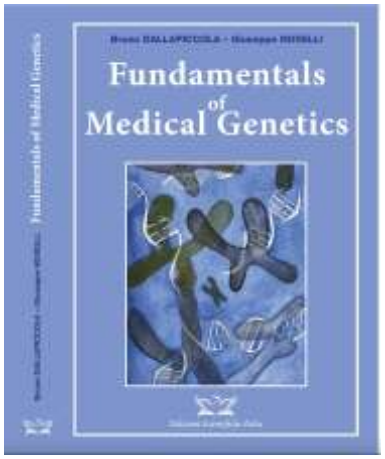

Contributo delle scienze OMICHE nella medicina cardiovascolare

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Academia Europaea

Pasquale De Vico

THE NUMBER 1 KILLER

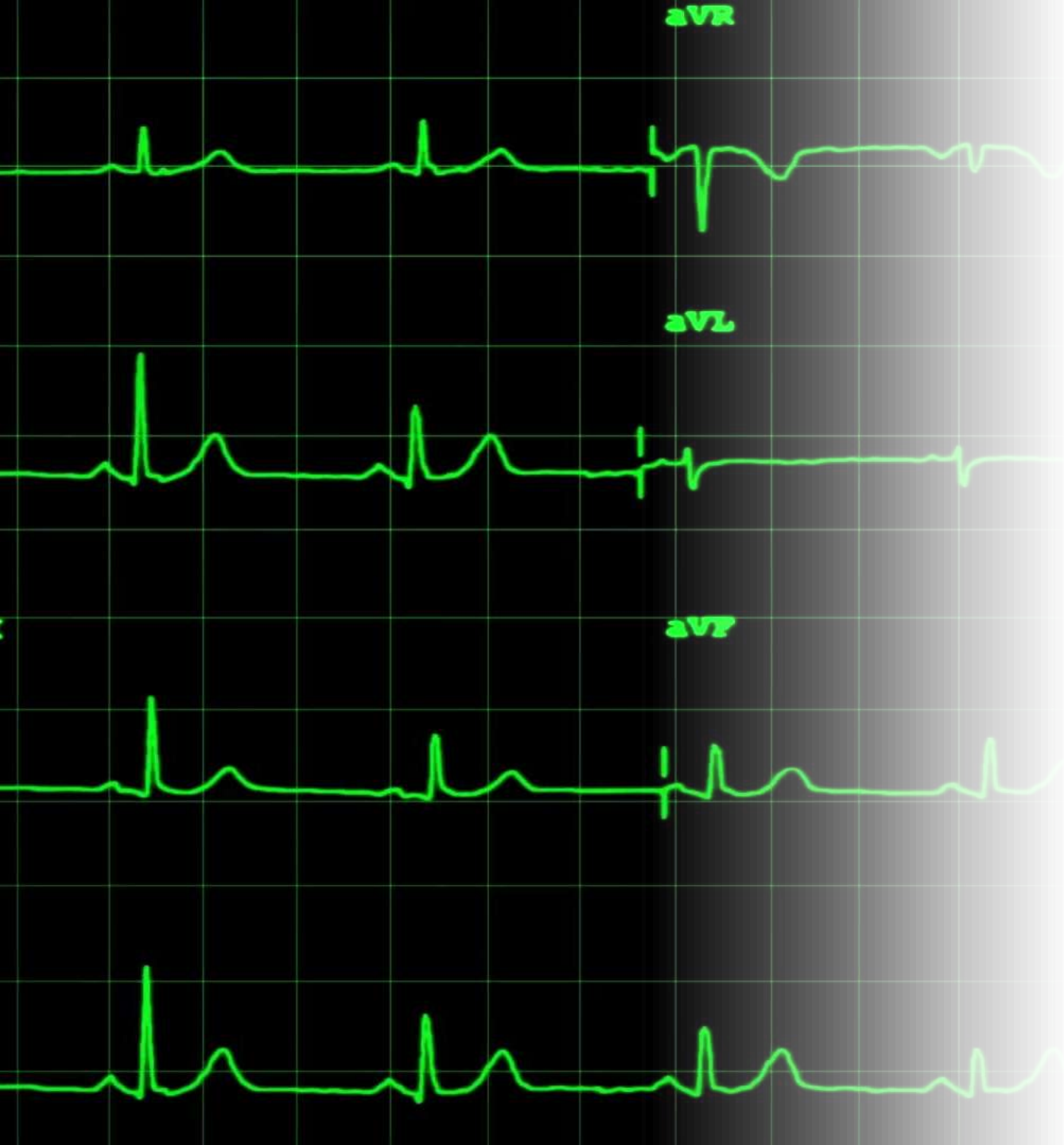
Cardiovascular disease (CVD) is the world's biggest killer.

At least 80% of premature deaths from cardiovascular disease could be avoided.

17.9M
deaths per year

1 in 10
Aged 30-70
die from CVD

31%
of all deaths are
from CVD



CVDs include

- Hypertension
- Atherosclerosis
- Myocardial ischemia
- Cerebrovascular ischemia
- Renal ischemia
- GI ischemia
- Peripheral vascular disease
- Heart failure

Cardiovascular diseases (CVD)

- There have been significant advances in the understanding of the pathogenesis of CVD
- This has led to a significant decrease in mortality from CVD over the last 50 years
- Still, CVDs remain the primary cause of morbidity and death

Genomics (Study of Genes and Their Functions)

- **Disease Risk Prediction**: Genome-wide association studies (GWAS) have identified genetic variants linked to cardiovascular diseases (CVDs), such as coronary artery disease (CAD).
- **Monogenic Disorders**: Identification of mutations in genes like *MYH7* (hypertrophic cardiomyopathy), *LMNA* (DCM), and *KCNQ1* (Long QT syndrome).
- **Pharmacogenomics**: Tailoring antiplatelet (e.g., *CYP2C19* testing for clopidogrel response) and anticoagulant therapies (e.g., warfarin dosing based on *VKORC1/CYP2C9* variants).

Causes of sudden cardiac death

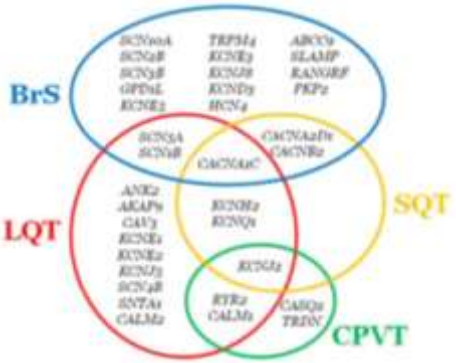
Aortic
- Rupture
- Dissection
- Marfans syndrome

Electrical abnormalities
- Brugada syndrome
- Long QT Syndrome
- Short QT Syndrome
- CPVT
- WPW

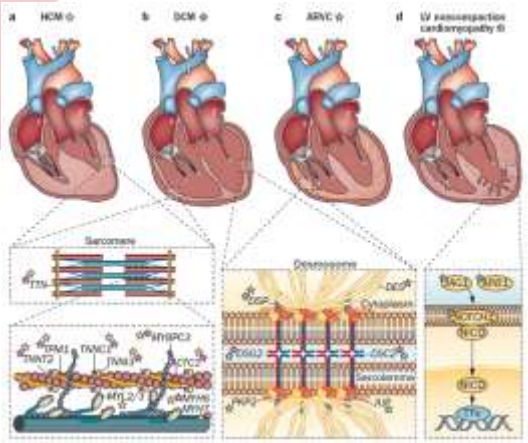
Valvular
- Aortic stenosis
- Mitral valve prolapse

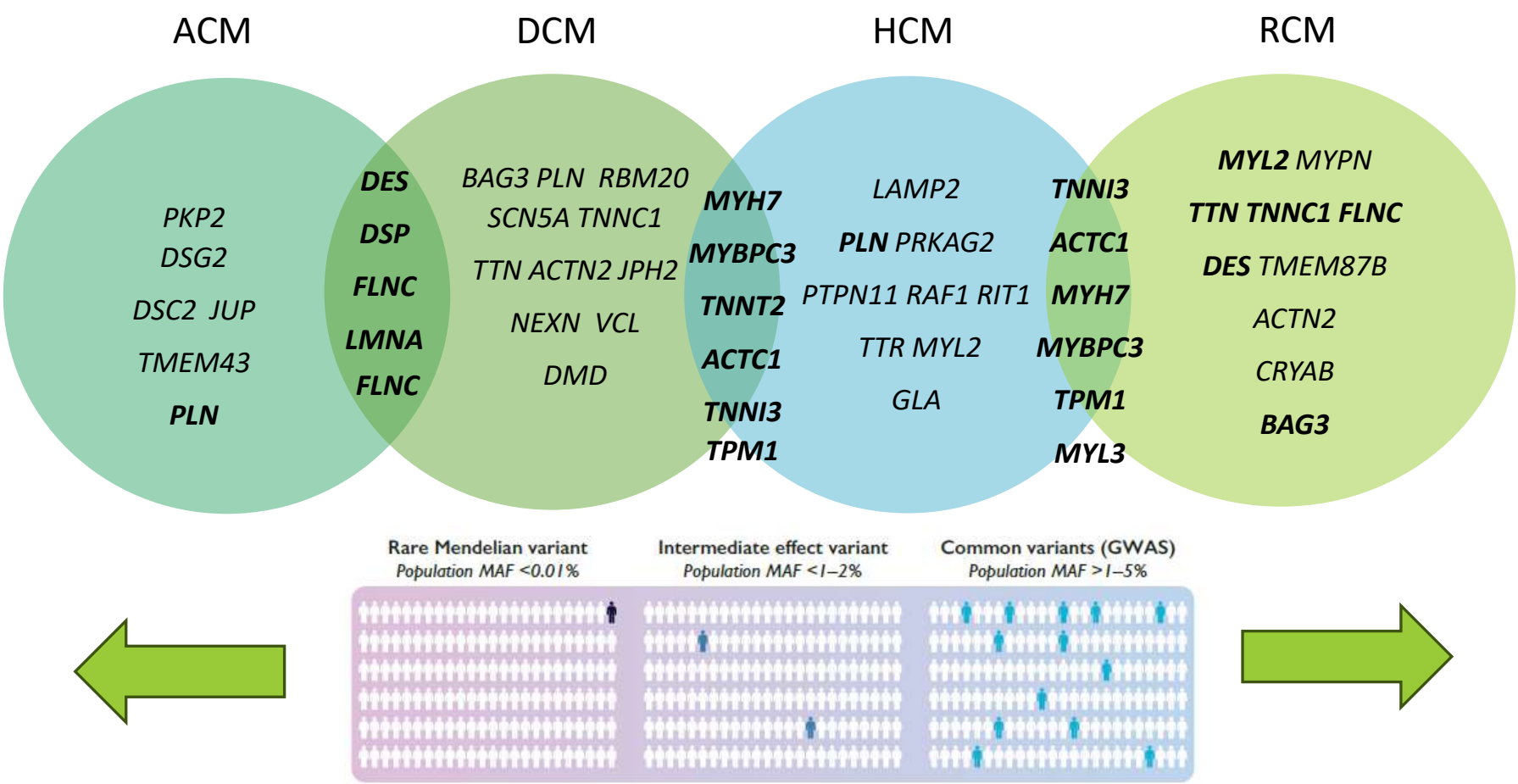
Coronary
- Coronary artery disease
- Coronary artery anomalies

Muscle disorders
- HCM
- ARVC
- DCM
- Myocarditis
- Left ventricular non compaction



Miscellaneous
- Electrolyte abnormalities
- Commotio cordis
- Drugs (illicit and prescribed)



