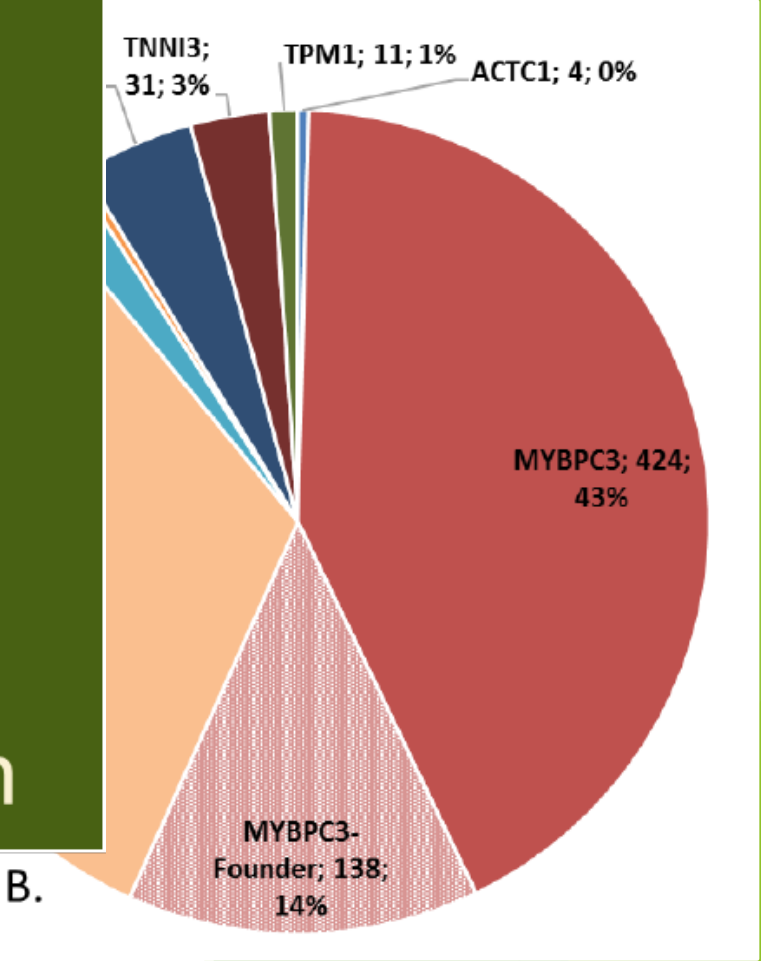
**TNNT2 Arg286Cys**



# Genetic basis for HCM: mutations in sarcomere contractile unit genes



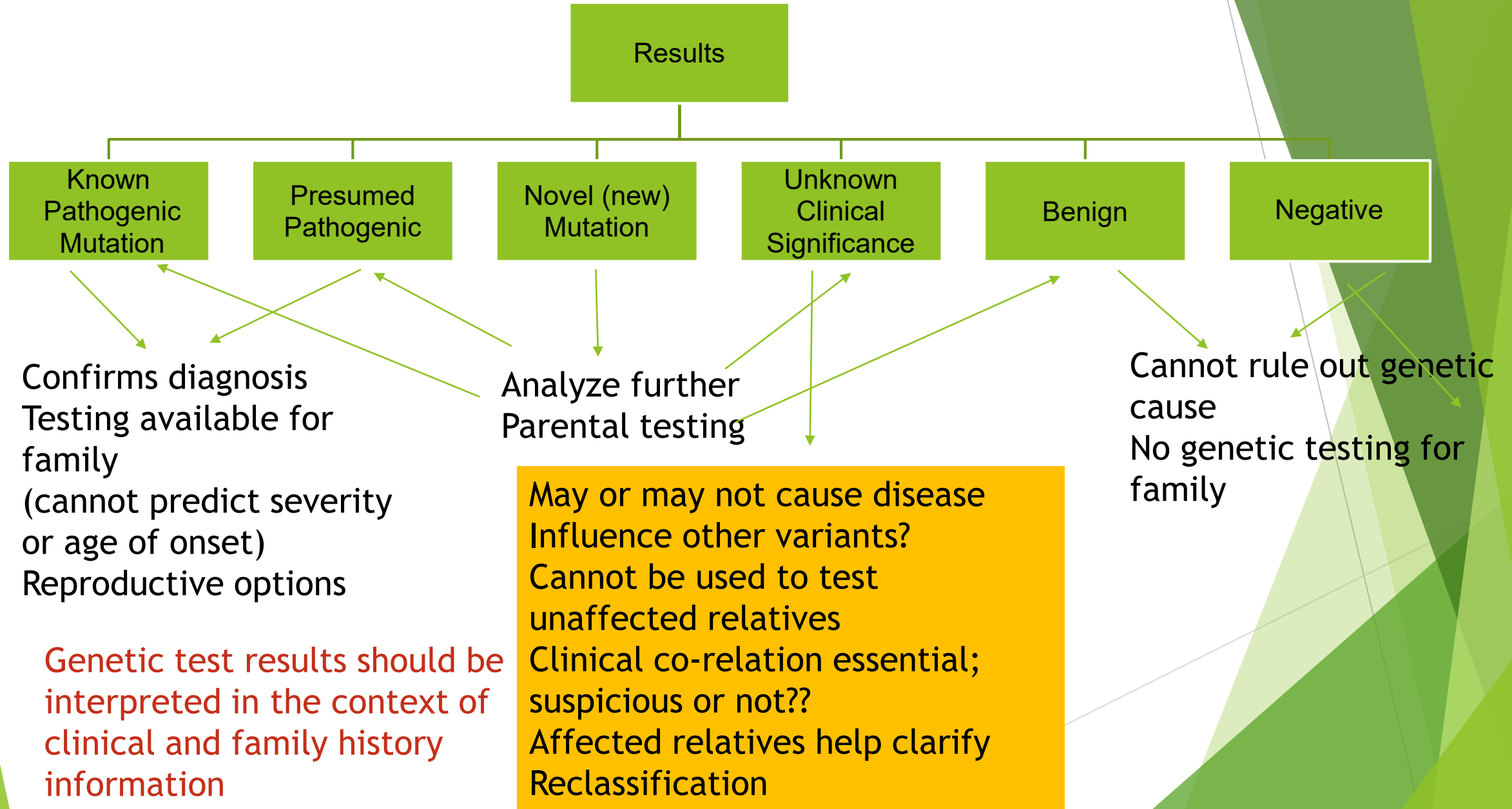
- ▶ Improved Diagnosis of Familial Disease
- ▶ Prognosis
- ▶ Mechanistic Understanding
- ▶ Emerging Treatments Targeted to Mechanism



Morita, H. et al. J. Clin. Invest. 2005;115:518-526

Ho, et al., Circ 2018

# Genetic test results





- ▶ Insurance reimbursement variable
- ▶ Prices plummeted: \$250 OOP for proband. May be no charge for family.
- ▶ Comparison: Cost of clinical screening >\$2000 per exam



# Discrimination

- ▶ ‘Genetic Information Non-Disclosure Act’ (GINA) signed into law on May 21<sup>st</sup>, 2008.
  - Prohibits a group health plan for requesting, requiring, obtaining or using genetic testing results
  - Prohibits employer from discriminating based on genetic information (hiring, firing, raises, promotions)
  - Not included: life, disability & long-term care insurance
  - Exceptions

# Genetic Basis of DCM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY  
© 2018 THE AUTHORS. PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION. THIS IS AN OPEN ACCESS ARTICLE UNDER THE CC BY LICENSE (<http://creativecommons.org/licenses/by/4.0/>).

