

## **CARDIOMIOPATIE: HOT TOPICS**

**Dalle varianti rare al rischio poligenico:  
nuove prospettive sulle basi  
genetiche delle cardiomiopatie**

**MANGO RUGGIERO**



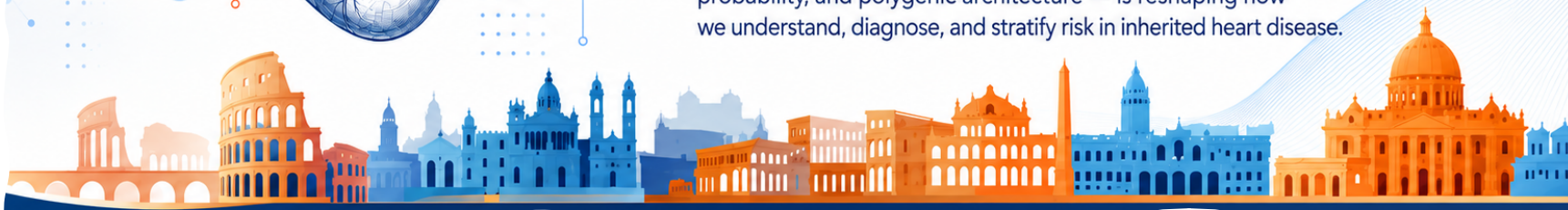
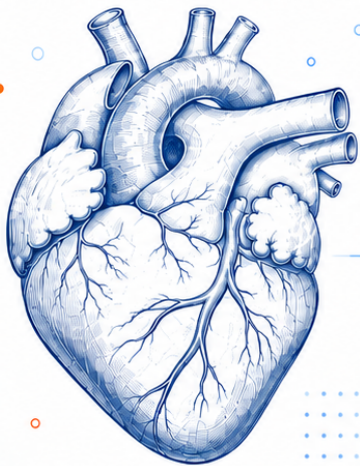
## CARDIOMIOPATIE: HOT TOPICS



CARDIOVASCULAR GENETICS

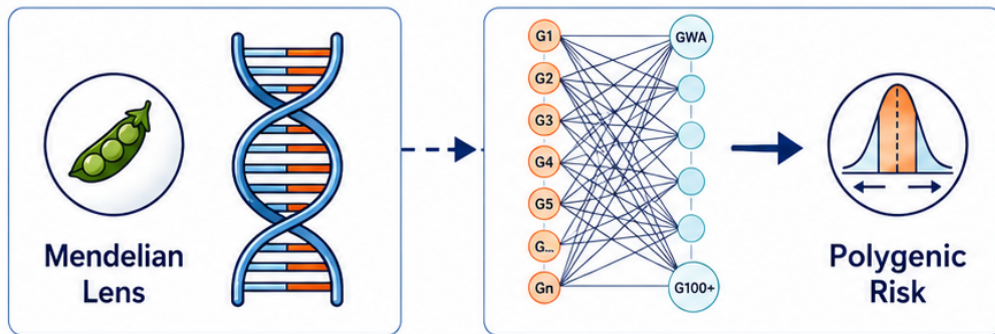
# The End of the Mendelian Era?

Cardiomyopathies are no longer purely Mendelian diseases. A new genetic framework — one that embraces complexity, probability, and polygenic architecture — is reshaping how we understand, diagnose, and stratify risk in inherited heart disease.





# From Single-Gene to Polygenic Thinking



For decades, cardiomyopathies were understood through a **Mendelian lens: one pathogenic variant, one disease, one inheritance pattern**. This model served as a powerful diagnostic anchor—but it left critical questions unanswered.



Why do carriers of the same variant differ so dramatically?



Why do some patients have no identifiable monogenic cause?



Why does disease severity vary within families?





