Dilated Cardiomyopathy: Genetic Testing- Who, What and Why?

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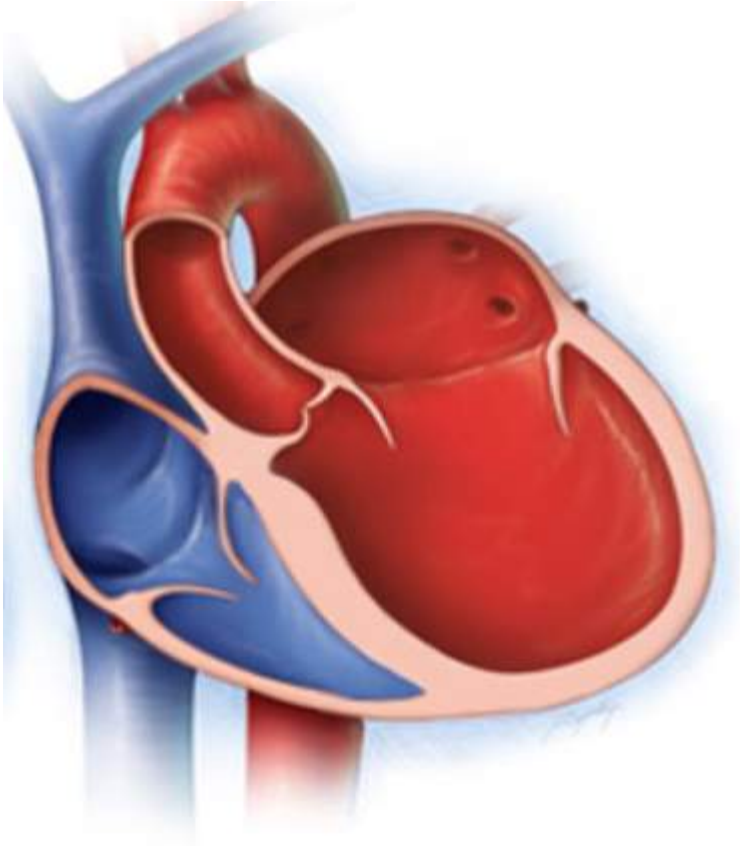
No Disclosures

Dilated Cardiomyopathy (DCM)

- Definition of Dilated Cardiomyopathy (DCM)
  - Left ventricular end-diastolic dilation with left ventricular systolic dysfunction
- Rate of 0.57 per 100,000
- Impact DCM
  - 45% of heart transplants due to DCM
  - 50% of patients with DCM progress to heart failure, transplantation or death within 2 years of diagnosis
  - 2-3% SCD