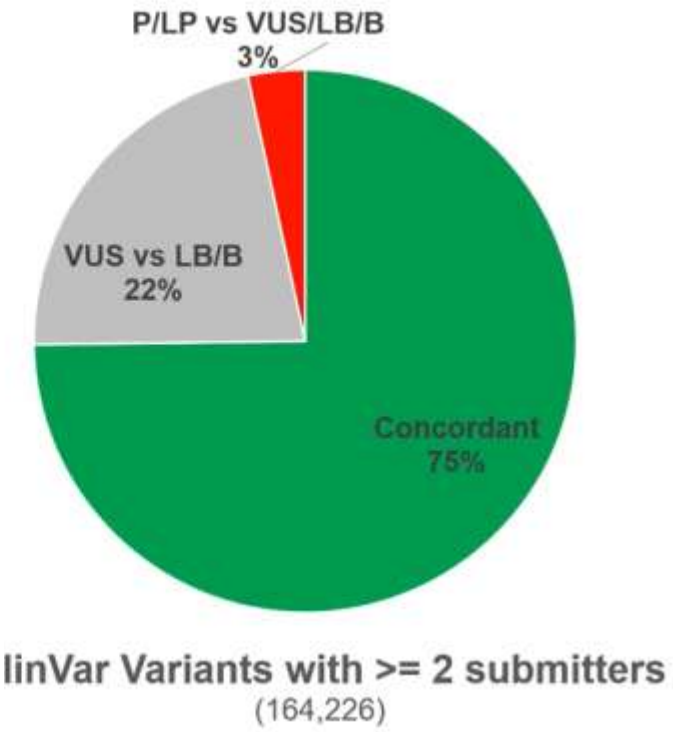

ACM
DCM
HCM
RCM
PKP2
DSG2
DSC2 JUP
TMEM43
PLN
DES
DSP
FLNC
LMNA
FLNC
BAG3 PLN RBM20
SCN5A TNNC1
TTN ACTN2 JPH2
NEXN VCL
DMD
MYH7
MYBPC3
TNNT2
ACTC1
TNNI3
TPM1
LAMP2
PLN PRKAG2
PTPN11 RAF1 RIT1
TTR MYL2
GLA
TNNI3
ACTC1
MYH7
MYBPC3
TPM1
MYL3
MYL2 MYPN
TTN TNNC1 FLNC
DES TMEM87B
ACTN2
CRYAB
BAG3
Rare Mendelian variant
Population MAF <0.01%
Intermediate effect variant
Population MAF <1–2%
Common variants (GWAS)
Population MAF >1–5%

Discrepanies in variant interpretation

Variant interpretation is not black and white
Equally trained professionals can interpret the same variant differently

Why?

- Lack of data available
- Use of different interpretation software
- Different interpretation of ACMG codes
- **Biology…..**



The “First Rule” in Variant Interpretation?

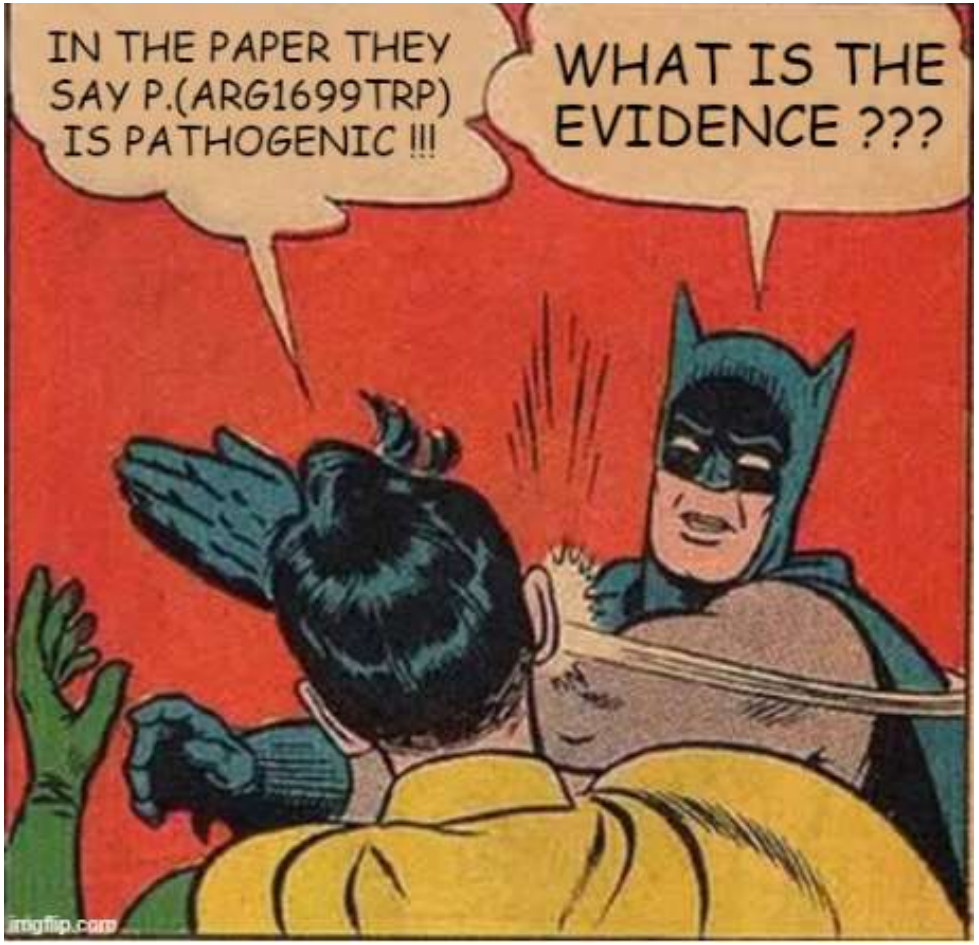
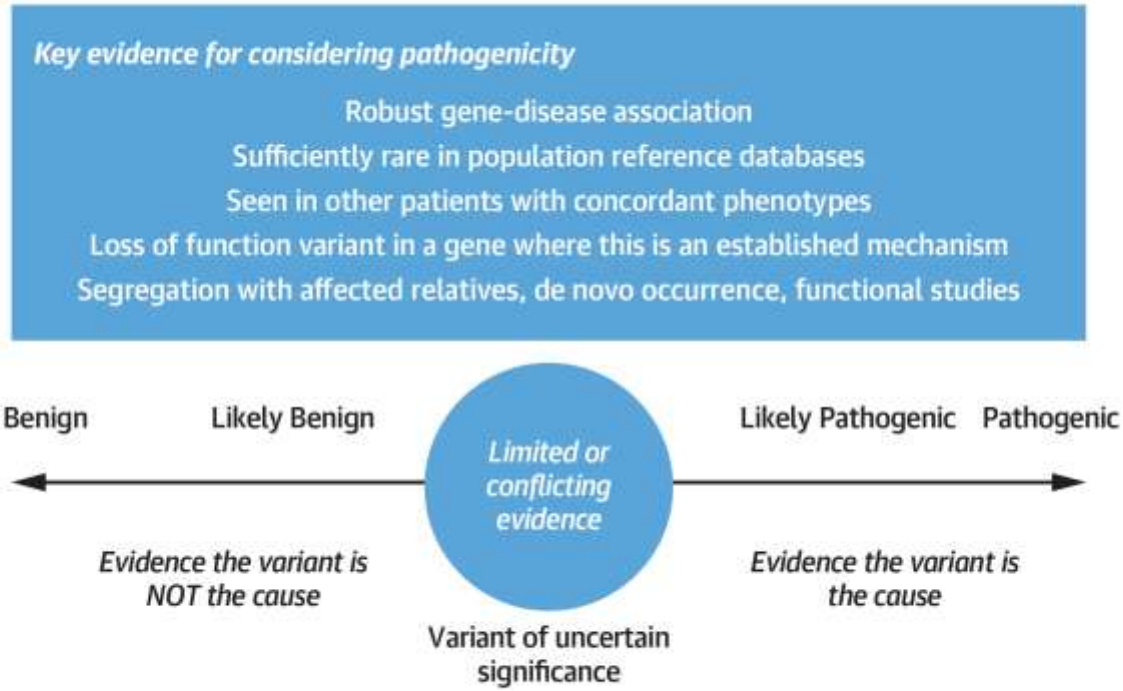


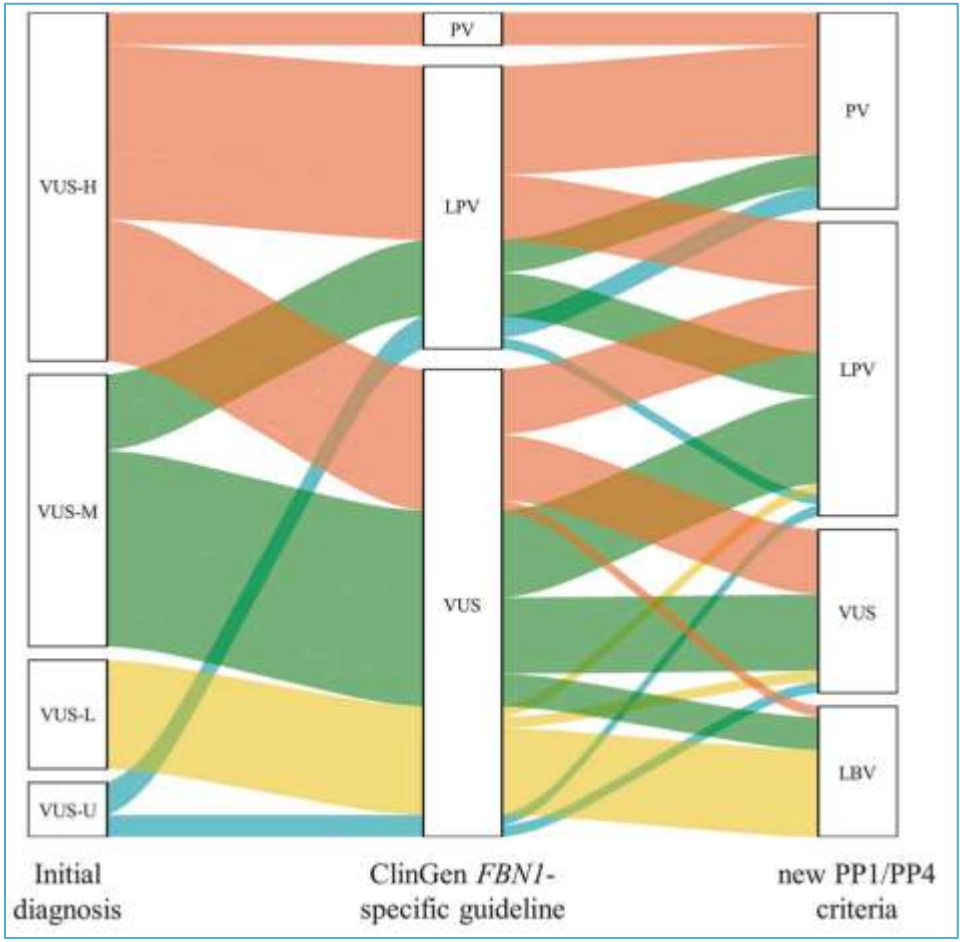
FIGURE 3 Key Aspects of Variant Classification



Range of evidence to classify variants along the pathogenicity spectrum from benign (no clinical utility) to pathogenic (most clinical utility).

Reassessment of FBN1 variants of uncertain significance using updated ClinGen guidance for PP1/BS4 and PP4 criteria

- FBN1 VUSs according to the new PP1/PP4 criteria, the rate of reclassification from VUS to PV/ LPV significantly increased from 40.3% to 62.5%.