## MONOGENIC

Chromosome 14



β-myosin heavy chain with **ALTERED** function



Hypertrophic  
Cardiomyopathy

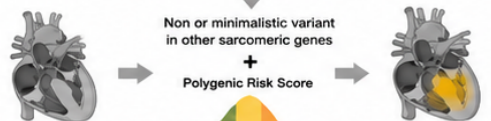


## OLIGOGENIC

Chromosome 14



β-myosin heavy chain with **ATTENUATED** function

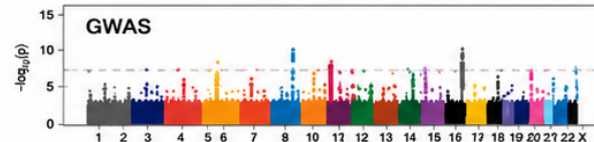


Hypertrophic  
Cardiomyopathy



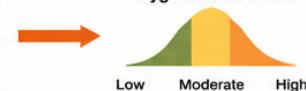
## POLYGENIC

Whole Genome

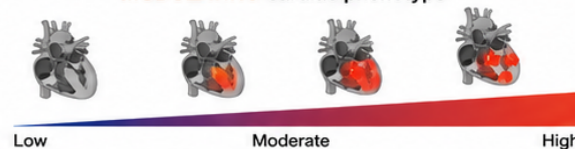


| Variant | Gene     | SNP    | OR   |
|---------|----------|--------|------|
| 1       | rs123456 | Gene A | 1.05 |
| 2       | rs234567 | Gene B | 1.04 |
| ...     | ...      | ...    | ...  |
| n       | rsN      | Gene N | 1.02 |

Polygenic Risk Score



Polygenic background of  
**MODULATING** cardiac phenotype



**Cardiomyopathies lie on a genetic continuum:**  
from rare, highly penetrant variants to common, low-effect risk alleles.  
Understanding this continuum is key to **prediction, prevention, and precision care.**



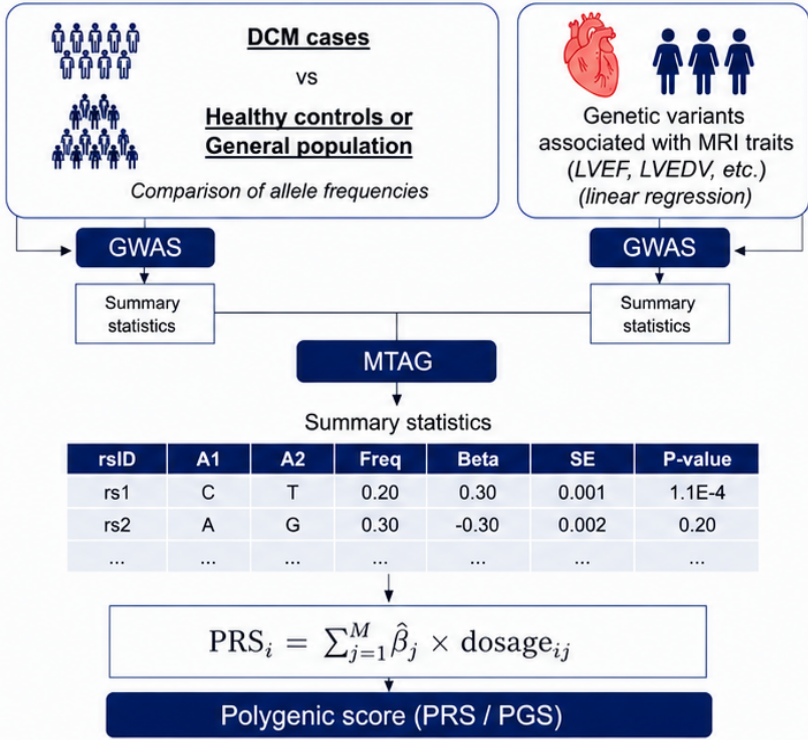
Integrated genetics.  
Better prediction.  
Personalized care.