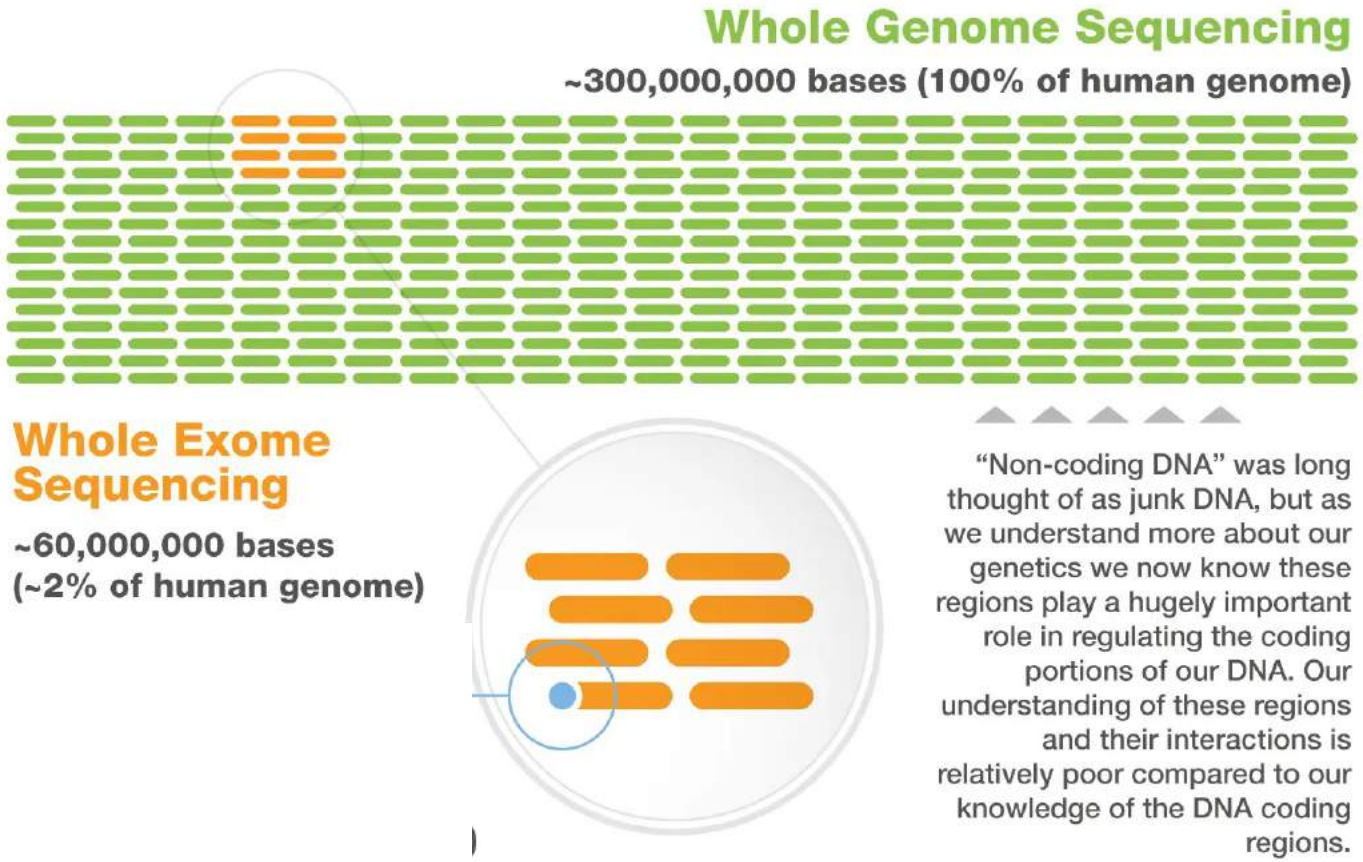


Genetics of Dilated Cardiomyopathy

- Classification
  - Primary
    - Genetic
      - Idiopathic
      - Familial
  - Secondary
- Inheritance
  - Autosomal Dominant
  - Recessive
  - X linked
  - Mitochondrial