European Journal of Human Genetics (2025) 33:666–674; https://doi.org/10.1038/s41431-025-01826-9

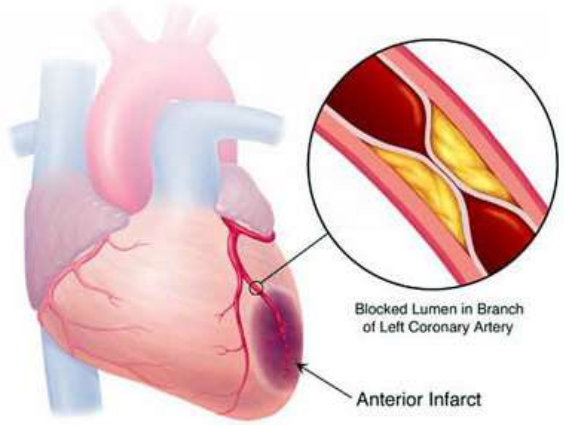
Genotype-Phenotype correlation can be **complex** … even in monogenic disorders

- Penetrance
- Expressivity
- Pleiotropy

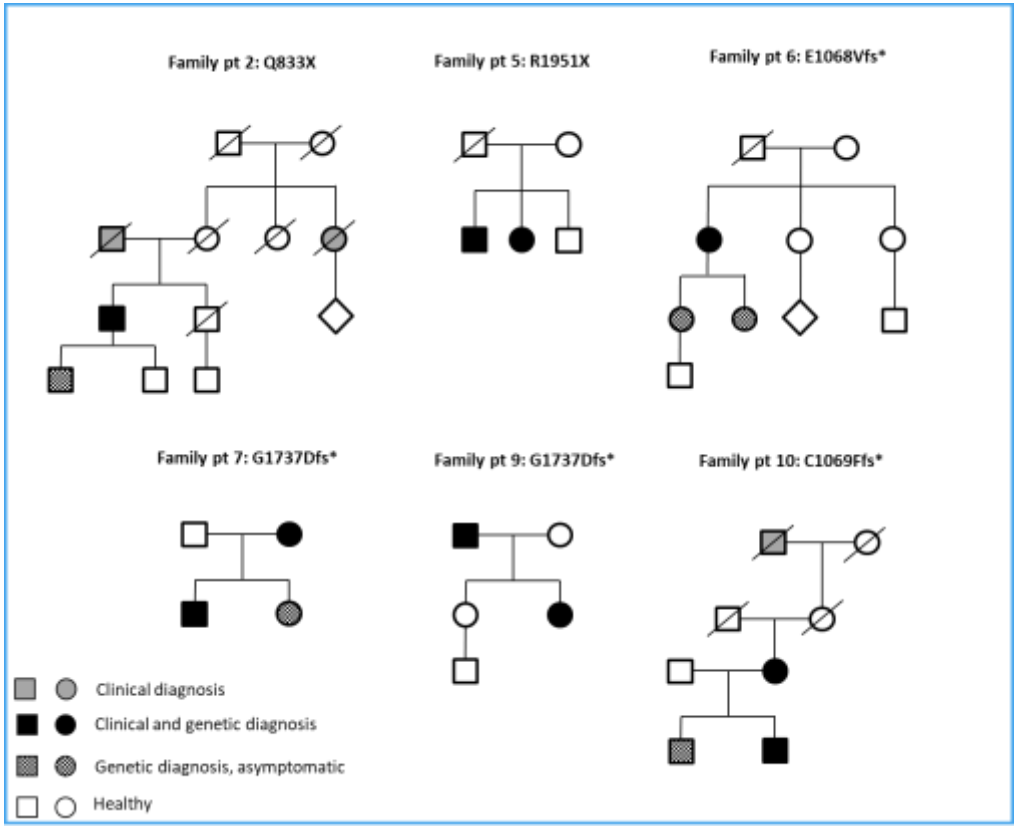
Even in a single gene disorder, genotype does not equal a specific phenotype.

Kathiresan S et al. Cell 2012

MODIFIER GENES **ENVIRONMENT**



Also in the other families the subsequent family segregation study revealed several clinically affected, apparently asymptomatic relatives.

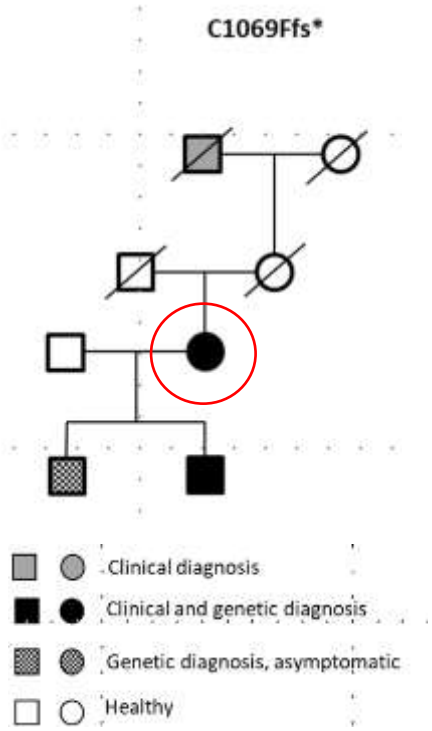


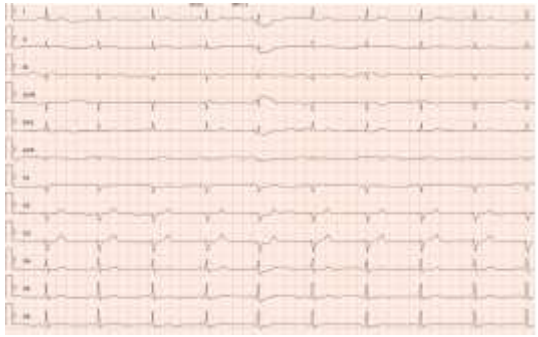
Clinical Features	Index Case
Mean age at diagnosis (years)	41.56 (IQR 49.75-31.25)
Sex:	
Female	50% (n=8)
Male	50% (n=8)
MAEs	12.5 % (n=2)
Syncope	12.5% (n=2)
Chest Pain	43.75% (n=7)
Palpitations	75% (n=12)
Myocarditis like episodes	43.75% (n=7)
NYHA Classification:	
Class I	56.25% (n=9)
Class II	43.75% (n=7)
Class III or IV	n=0
ICD:	**56.25% (9/16)**
Subcutaneous	22,22% (n=2)
Single-Chamber	22.22% (n=2)
Dual-Chamber	55.56% (n=5)
Left Ventricular Enlargement	56.25% (n=9)
Right Ventricular Enlargement	25% (n=4)
Mean LVEF% at diagnosis	48.56 (IQR 55.75 - 42)
Mean RVEF % at diagnosis	51.71 (IQR 57.75 - 43.75)
LGE:	**100% (16/16)**
Epicardial	6.25 % (n=1)
Subepicardial	56.25% (n=9)
Subendocardial	6.25% (n=1)
Intramural	25% (n=4)
Transmural	12.5% (n=2)
12 leads ECG anomalies:	**81.25% (13/16)**
QRS Complex:	75% (n=12)
Low voltage n=5	38.46% (n=5)
Fragmentation of QRS	38.46% (n=5)
Q wave	15.38% (n=2)
T Wave Inversion	15.38% (n=2)
Ventricular Ectopy:	
Frequent/Very Frequent	75% (n=12)
Occasional	25% (n=4)
Polymorphic	81% (n=13)

Di Lorenzo et al., 2023

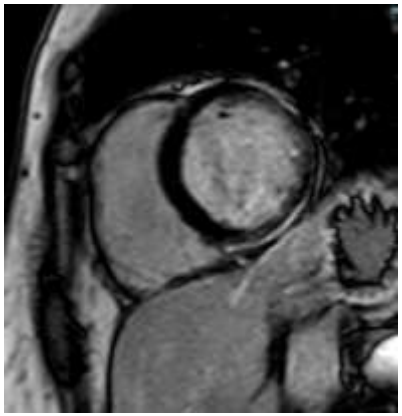
FAMIGLIA 3

The family segregation test showed that the variant was inherited from the mother, who was apparently unaffected and subjected to instrumental tests.





The ECG-Holter revealed:
6727 isolated polymorphic BEVs, 624 mono and polymorphic pairs, sometimes in phases of ventricular bi and trigeminy, 41 interpolated BEVs, 71 NSVTs (polymorphic triplets, two runs of 4 polymorphic beats at a heart rate of 150 bpm).



Cardiac MRI found: Left ventricle with end-diastolic and end-systolic volume indexed to the upper limits (FEVG 54%), right ventricle with end-diastolic and end-systolic volume indexed to the limits (FEVD 52%) Subepicardial LGE areas, also with mesocardial distribution, corresponding to the anterior, lateral and lower wall in the mid-basal segments, findings compatible with arrhythmogenic dysplasia with prevalent involvement of the Left ventricle

Di Lorenzo et al., 2023

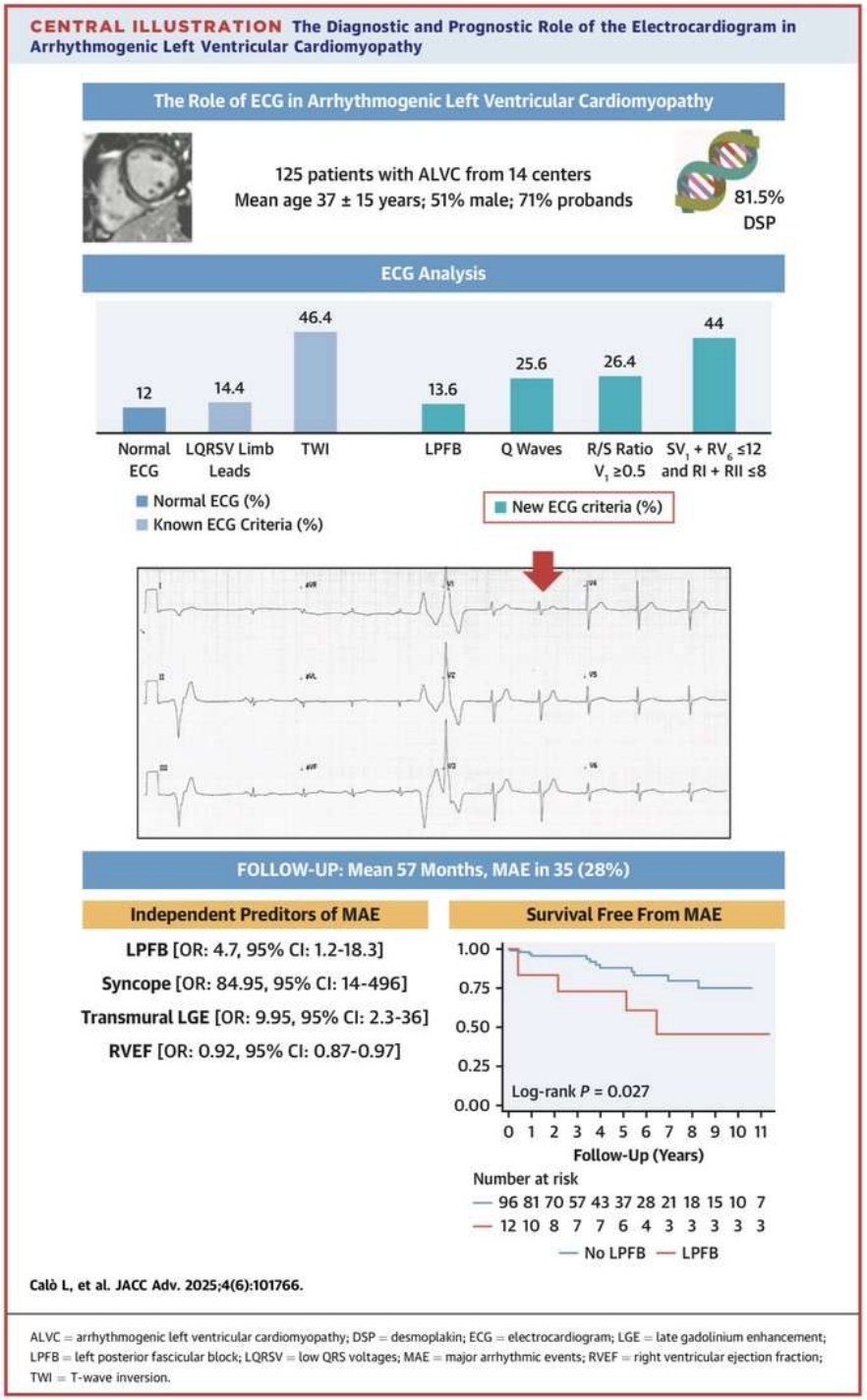
Desmoplakin-related Cardiomyopathy

JACC: ADVANCES VOL. 4, NO. 6, 2025

ORIGINAL RESEARCH

The Diagnostic and Prognostic Value of the 12-Lead ECG in Arrhythmogenic Left Ventricular Cardiomyopathy