## Genetic Etiology for Alcohol-Induced Cardiac Toxicity

THE LANCET

Volume 393, Issue 10166, 5–11 January 2019, Pages 61–73

THE LANCET

Substrate and cofactors  
may explain genetic  
susceptibility to alcohol  
induced cardiac toxicity  
in some people with type 2 diabetes.  
See page 61

Articles

Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial

- ▶ Genetic basis of DCM now established
- ▶ Negative family history does NOT rule out genetic DCM (variable expressivity)
- ▶ Genetic testing should be considered for DCM, even in setting of EtOH or peripartum
- ▶ Cardiomyopathy medications should not be stopped with EF recovery (the genetic substrate is still there)
- ▶ DCM patients' family members should be screened even if negative FamHx.

## Other Inherited Cardiovascular Indications for Genetic counseling and/or testing

- ▶ Dilated Cardiomyopathy
- ▶ Arrhythmogenic Cardiomyopathy
- ▶ Left Ventricular Non-Compaction
- ▶ Arrhythmias (Long QT, CPVT, Brugada)
- ▶ Aortic disease (Marfan syndrome, LDS, EDS, non-syndromic FTAAD)
- ▶ Vascular disease (SCAD, FMD)
- ▶ Familial Hypercholesterolemia
- ▶ Pulmonary Arterial Hypertension
- ▶ Neuromuscular disease with cardiac component