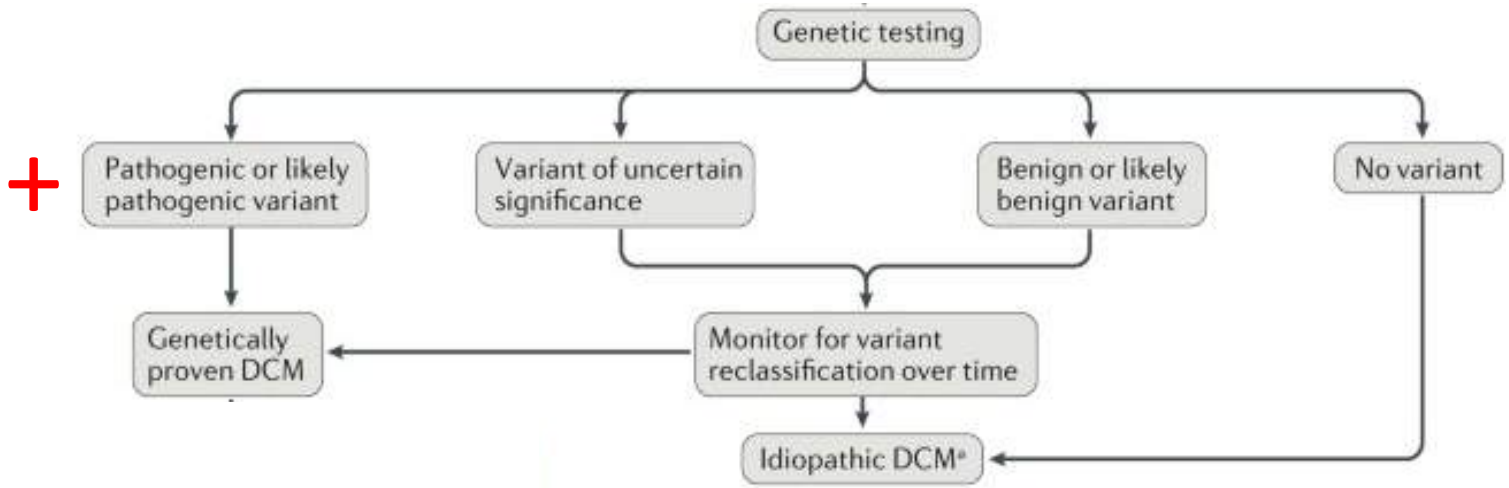
Types of Genetic Testing

- Panel Sequencing
- Genome wide sequencing
  - Whole exome
  - Whole genome

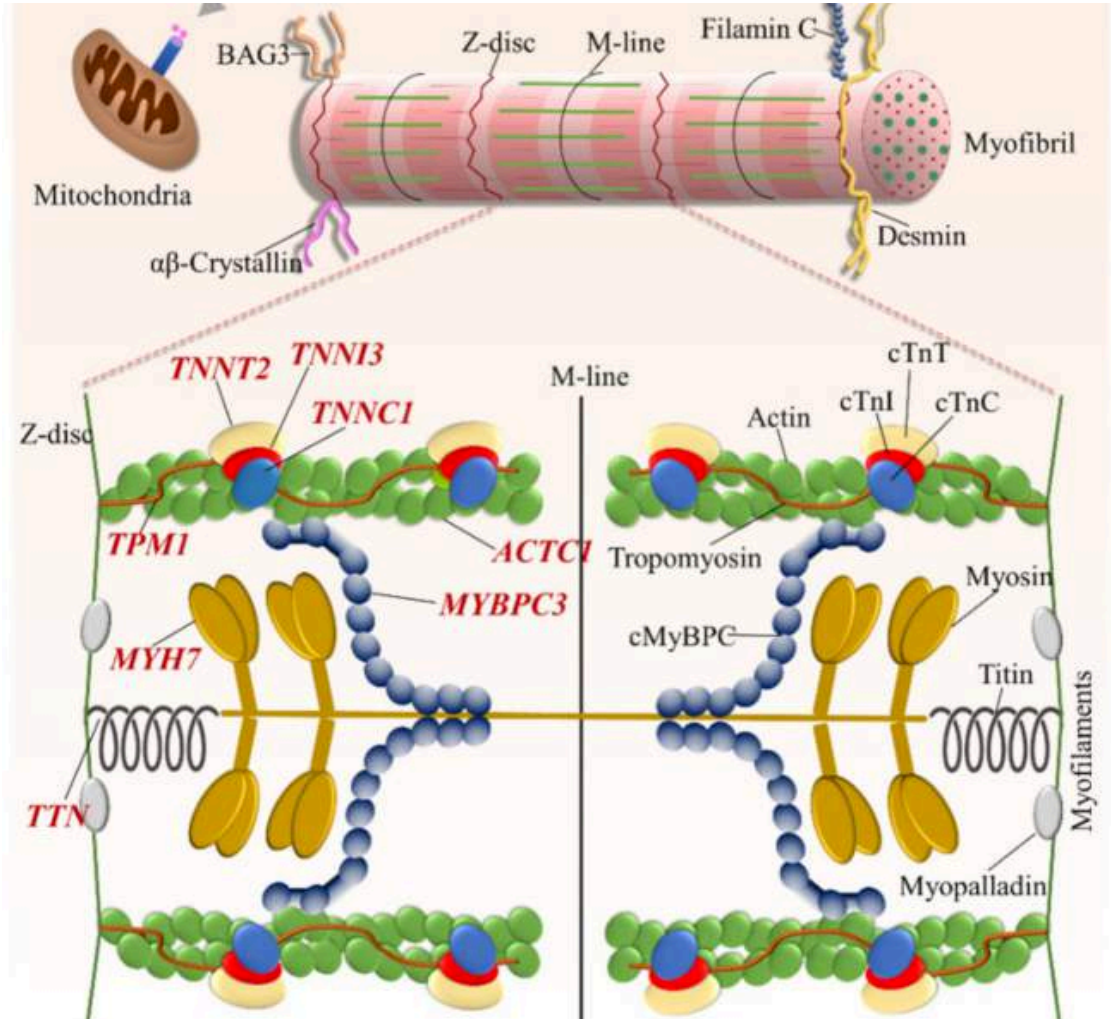


American College of Medical Genetics variant classification guidelines

- Genetic Variants
  - Pathogenic
  - Likely Pathogenic
  - Unknown
  - Likely Benign
  - Benign



Common Genes Associated with DCM



- Sarcomere
  - MYH7- Myosin Head
  - MYBPC3- Regulates position of myosin/actin
  - TNNT2- Troponin T
  - TNNI3- Troponin I
  - TTN- Titin
- Cytoskeleton
  - FLNC- actin binding proteins