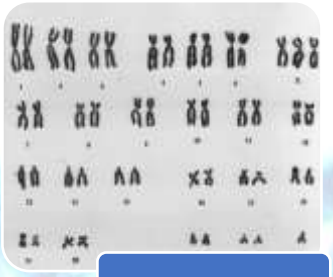
Leonardo Calò, MD,[a,b] Cinzia Crescenzi, MD,[a] Andrea Di Marco, MD, PhD,[c] Francesca Fanisio, MD,[a] Fabiana Romeo, MD,[a] Alessio Gargaro, MSc,[d] Annamaria Martino, MD, PhD,[a] Chiara Cappelletto, MD,[e] Marco Merlo, MD,[e] Mattia Targetti, MD,[f] Elisabetta Toso, MD,[g] Federica Toto, MD,[a] Maria Beatrice Musumeci, MD,[h] Giacomo Tini, MD,[h] Michele Ciabatti, MD,[i] Matteo Stefanini, MD,[j] Stefano Canestrelli, MD,[a] Elisa Fedele, MD,[a] Chiara Lanzillo, MD, PhD,[a] Armando Fusco, MD, PhD,[j] Federica Carla Sangiuolo, MD, PhD,[k] Cinzia Radesich, MD,[e] Maria Perotto, MD,[e] Maurizio Pieroni, MD,[i] Ruggiero Mango, MD, PhD,[l] Alessio Gasperetti, MD, PhD,[m] Camillo Autore, MD,[n] Michela Casella, MD, PhD,[o] Antonio Dello Russo, MD, PhD,[o] Davide Stolfo, MD, PhD,[e,p] Mikael Laredo, MD, PhD,[q] Estelle Gandjbakhch, MD, PhD,[q] Maddalena Graziosi, MD, PhD,[r] Elena Biagini, MD, PhD,[r] Costantina Catalano, MD,[r] Ludovica Barile, MD,[r] Fabrizio Drago, MD,[s] Marianna Cicenia, MD,[s] Anwar Baban, MD, PhD,[s] Gemma Pelargonio, MD, PhD,[t] Maria Lucia Narducci, MD,[t] Federica Re, MD,[u] Giovanni Peretto, MD,[v] Elena Paiotti, MD,[v] Carles Diez Lopez, MD,[w] Iacopo Olivotto, MD,[f,x] Fiorenzo Gaita, MD,[g] Gianfranco Sinagra, MD,[e,*] Giuseppe Novelli, MD, PhD[k,*]



OBJECTIVES: analyze the electrocardiogram (ECG) characteristics of ALVC, to correlate ECG with cardiac magnetic resonance and genetic data, and to evaluate its prognostic value

- Patients with ALVC have a very high risk of ventricular arrhythmias and sudden death.
- ECG analysis remains a key element in the evaluation of patients with ALVC.
- Recognition of some new ECG signs, on top of classical signs such as T-wave inversion and low QRS voltage in limb leads, can help in early diagnosis and risk stratification in these patients.
- Among the ECG parameters, LPFB emerges as noteworthy predictor of ventricular arrhythmias or sudden death also in a primary prevention scenario, increasing the risk 4-fold

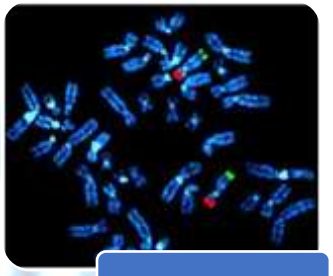
L'identificazione delle varianti strutturali. Tecniche; vantaggi e limiti



Cariotipo

- Intero genoma
- Non necessita di un'indicazione a priori
- Mosaicismi

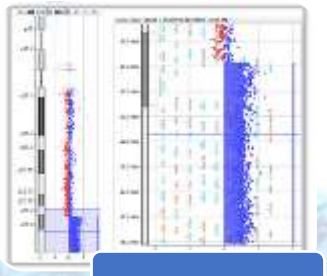
- Risoluzione (5-10 Mb)
- Necessita di materiale vitale o tessuti replicanti in vitro
- Contenuto genico
- Fenomeni di selezione o artefatti in vitro



FISH

- Indagine locus-specifica
- Necessita di un'indicazione a priori

- Risoluzione (40-200 kb)
- Nuclei in interfase o preparati bioptici in paraffina



CMA

- Risoluzione (10-20 kb)
- Genotipizzazione del campione

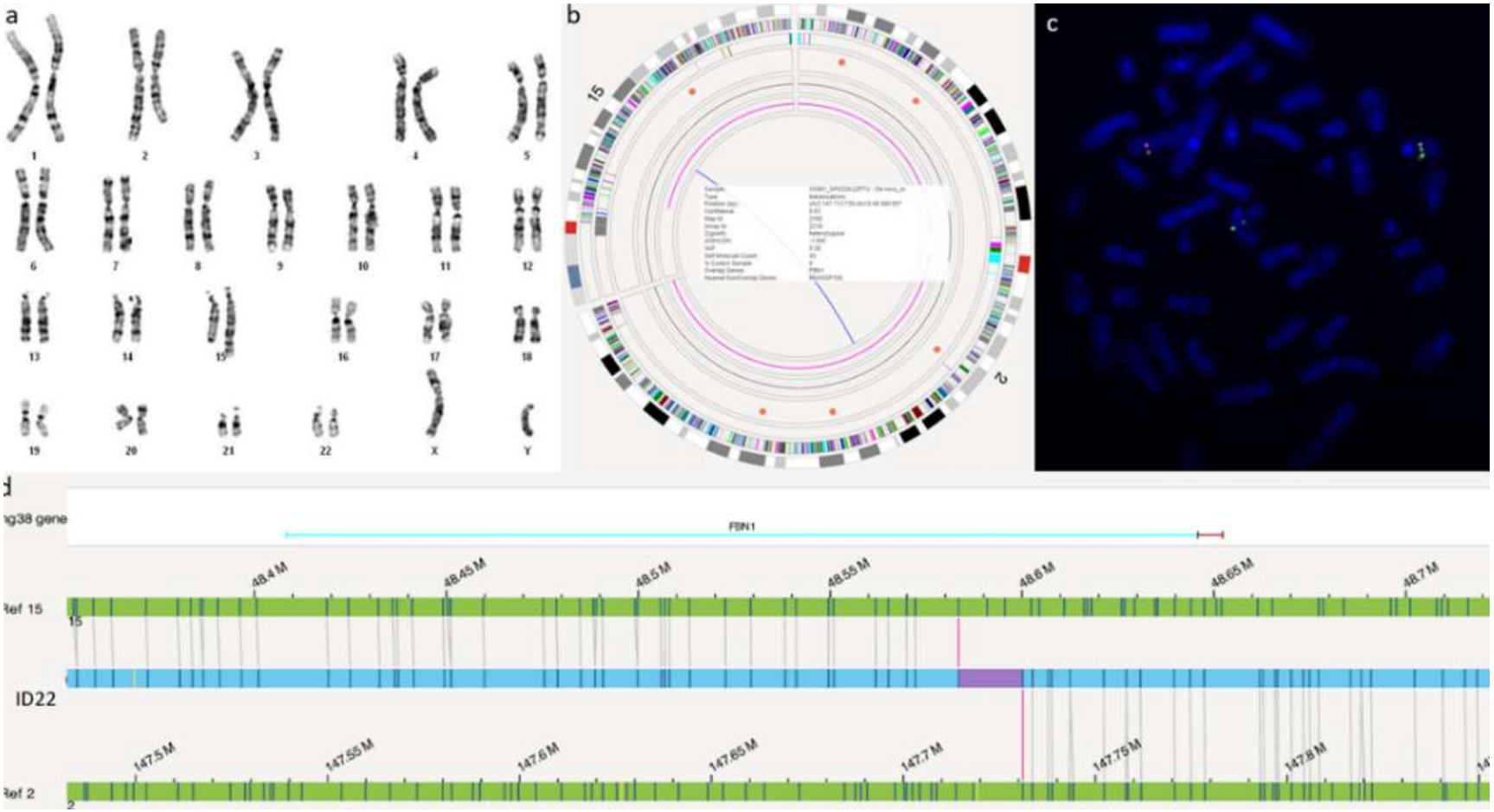
- Contenuto genico
- Riarrangiamenti bilanciati