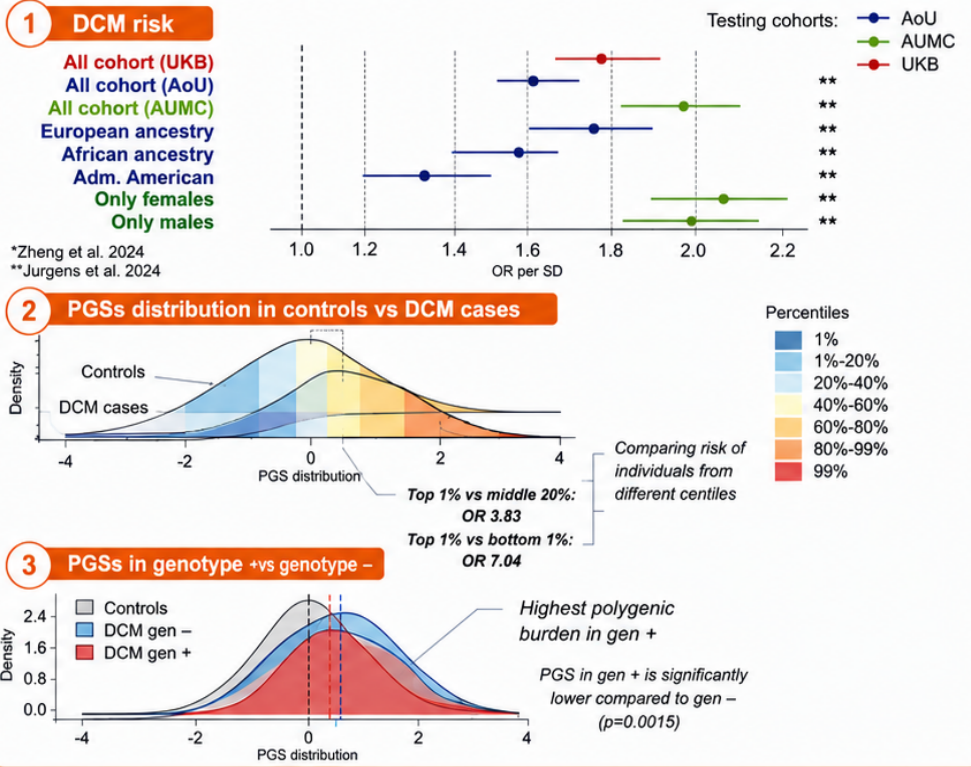




## A. GWAS and PRS Development



## B. Validation and Performance of PGSs





# HCM PGS Performance in the General Population



**Top centile**  
**10.9/1,000**

HCM prevalence  
(per 1,000 individuals)

**≈ 14x**  
higher risk  
vs bottom  
centile



**Median centile**  
**0.8/1,000**

HCM prevalence  
(per 1,000 individuals)