Hassoun R, Budde H, Mügge A, Hamdani N. Cardiomyocyte Dysfunction in Inherited Cardiomyopathies. Int J Mol Sci. 2021 Oct 15;22(20):11154.

Genetic Causes of Cardiomyopathy in Children: First Results from the Pediatric Cardiomyopathy Genes Study

- 2013-2016
- Primary <18 years old
- 152 patients- 81 (53%) had genetic testing
- Exome sequencing- 37 genes
- 41% had a family history
- Institutional Variation 0-97%
- Findings in DCM
  - Positive results in Familial 35% > Idiopathic 9%
  - No dominant gene with variants

Ware SM et al.;. J Am Heart Assoc. 2021

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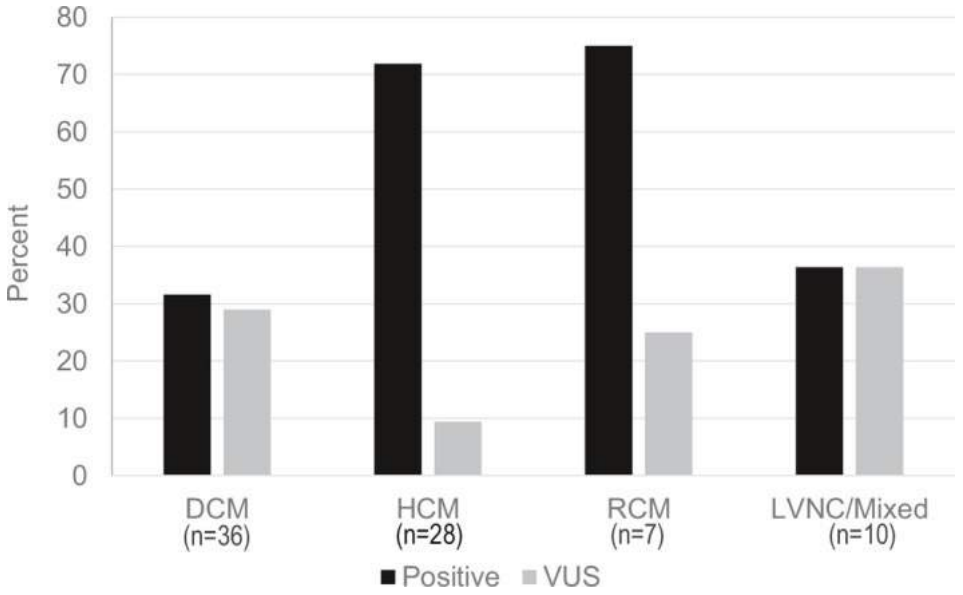
Genetic Causes of Cardiomyopathy in Children