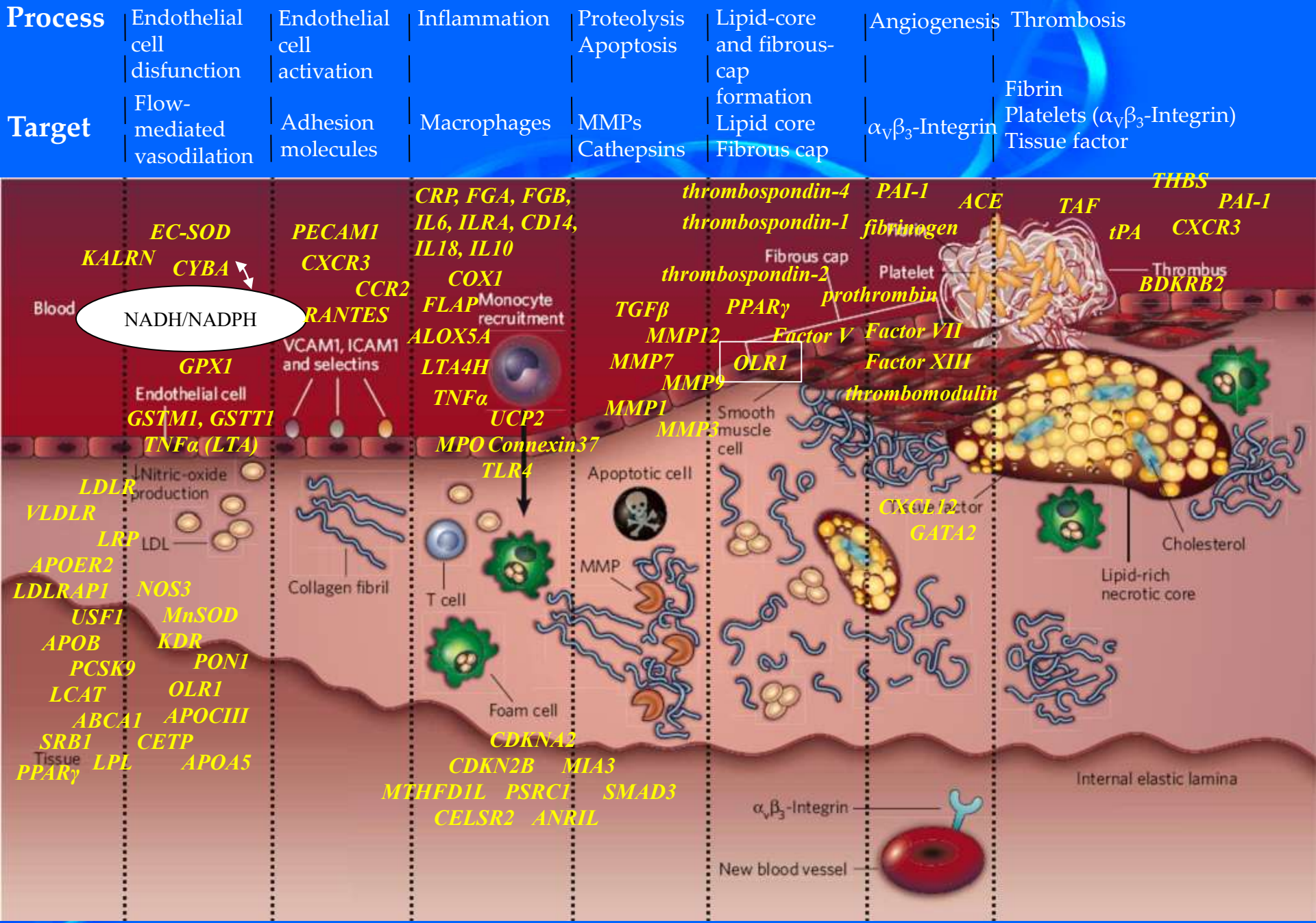
OGM

- Limiti di natura interpretativa

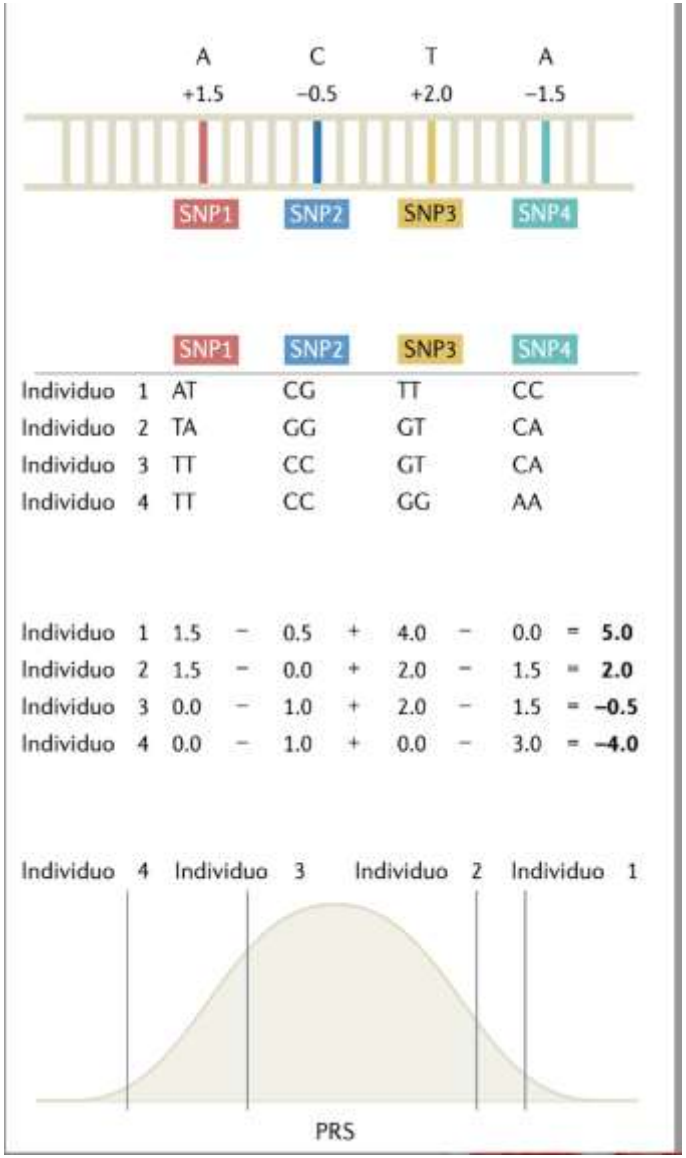
- Risoluzione (>500 bp)
- Non necessita di materiale vitale o tessuti replicanti in vitro

t(2;15)(5'-FBN1_bis+;3'-FBN1+)




Process
Endothelial cell disfunction
Endothelial cell activation
Inflammation
Proteolysis Apoptosis
Lipid-core and fibrous-cap formation
Angiogenesis
Thrombosis
Target
Flow-mediated vasodilation
Adhesion molecules
Macrophages
MMPs Cathepsins
Lipid core Fibrous cap
$\alpha_V\beta_3$-Integrin
Fibrin Platelets ($\alpha_V\beta_3$-Integrin) Tissue factor
EC-SOD
KALRN
CYBA
Blood
NADH/NADPH
GPX1
Endothelial cell
GSTM1, GSTT1
TNFα (LTA)
PECAM1
CXCR3
CCR2
RANTES
VCAM1, ICAM1 and selectins
CRP, FGA, FGB, IL6, ILRA, CD14, IL18, IL10
COX1
FLAP
Monocyte recruitment
ALOX5A
LTA4H
TNFα
UCP2
MPO
Connexin37
TLR4
thrombospondin-4
thrombospondin-1
thrombospondin-2
TGFβ
PPARγ
MMP12
MMP7
MMP9
MMP1
MMP3
Fibrous cap
Smooth muscle cell
Apoptotic cell
MMP
Factor V
OLR1
prothrombin
Factor VII
Factor XIII
thrombomodulin
PAI-1
fibrinogen
ACE
TAF
tPA
THBS
PAI-1
CXCR3
Platelet
Thrombus
BDKRB2
CXCL12
GATA2
Cholesterol
Lipid-rich necrotic core
↓Nitric-oxide production
LDLR
VLDLR
LRP
LDL
APOER2
LDLRAP1
NOS3
USF1
MnSOD
APOB
KDR
PCSK9
PON1
LCAT
OLR1
ABCA1
APOCIII
SRB1
CETP
Tissue
LPL
APOA5
PPARγ
Collagen fibril
T cell
Foam cell
CDKNA2
CDKN2B
MIA3
MTHFD1L
PSRC1
SMAD3
CELSR2
ANRIL
$\alpha_V\beta_3$-Integrin
New blood vessel
Internal elastic lamina
Approximate AHA lesion stage
I
II
III
IV
V
VI
Modified from Watkins and Farrall 2006

Polygenic Score



Dallapiccola – Novelli, Falco Ed. 2022

Polygenic Risk Score

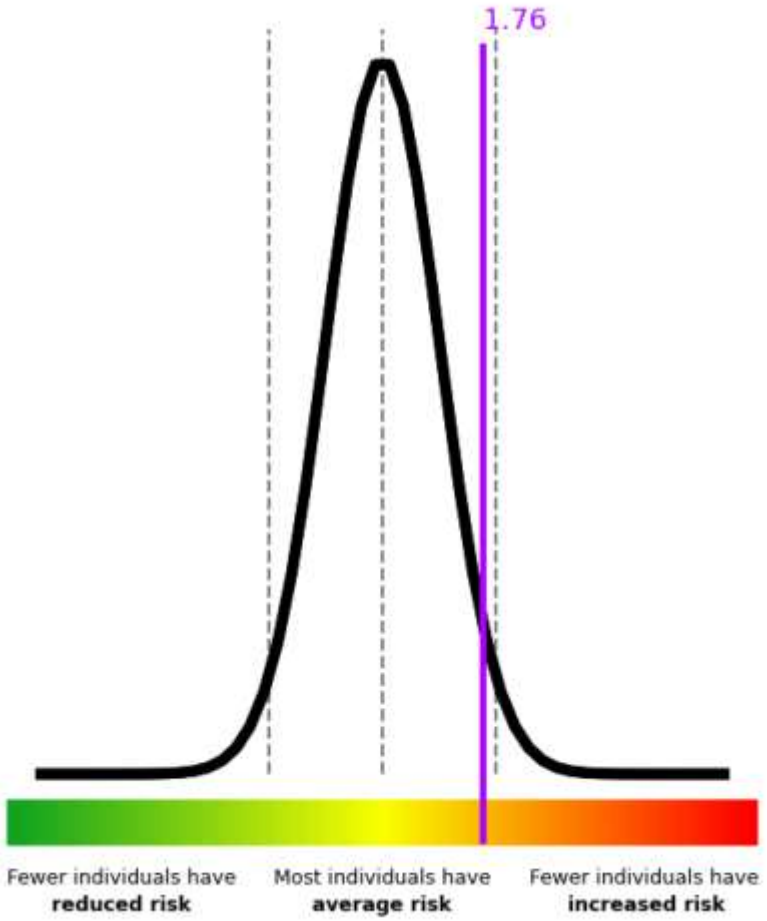
- Some gene variants confer very high risk of getting a particular disease
- Some gene variants confer very small risk of getting a particular disease
- Some gene variants confer no risk of getting a particular disease
- Some gene variants protects from the risk of getting a particular disease

Polygenic Risk Score can help personalize preventive measures, treatment decisions and wellbeing.

Polygenic risk score

The Polygenic Risk Score is a genomic test based on Whole Genome Sequencing that measures your genetic risk of developing PRS Coronary Artery Disease .

Your risk score
1.76



Disease Description

Coronary artery disease is a condition in which there is an inadequate supply of blood and oxygen to the myocardium. It results from occlusion of the coronary arteries and results in a demand-supply mismatch of oxygen. It typically involves the formation of plaques in the lumen of coronary arteries that impede blood flow. It is the major cause of death in the US and worldwide. At the beginning of the 20th century, it was an uncommon cause of death. Deaths due to CAD peaked in the mid-1960s and then decreased however, it still is the leading cause of death worldwide

High polygenic score identified in 17% of patients and confers a 3.7-fold increase in risk

100 patients with myocardial infarction

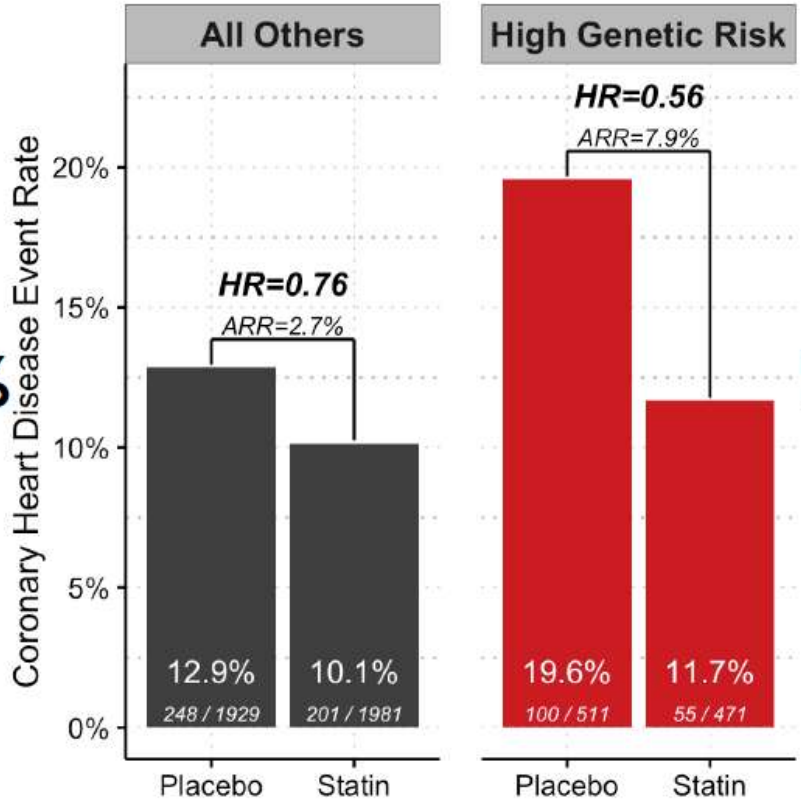
	↑ Risk
Monogenic	3.8-fold
High polygenic	3.7-fold

Khera*, Chaffin*, *under review*

Among those at high polygenic risk, statins confer greater benefit (to prevent first MI)

Pradeep Natarajan

RRR = 24%



RRR = 44%

Natarajan*, Young*, *Circulation* (2017)

“We envision polygenic risk scores as a way to identify people at high or low risk for a disease, perhaps as early as birth, and then use that information to target interventions — either lifestyle modifications or treatments — to prevent disease. For heart attack, I foresee that each patient will have the opportunity to know his or her polygenic risk number in the near future, similar to way they can know their cholesterol number right now.”