**≈ 3x**  
higher risk  
vs bottom  
centile



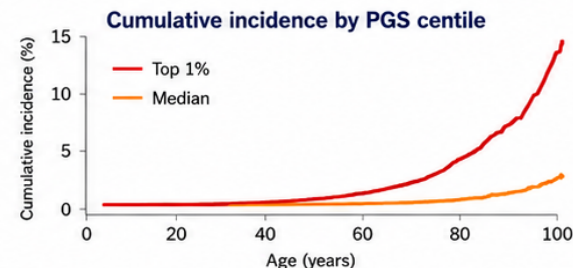
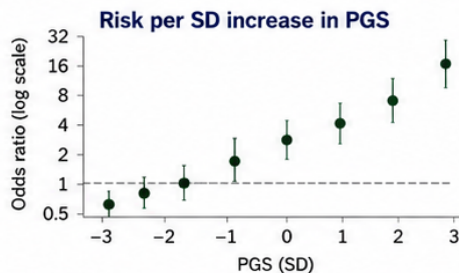
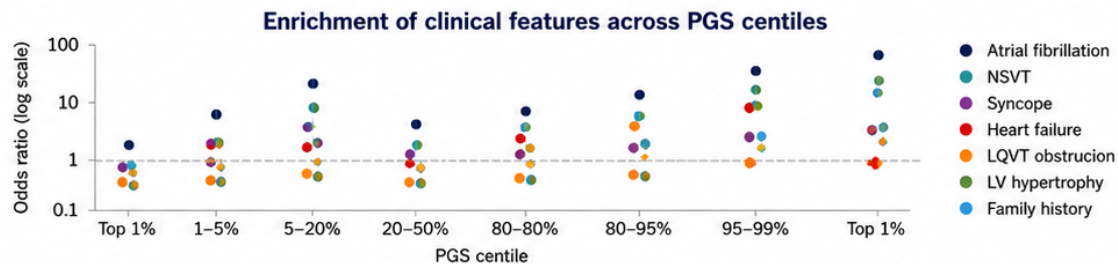
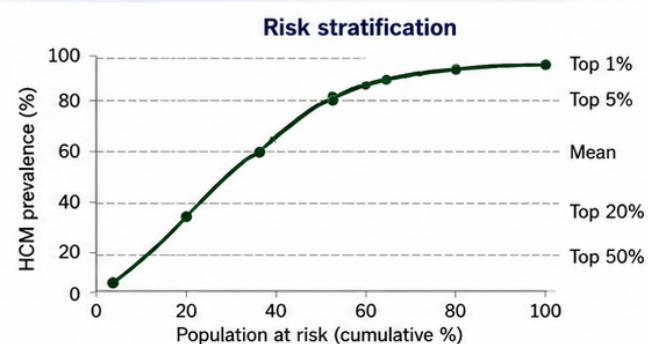
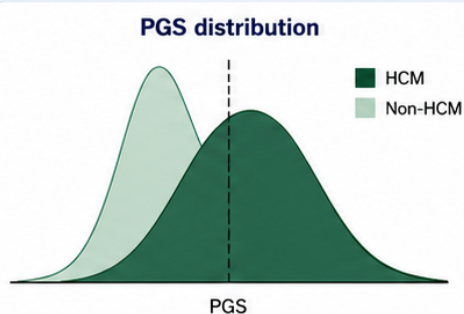
**Bottom centile**  
**0.3/1,000**

HCM prevalence  
(per 1,000 individuals)

**Reference**  
lowest risk



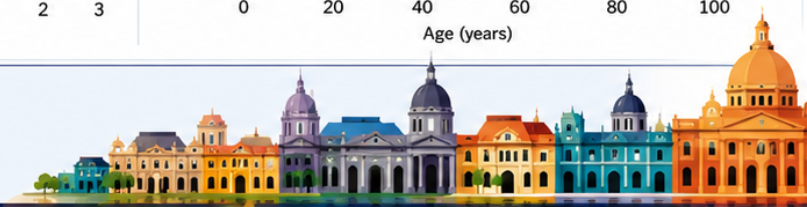
**OR 36.6 — top vs bottom centile**



## Reference:

Zheng SL, Jurgens SJ, McGurk KA, et al. Evaluation of polygenic scores for hypertrophic cardiomyopathy in the general population and across clinical settings.

*Nature Genetics*. 2025;57:563–571. doi:10.1038/s41588-025-02094-5.



# Evaluation of Polygenic Scores (PGS) for Hypertrophic Cardiomyopathy (HCM)

## Key Findings Across Clinical Settings

### 4 PGS stratifies risk in relatives of HCM probands

100,000 Genomes Project  
(288 relatives)

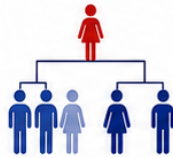
Risk of developing HCM  
Top vs. Middle PGS quintile  
**OR = 4.17**  
(95% CI 2.36 – 7.37)  
 $P = 2 \times 10^{-7}$

Erasmus MC Registry  
(214 relatives)

Risk of developing HCM  
Top vs. Middle PGS quintile  
**OR = 3.10**  
(95% CI 1.56 – 6.16)  
 $P = 0.001$

Among relatives, higher PGS is associated with:

- ✓ Greater risk of developing HCM
- ✓ Earlier age at HCM diagnosis
- ✓ Increased left ventricular wall thickness
- ✓ Increased risk of adverse cardiovascular events



PGS can help prioritize screening intensity and surveillance in families.