- **Findings:**
  - **First-degree relative surveillance- 89% familial vs 42% idiopathic**
  - **VUS and P/LP almost = in DCM**
  - **14 children with new positive molecular findings**



- **Conclusion**
  - **Without testing all patients with familial or idiopathic DCM, potential molecular causes are being missed**
  - **Reclassification alters care for family members**

Ware SM et al.;. J Am Heart Assoc. 2021

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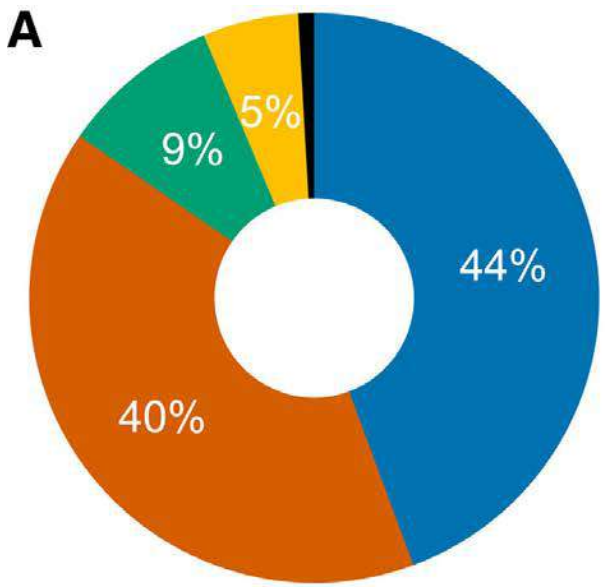
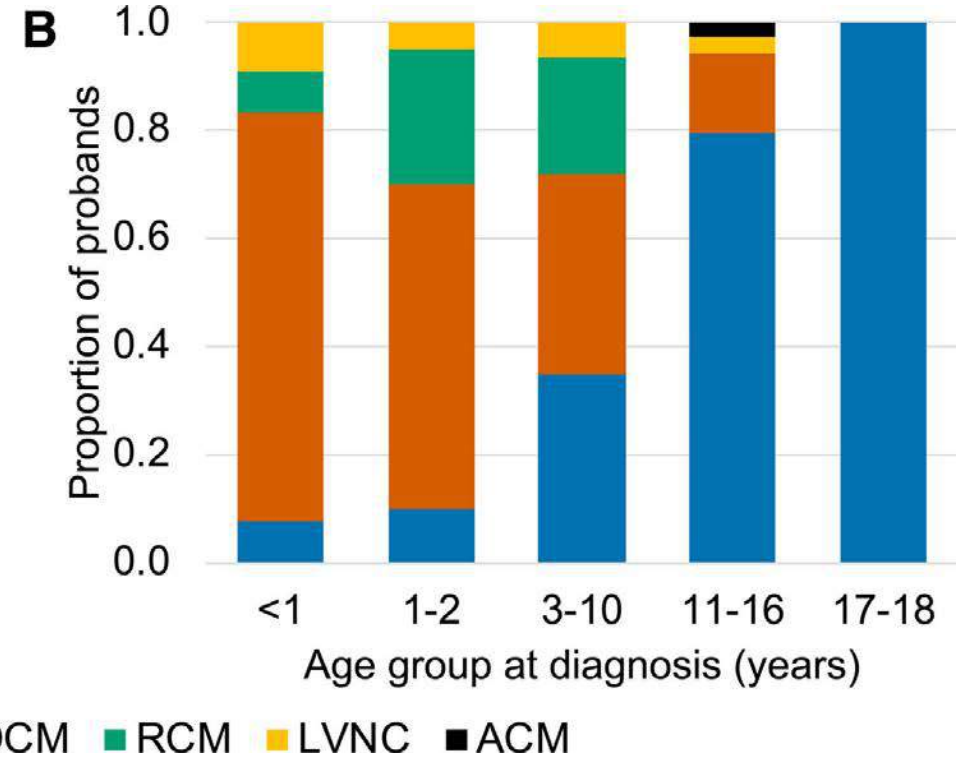
Genetic Basis of Childhood Cardiomyopathy