Sekar Kathiresan

GWAS: Missing Heritability

- Missing heritability: Significant GWAS SNPs explain a small proportion of disease heritability.
- Possible reasons:
  - GxG and GxE interactions?
  - Many common causal variants: Each with a small effect?
  - Rare variants?

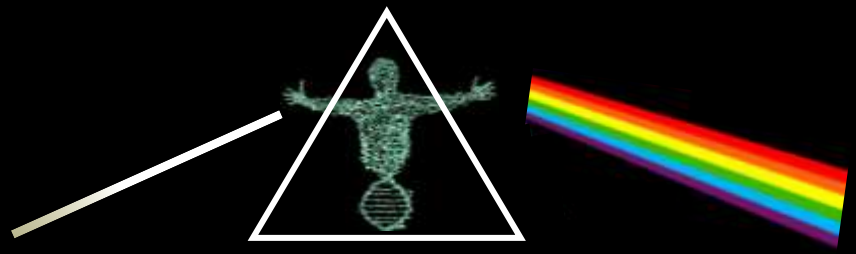
THE SAME GENOME

CATERPILLAR

BUTTERFLY

The dark side of the human genome

… 3 billion of base pairs …



1 – 2 %
PROTEIN
CODING GENES

98% NON CODING GENOME

70% REPETITIVE ELEMENTS

46% TRANSPOSABLE ELEMENTS

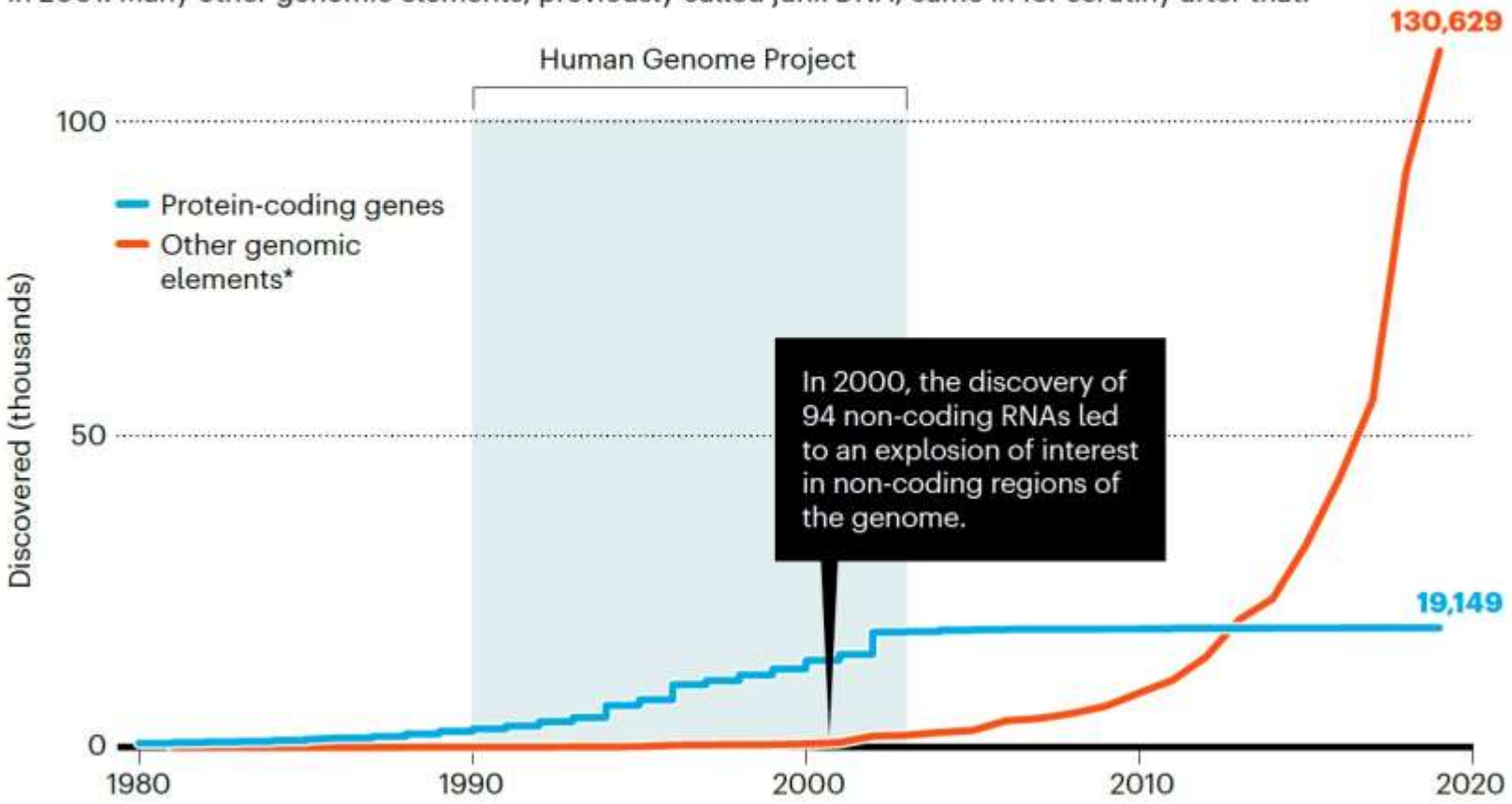
18% LINE1

TWENTY YEARS OF JUNK, STARS AND DRUGS

What genomics researchers have studied, when and why — as traced by bibliometric analysis.

Non-coding elements

Most protein-coding genes were discovered before the first draft of the Human Genome Project (HGP) in 2001. Many other genomic elements, previously called junk DNA, came in for scrutiny after that.



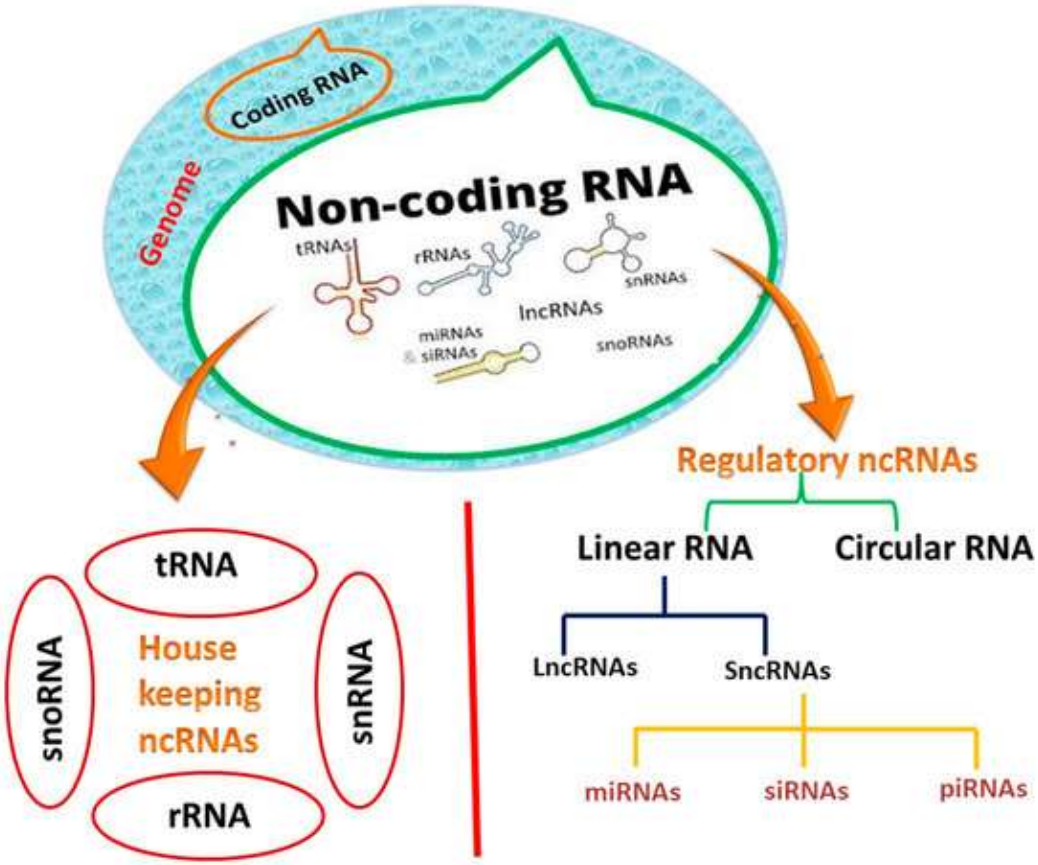
Transcriptomics (Study of RNA Expression Patterns)

Biomarker Discovery: RNA sequencing (RNA-seq) reveals dysregulated genes in heart failure (e.g., *BNP*, *ANP*) and atherosclerosis.

Non-Coding RNAs: MicroRNAs (miR-208a in myocardial infarction) and long non-coding RNAs (e.g., *MALAT1* in vascular remodeling) serve as diagnostic markers.

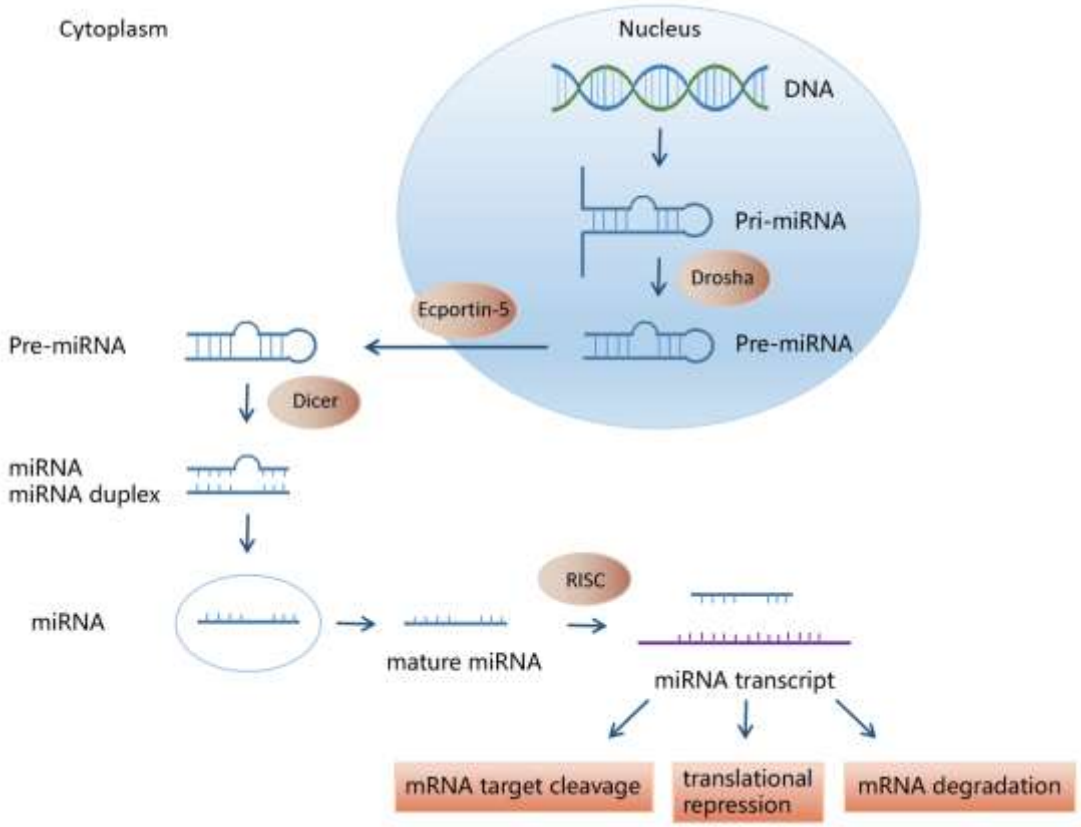
Single-Cell RNA-seq: Identifies cell-specific pathways in cardiac fibrosis and endothelial dysfunction.