### 5 PGS predicts adverse outcomes in individuals with HCM

UK Biobank  
(262 cases with HCM)



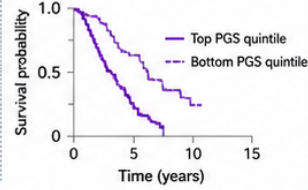
All-cause mortality  
Top vs. Bottom PGS quintile  
**HR = 3.88**  
(95% CI 2.30 – 6.56)  
 $P = 4.7 \times 10^{-7}$



Major adverse cardiovascular events  
Top vs. Bottom PGS quintile  
**HR = 3.50**  
(95% CI 2.40 – 5.11)  
 $P = 3.3 \times 10^{-9}$

100,000 Genomes Project  
(191 cases with HCM)

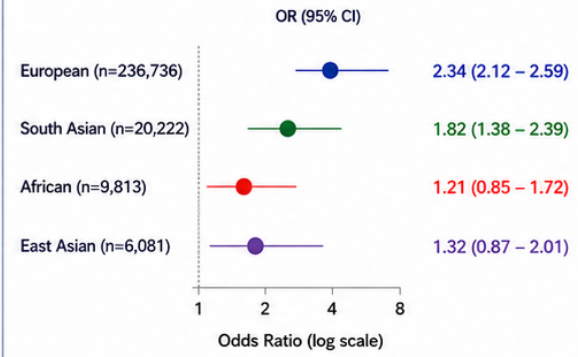
All-cause mortality  
Top vs. Bottom PGS quintile  
**HR = 6.30**  
(95% CI 2.60 – 15.2)  
 $P = 2.0 \times 10^{-5}$



Higher PGS is strongly associated with increased risk of death and adverse events in patients with HCM.

### 6 Performance across ancestries

Odds of HCM per 1 SD increase in PGS ( $PGS_{mtag}$ )



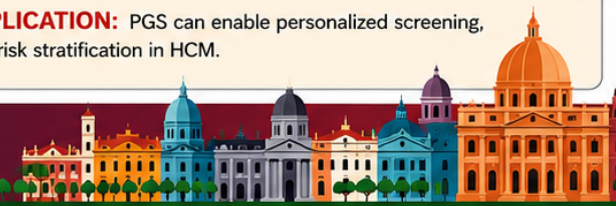
PGS performance is highest in individuals of European ancestry and lower in non-European populations.



**KEY TAKEAWAY:** PGS for HCM provides significant value for risk prediction in the general population, refines penetrance estimates for pathogenic variant carriers, informs screening in relatives, and predicts outcomes in affected individuals.



**CLINICAL IMPLICATION:** PGS can enable personalized screening, surveillance, and risk stratification in HCM.





# Common Genetic Modifiers Influence Cardiomyopathy Susceptibility Among Carriers of Rare Pathogenic Variants

## 1 Rare pathogenic variants markedly increase cardiomyopathy risk

| Disease                                                                                                                      | Variant type                         | Hazard Ratio (HR) vs non-carriers    |
|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------------------------------|
|  <b>HCM</b><br>(Hypertrophic Cardiomyopathy) | Pathogenic / Likely Pathogenic (PLP) | <b>68.0</b><br>(95% CI 40.4 – 114.5) |
|  <b>DCM</b><br>(Dilated Cardiomyopathy)      | Pathogenic / Likely Pathogenic (PLP) | <b>12.8</b><br>(95% CI 8.8 – 18.6)   |



Rare pathogenic variants in established cardiomyopathy genes are strongly associated with disease development.

## 2 AI-based variant prediction expands carrier detection

Additional carriers identified using AlphaMissense prediction



**+4,148**  
additional  
HCM carriers



**+9,716**  
additional  
DCM carriers



Including predicted damaging missense variants markedly increases the number of carriers and study power.

## 3 Carriers develop disease earlier

Difference in age at diagnosis vs non-carriers



**HCM**

PLP variants

**–5.5 years**

(95% CI –8.4 to –2.7)

pLoF variants

**–7.4 years**

(95% CI –10.6 to –4.1)



**DCM**

PLP variants

**–5.7 years**

(95% CI –9.0 to –2.4)

pLoF variants

**–2.6 years**

(95% CI –4.7 to –0.5)



**KEY TAKEAWAY:** Rare pathogenic variants strongly increase cardiomyopathy risk and are associated with earlier disease onset.