- Australia 2022
- 221 children <18 years
- 42% had a family history
- Exome and genome testing





- Bagnall RD, et al. Circ Genom Precis Med. 2022

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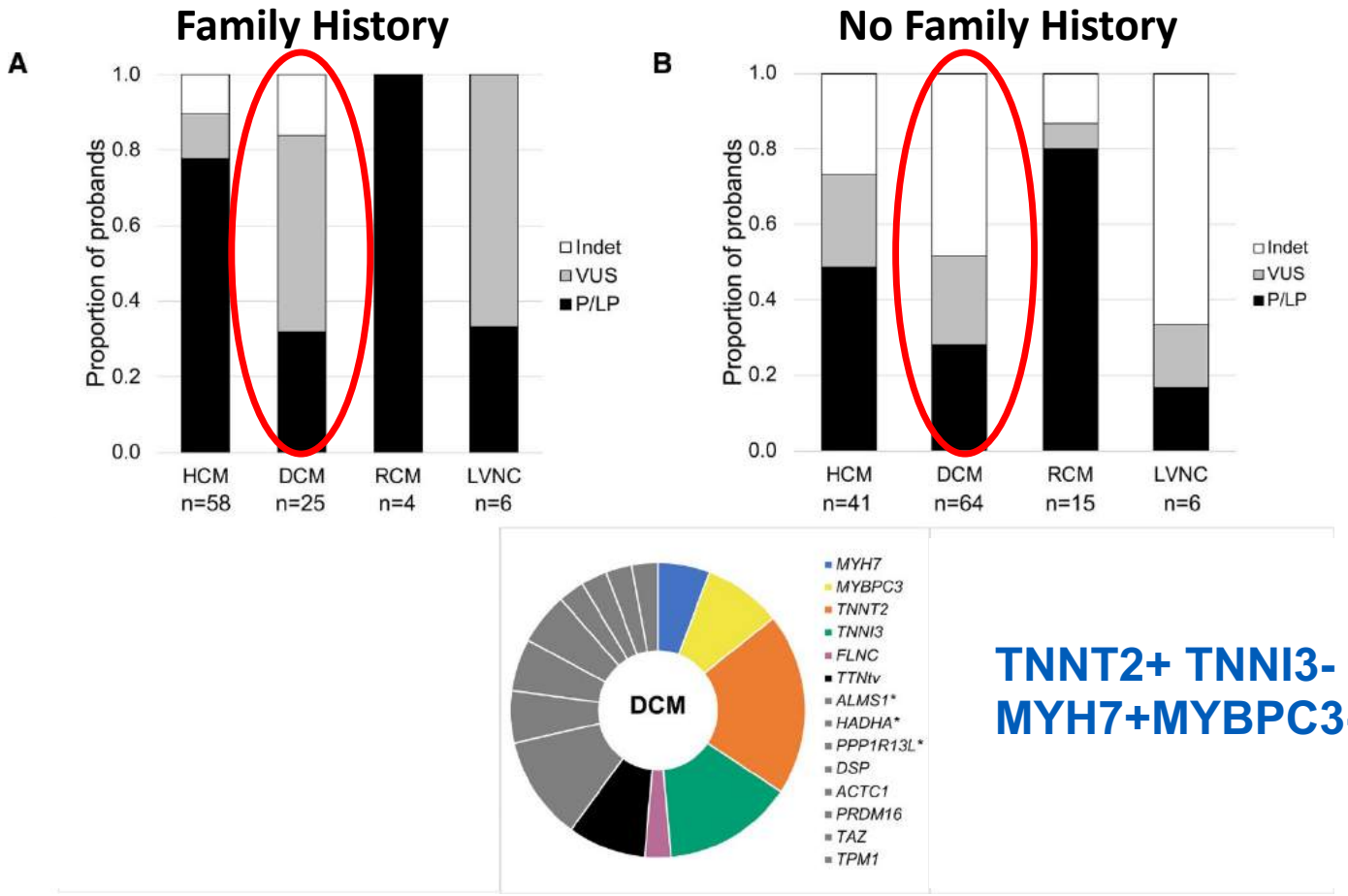
Genetic Basis of Childhood Cardiomyopathy