- ~25,000 - 95,243 lncRNA genes
- 323,950 transcripts



- **~2,000 mature miRNAs** (recorded in the latest version of **miRBase**, the primary miRNA database, v22.1 as of 2023).

- These are derived from **~1,900 miRNA genes** (since some miRNAs arise from the same primary transcript).



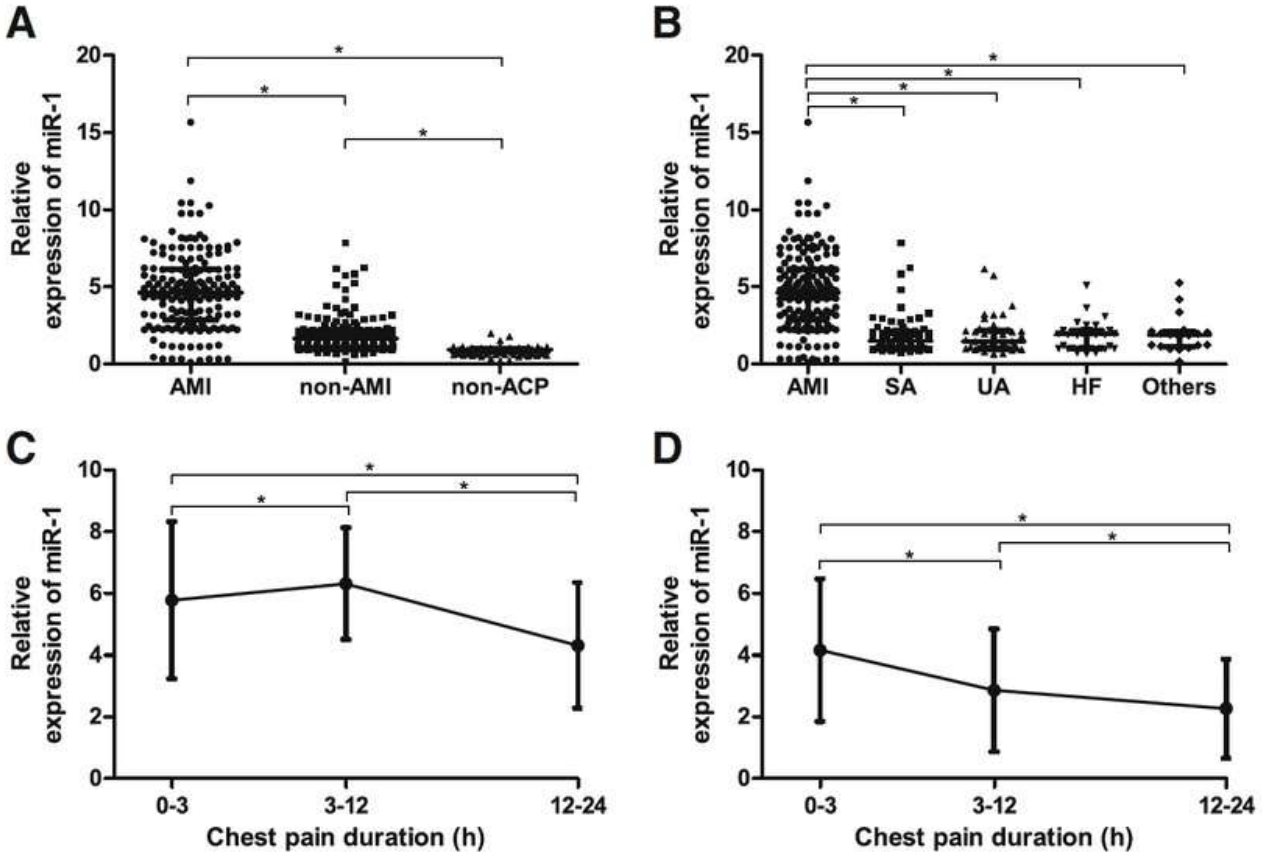


Fig. 1 The plasma concentrations of miR-1 in AMI group, non-AMI group and non-ACP group (**a**). The levels of plasma miR-1 in subgroups of the non-AMI patients (**b**). The changes in different time of miR-1 concentrations in patients without reperfusion therapy (**c**) and with primary percutaneous coronary intervention in AMI group (**d**). * = $P < 0.001$

Role in Cardiovascular Diseases

- **Arrhythmias & Cardiac Conduction**
- **Targets:** *GJA1* (Connexin 43, gap junction protein), *KCNJ2* (Kir2.1, inward rectifier K^+ channel).
- **Effect:**
  - Overexpression → Slowed conduction, **prolonged QT interval**, arrhythmias.
- **B. Cardiac Hypertrophy & Heart Failure**
- **Targets:** Represses growth-related genes (*IGF-1, calmodulin, HDAC4*).
- **Effect:**
  - **Upregulated miR-1** → Attenuates pathological hypertrophy.
  - **Downregulated miR-1** (in human heart failure) → Loss of anti-hypertrophic control.
- **C. Myocardial Ischemia & Infarction**
- **Targets:** *HSP60, HSP70* (heat shock proteins), *Bcl-2* (anti-apoptotic).
- **Effect:**
  - **Ischemia-induced miR-1↑** → Promotes **apoptosis** of cardiomyocytes.
  - **miR-1 inhibition** → Reduces infarct size in animal models.
- **D. Atherosclerosis & Vascular Remodeling**
- **Targets:** *PIM1* (anti-apoptotic kinase), *ET-1* (endothelin-1, vasoconstrictor).
- **Effect:**
  - **Endothelial miR-1↓** → Contributes to inflammation and plaque instability.
  - **Smooth muscle miR-1↑** → Inhibits proliferation (protective against stenosis).

Cardiovascular Diseases

- **Endothelial Dysfunction & Atherosclerosis:**
  - **artery disease (CAD)** patients.
- **Myocardial Fibrosis & Hypertrophy:**
  - Regulates **TGF-β/Smad3** signaling (key in fibrosis).
  - Overexpression reduces **cardiac fibroblast activation**.
- **Anti-fibrotic Effects:**
  - Inhibits **collagen synthesis** (targets *COL1A1*, *COL3A1*).
  - Blocks **TGF-β-driven fibroblast activation**.

TGF-β overdrive → Fibroblast-to-myofibroblast transition → **Fibrosis, aortic aneurysm, valve dysfunction**.

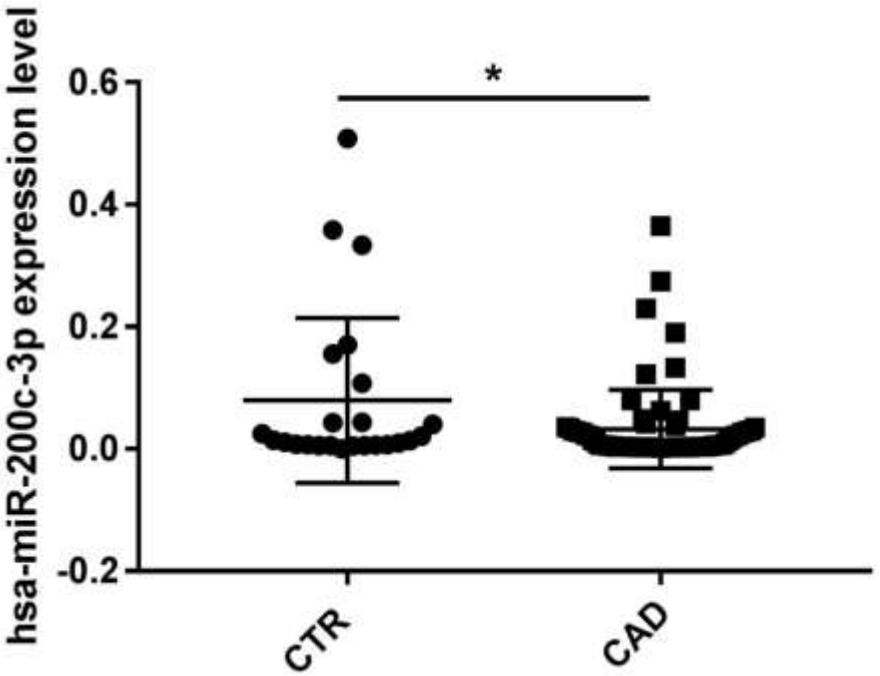
International Journal of *Molecular Sciences*

MDPI

Article

Downregulation of circulating hsa-miR-200c-3p correlates with dyslipidemia in patients with stable coronary artery disease

Chiara Vancheri [1], Elena Morini [1], Francesca Romana Prandi [2], Francesco Barillà [2], Francesco Romeo [2,3], Giuseppe Novelli [1,4,5] and Francesca Amati [1,*].



Proteomics (Study of Protein Expression and Modifications)

Diagnostic Biomarkers: Troponins (myocardial injury), natriuretic peptides (heart failure), and novel markers like GDF-15.

Post-Translational Modifications (PTMs): Phosphorylation, acetylation, and glycosylation changes in heart disease.

Personalized Medicine: Mass spectrometry-based proteomics helps stratify patients for targeted therapies.