## 1 Risk of HCM increases with higher polygenic risk



Per 1 SD increase in HCM PRS

**HR  $\approx$  2.0**

(95% CI 1.8 – 2.3)

## 2 High vs Low Polygenic Risk (Top 20% vs Bottom 20%)



## 3 Combined effect: Variant status and PRS

Compared with non-carriers with intermediate PRS (reference)

Hazard Ratio (HR)  
for HCM



Non-carriers

Reference



Variant carrier +  
Intermediate PRS

Increased risk  
(HR > 1)



Variant carrier +  
High PRS (Top 20%)

**48.1**

(95% CI 27.5 – 84.2)



### CLINICAL INTERPRETATION

Two individuals carrying the same sarcomeric mutation may have dramatically different disease risk depending on their polygenic background.





# Polygenic Risk Modifies DCM Penetrance



## 1 Risk of DCM increases with higher polygenic risk



Per 1 SD increase in DCM PRS

**HR  $\approx$  1.4**

(95% CI 1.2 – 1.6)

## 2 High vs Low Polygenic Risk (Top 20% vs Bottom 20%)



LOW RISK

HIGH RISK

## 3 Combined effect: Variant status and PRS

Compared with non-carriers with intermediate PRS (reference)

Hazard Ratio (HR)  
for DCM



Non-carriers

Reference



Variant carrier +  
Intermediate PRS

Increased risk  
(HR > 1)



Variant carrier +  
High PRS (Top 20%)

**8.2**  
(95% CI 5.1 – 13.2)



**KEY TAKEAWAY:** Polygenic background influences not only disease occurrence but also the severity of cardiomyopathy phenotypes.

## 4 Disease severity is influenced by polygenic risk

### HCM



Higher PRS associated with:

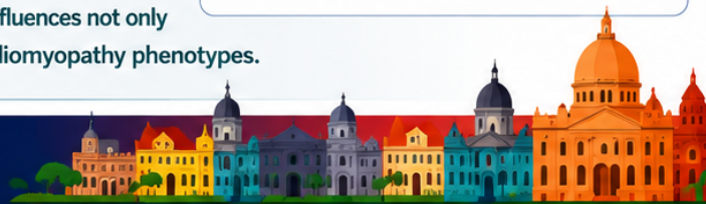
- Greater LV wall thickness
- More severe hypertrophy

### DCM



Higher PRS associated with:

- Lower LVEF
- More severe ventricular dysfunction



# KEY TAKE-HOME MESSAGES



PLP and pLoF variants confer the **highest risk** for HCM and DCM and are associated with **earlier onset** and **more severe disease**.



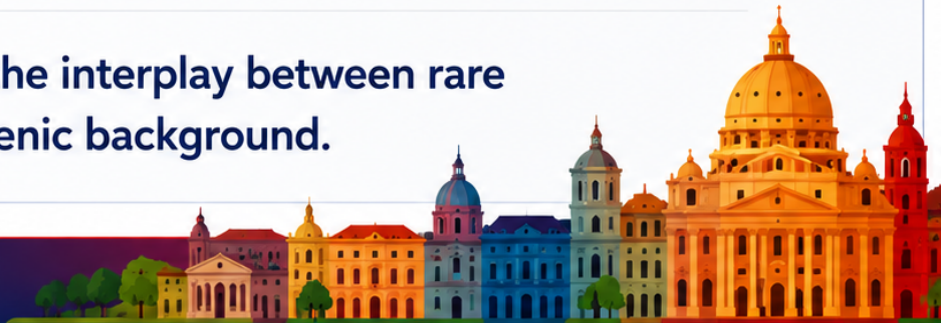
pDM variants (missense) predicted damaging by AI show a **smaller** but **significant effect**, highlighting a large reservoir of **potentially** disease-contributing variants.



Combining rare variant status with **polygenic risk scores (PRS)** further refines risk prediction and phenotypic severity.