TNNT2+ TNNI3- 40%
MYH7+MYBPC3- 17%

Bagnall RD, et al. Circ Genom Precis Med. 2022

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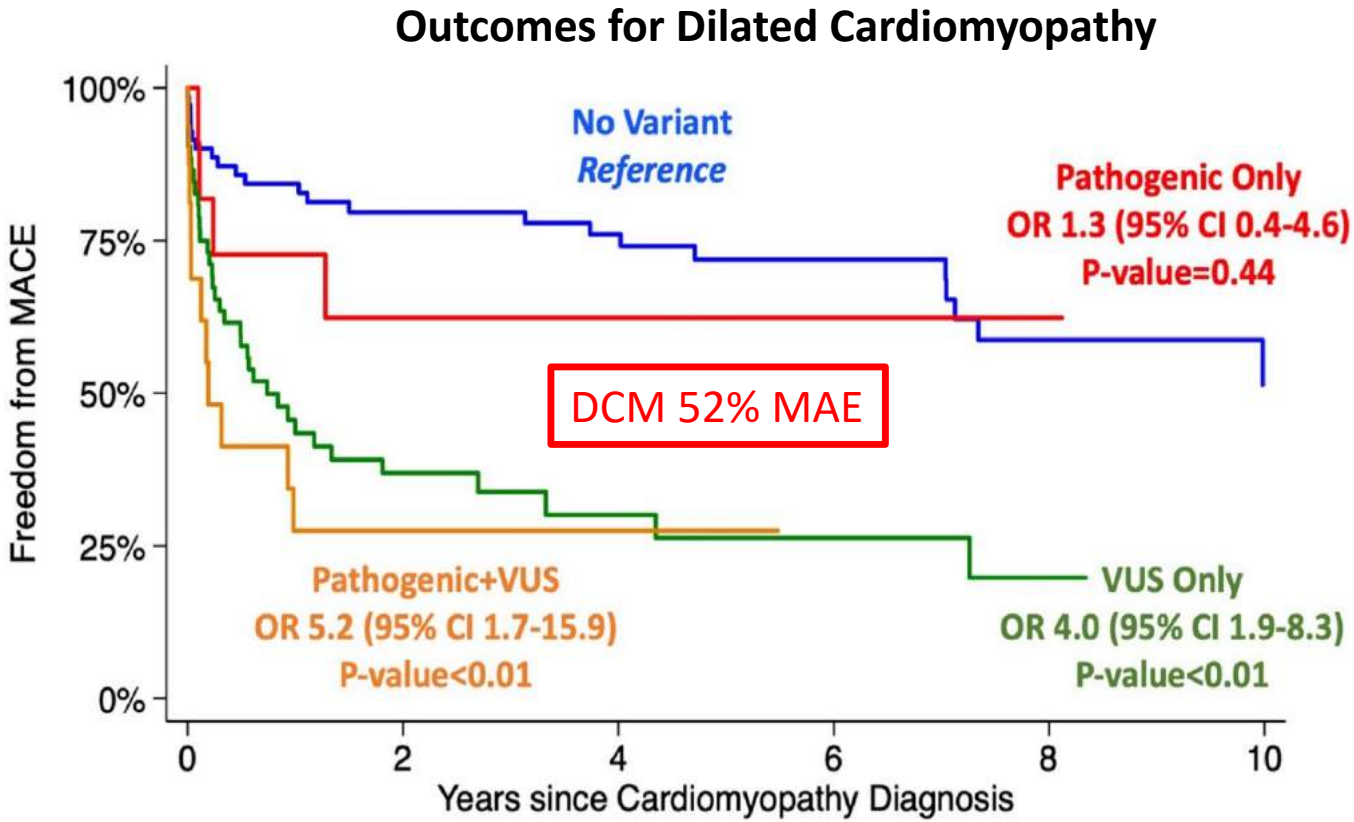
Genetic Basis of Childhood Cardiomyopathy