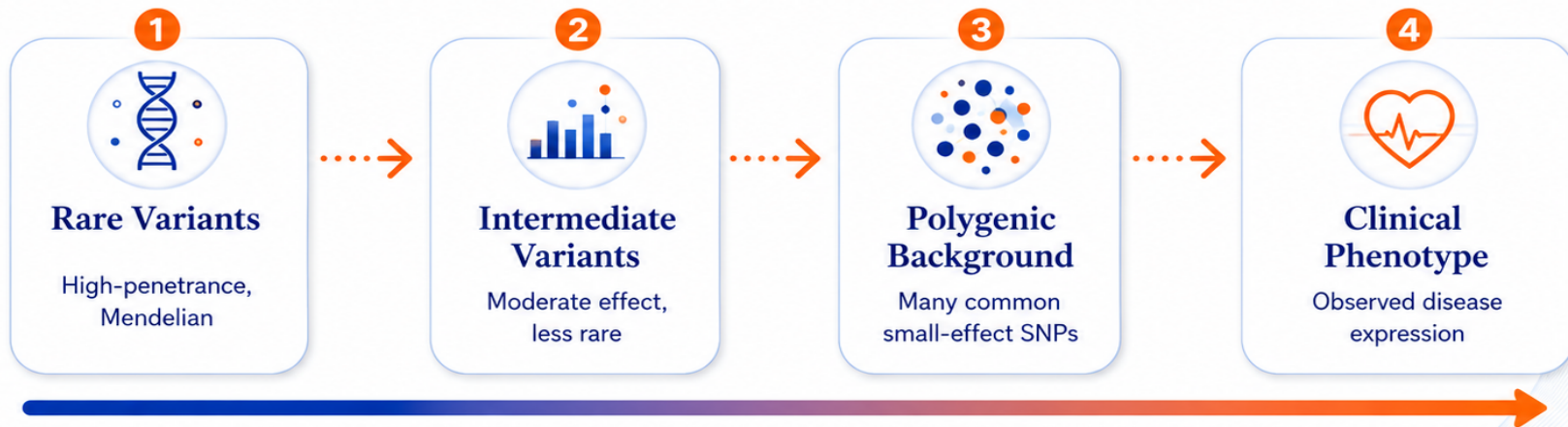
Cardiomyopathy results from the interplay between rare pathogenic variants and polygenic background.





# The Genetic Continuum

Cardiomyopathy risk exists on a spectrum — from rare high-penetrance variants to common polygenic burden. Most patients fall somewhere in between.

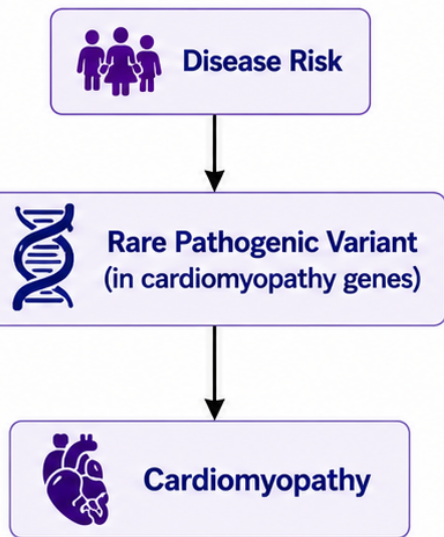


This continuum reframes cardiomyopathy not as a binary genetic event, but as the cumulative output of layered genetic risk — rare and common acting in concert.