- DCM genetic yield
  - 28 unique variants found in 26 patients
  - 32% positive in familial cases
  - 27% positive idiopathic (50% de novo)
  - DCM lowest diagnostic yield at 29%
- Conclusions:
  - Better yield with genome wide testing
  - Shared genes with adults but predominance/associations were different
  - Reclassification of 12 variants from VUS to LP

Genetic Variant Burden and Adverse Outcomes in Pediatric Cardiomyopathy

- Retrospective single center
- Genetic testing 2010-2018 <21 years
- 338 patients
- Composite outcome- Major Adverse Event (MAE)
  - VAD, ECMO, transplant, aborted arrest or death



Burstein DS, et al. Pediatr Res. 2021.

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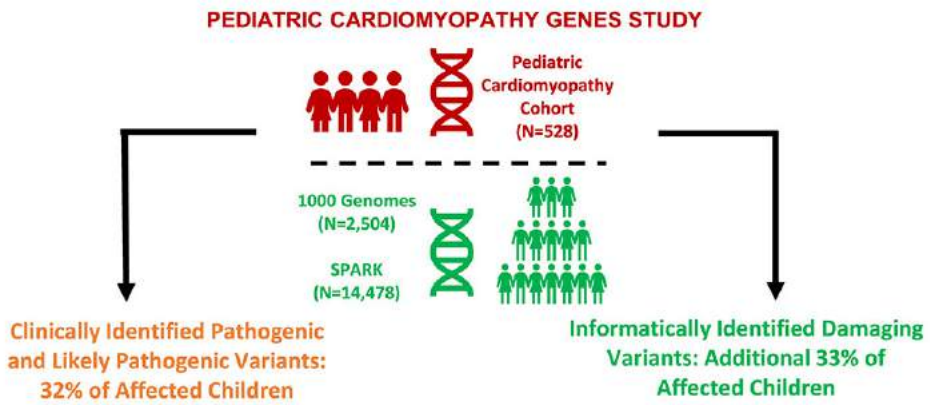
The Future



- Increase the identification of genetic variants
- Pediatric genotype: phenotype associations
- Therapies directed at the molecular basis of the disease instead of symptoms
- Adults
  - Levosimendan- a Ca+ sensitizer binds to Troponin C and stabilizes the open configuration
- Gene therapy- started in HCM MYBPC3
- Utilization of pluripotent stem cells and differentiation into cardiac cells

Ware SM et al. Pediatric Cardiomyopathy Registry Study Group. The genetic architecture of pediatric cardiomyopathy. Am J Hum Genet. 2022

Summary

- Genetic testing needs to be done in all familial and idiopathic patients with first-degree relative surveillance unless ruled out
- Retesting needs to be done every 1-2 years
- We need further studies to continue to identify pathogenic variants
- Genetic testing is not just for diagnosis but also prognosis
- Therapies directed at molecular causes looks promising


Thank you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