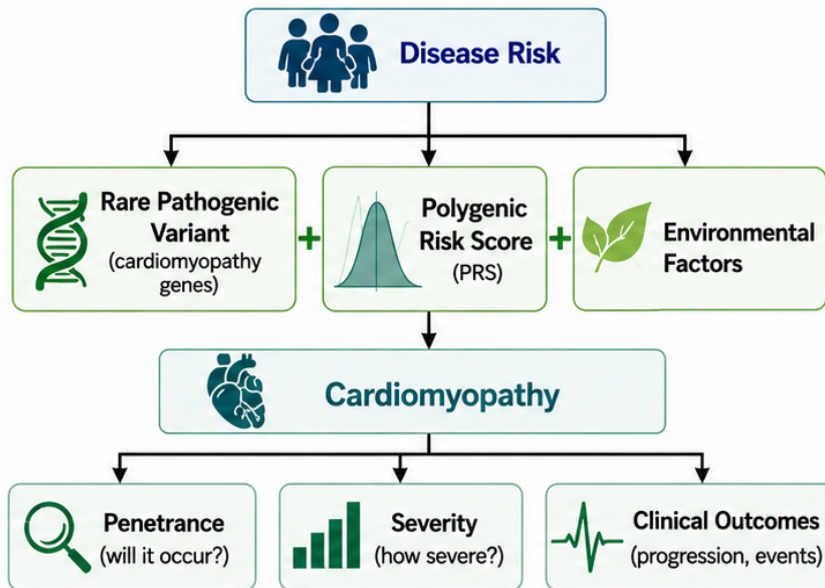
# Integrated Genetic Model of Cardiomyopathy



## A Traditional (Monogenic) View



## B Emerging (Polygenic) Model



## C Clinical Implications

-  Improved risk stratification of variant carriers
-  Personalized screening of family members
-  Better estimation of penetrance
-  More accurate surveillance strategies
-  Precision cardiovascular genetics



**TAKE HOME MESSAGE:** Cardiomyopathy expression results from the interaction between rare pathogenic variants and common polygenic modifiers, shaping disease risk and severity.





# THE END OF MENDELIAN DISEASE?

## From Monogenic to Integrated Genetic Risk



### WHAT WE HAVE LEARNED



Rare pathogenic variants remain **the strongest determinants** of cardiomyopathy risk.



**Polygenic Risk Scores (PGS)** significantly modify disease penetrance, severity, and clinical outcomes.



Individuals carrying the same pathogenic variant may **experience markedly different clinical trajectories** because of their polygenic background.



**Cardiomyopathy risk results from the interaction between:**

- Rare pathogenic variants
- Common genetic modifiers
- Environmental and lifestyle factors

### CARDIOMYOPATHY RISK IS MULTIFACTORIAL AND CONTINUOUS

**RARE PATHOGENIC VARIANTS**



High impact  
Low frequency

+

**POLYGENIC RISK**



Small effect  
Common variants

+

**ENVIRONMENTAL / LIFESTYLE FACTORS**



Modifiable contributors

=

**DISEASE EXPRESSION**



- Penetrance
- Age at onset
- Severity
- Clinical outcomes



### NEW PARADIGM



**Mendelian Disease**  
(Single gene – deterministic)



**Genetic Continuum**  
(Multiple genes – probabilistic)



**Integrated Genomic Risk**  
(Personalized prediction and prevention)



### TAKE-HOME MESSAGE

Cardiomyopathies should no longer be viewed as purely monogenic disorders. The future of cardiovascular genetics lies in integrating rare variants and polygenic risk to improve prediction, surveillance, and precision medicine.



### ANSWER TO THE QUESTION

**“The end of Mendelian disease?”**

**NO.**

But the end of a purely Mendelian interpretation of inherited cardiomyopathies.





# THANK YOU FOR YOUR ATTENTION!

*Science evolves. Knowledge grows. Patients benefit.*

“ I believe that AI will be either the **best** or **worst** thing ever to happen to humanity.

Stephen Hawking

“ AI is one of the most profound things we're working on as humanity.

Sundar Pichai

“ The real revolution is not when machines think like humans, but when they help us think beyond our limits.

Fei-Fei Li



RARE  
VARIANTS



POLYGENIC  
RISK



ENVIRONMENT  
& LIFESTYLE



ARTIFICIAL  
INTELLIGENCE



BIG DATA &  
ANALYTICS



PRECISION  
MEDICINE



This perspective perfectly mirrors a famous observation by the Nobel Laureate molecular biologist Sydney Brenner, who stated:

“Progress in science depends on  
new techniques, new discoveries, and new ideas,  
probably in that order.”

”

## TAKE-HOME MESSAGE

The future of cardiomyopathy research lies in the **integration of genetics, artificial intelligence, and clinical insight** to improve prediction, prevention, and personalized care.