Cardiovascular proteomics – a route to biomarker search

ESC European Society of Cardiology

European Heart Journal - Digital Health (2023) 00, 1–11
https://doi.org/10.1093/ehjdh/ztad056

ORIGINAL ARTICLE

Machine learning–based biomarker profile derived from 4210 serially measured proteins predicts clinical outcome of patients with heart failure

Marie de Bakker[1], Teun B. Petersen[1,2], Anja J. Rueten-Budde[2], K. Martijn Akkerhuis[1], Victor A. Umans[3], Jasper J. Brugts[1], Tjeerd Germans[3], Marcel J.T. Reinders[4], Peter D. Katsikis[5], Peter J. van der Spek[6], Rachel Ostroff[7], Ruicong She[8], David Lanfear[9,10], Folkert W. Asselbergs[11,12], Eric Boersma[1], Dimitris Rizopoulos[2,13], and Isabella Kardys[1,*]

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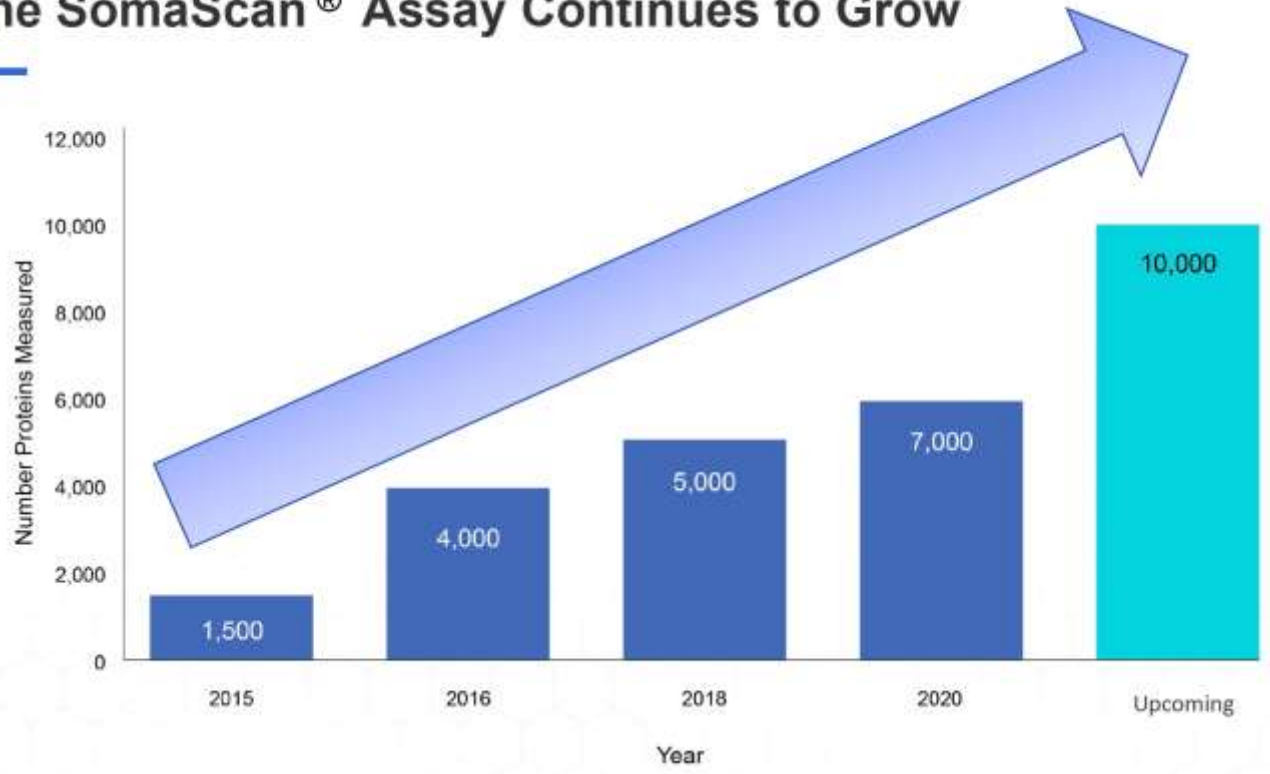
Received 21 June 2023; revised 6 September 2023; accepted 3 October 2023; online publish-ahead-of-print 4 October 2023

Conclusions

Nine proteins, related to cardiac remodelling and atherosclerosis, and derived from 4210 serially measured circulating proteins, provided the optimal multivariable, dynamic model for the occurrence of adverse clinical events in patients with HFrEF, along with the MAGGIC risk score, NT-proBNP, and hs-TnT: ST2, TrpRS, HIST3H2A, angiotensinogen, deltex-1, TSP-4, ADAMTSL-2, ANTXR1, and cathepsin D. Two proteins showed the strongest associations (NT-proBNP and angiotensinogen). Altogether, our study shows that proteomic profiling could provide information for risk assessment beyond established risk factors, and underlines that repeated measurements of multiple circulating proteins may convey incremental prognostic value over clinical characteristics and repeatedly measured established biomarkers.

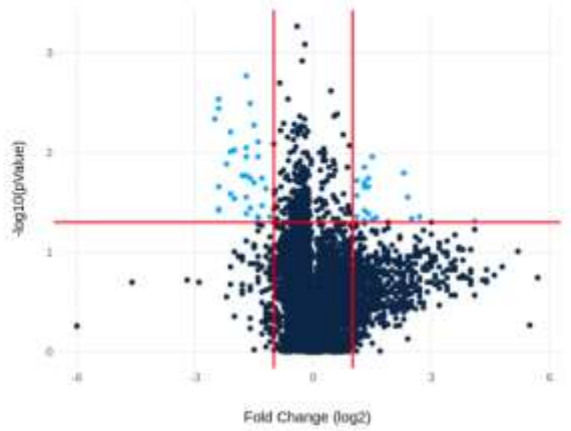
The SomaScan® Assay Continues to Grow



P-value = 0.05 and Log2FC= 1.0

UNDER EXPRESSED

Sequence ID	UniProt ID	Gene Symbol	Fold.Change	p.value
7011-8	Q6PIL6	KCNIP4	-1.7	0.0017
10501-3	Q99LC4	Igh	-2.4	0.0029
10734-339	Q6H9Q3	GAL3ST2	-1.6	0.0032
14284-23	Q9P2K8	EIF2AK4	-2.4	0.0036
14505-2	Q99LC4	Igh	-2.5	0.0046
10477-162	Q99LC4	Igh	-1.5	0.0053
10570-26	O15041	SEMA3E	-2.1	0.0062
23362-26	Q9BX93	NT5C1A	-1.4	0.0076
10675-223	Q9Y320	TMX2	-1	0.0082
7762-30	O75324	SNN	-1.7	0.0089
9374-24	Q16517	NINAT	-2	0.0094
7884-15	Q16832	DDR2	-2.1	0.0098
16049-43	P78380	OLR1	-1.7	0.011
10426-21	O14653	GOSR2	-1.4	0.011
14757-144	P55075	FGF8	-2.2	0.013
18410-26	Q8N4G2	ARL14	-1.8	0.017
9322-15	Q15293	RCN1	-1.7	0.017
10470-34	Q6PKC3	TXNDC11	-1.6	0.018
8402-22	Q9NRR1	CYTL1	-1.3	0.018
10600-24	O14967	CLGN	-1.5	0.02
10555-43	Q99LC4	Igh	-2.4	0.022
22472-4	Q99081	TCF12	-1.2	0.023
13068-139	O14618	CCS	-0.98	0.024
22776-40	Q15466	NR0B2	-2.1	0.026
25251-6	O14638	ENPP3	-0.99	0.026
16837-20	O15519	CFLAR	-1.7	0.028
10607-4	Q99LC4	Igh	-2	0.029
23304-1	Q9B592	NIPSNAP3B	-1.3	0.034
9507-55	Q14512	FGFBP1	-1.6	0.036
10511-10	P12111	COL6A3	-2.4	0.037
21464-2	Q13490	BIRC2	-1	0.037
10583-14	Q99LC4	Igh	-2.4	0.038
12034-28	Q01518	CAP1	-1.7	0.041
13011-20	P46783	RPS10	-1.4	0.044
23519-91	A6NGB7	TMEM221	-1.1	0.044
21426-68	Q5TA50	CPTP	-1.4	0.046
23399-35	Q8NFH5	NUP35	-1	0.05
16021-30	P55286	CDH8	-1.4	0.052
9916-146	Q9NT99	LRRC4B	-1.3	0.054



OVER EXPRESSED

Sequence ID	UniProt ID	Gene Symbol	Fold.Change	p.value
23903-3	P00505	GOT2	1.5	0.011
3708-62	P01023	A2M	1.3	0.014
14636-25	P52758	RIDA	2.3	0.016
3204-2	P09960	LTA4H	1.4	0.018
4435-66	Q6UWV6	ENPP7	1.1	0.019
18901-26	P0DMV9	HSPA1B	1.3	0.02
5803-24	P01024	C3	1.4	0.022
10506-53	O15173	PGRMC2	1.3	0.022
16322-10	Q6WU39	MZB1	1.1	0.027
4157-2	P00734	F2	2.4	0.028
16780-6	P0DMV8	HSPA1A	1.3	0.038
4220-39	P16591	FER	1.4	0.041
21563-3	Q6BZM1	PLA2G12A	2.7	0.044
10705-14	Q8NDV1	ST6GALNAC3	1.1	0.044
13492-44	P38646	HSPA9	1.6	0.045
18215-48	Q96F85	CNRIP1	2.5	0.046
22954-10	O15247	CLIC2	1.5	0.047
10039-48	P09104	ENO2	1.3	0.048
8458-16	P37840	SNCA	4.1	0.049
18387-7	P50502	ST13	3	0.05
4337-49	P02741	CRP	1.9	0.05
24472-28	Q9H0F6	SHARPIN	1.3	0.051
16618-7	Q07108	CD69	1.1	0.051
6103-70	Q96RD9	FCRL5	1.1	0.055
21955-36	P46379	BAG6	1.9	0.057
20054-28	P21399	ACO1	1	0.058
11634-32	O43665	RGS10	4.1	0.059

unpublished

Metabolomics (Study of Metabolic Pathways)

- **Metabolic Signatures**: Elevated TMAO (trimethylamine N-oxide) predicts atherosclerosis; altered fatty acid oxidation in heart failure.
- **Energy Metabolism**: Shifts from glucose to ketone utilization in failing hearts.
- **Therapeutic Targets**: Modulating metabolites like succinate (ischemia-reperfusion injury)

Present Day Healthcare is Broken

We need to be keeping people healthy instead of waiting until they are ill

1

Travel to a physician for a health check

2

The office looks the way it did **40 years ago**

3

A large aliquot of blood is drawn **which hurts!**

4

Very **few measurements** are made, many questionable

5

Treat you based on **population averages**

Health is a product of Genome & Exposome

Genome

Exercise

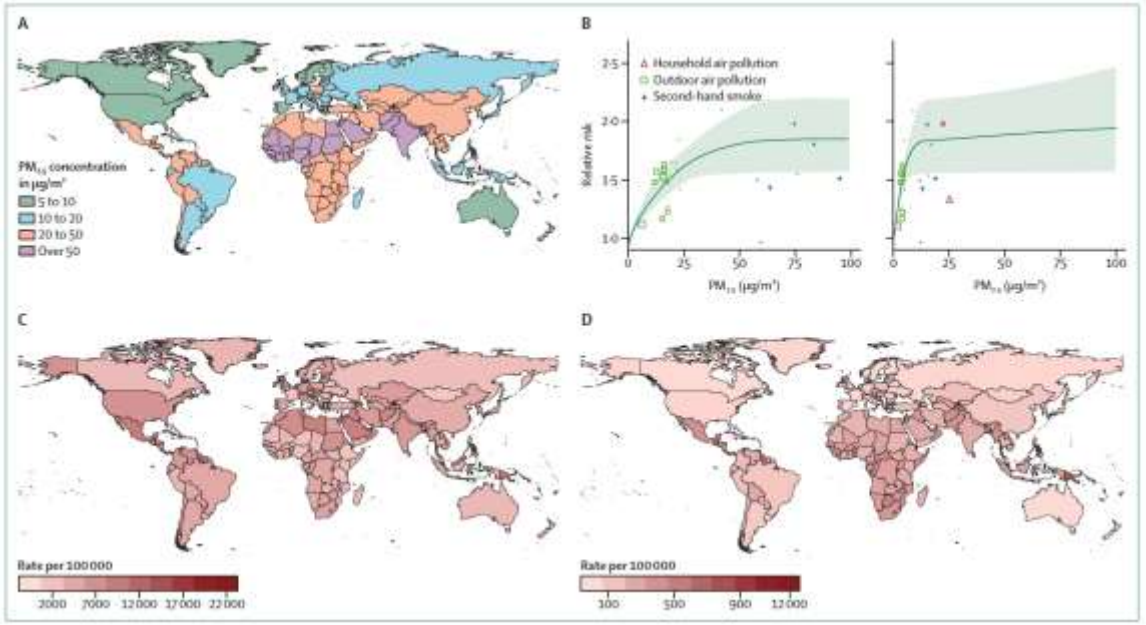
Pathogens

Food

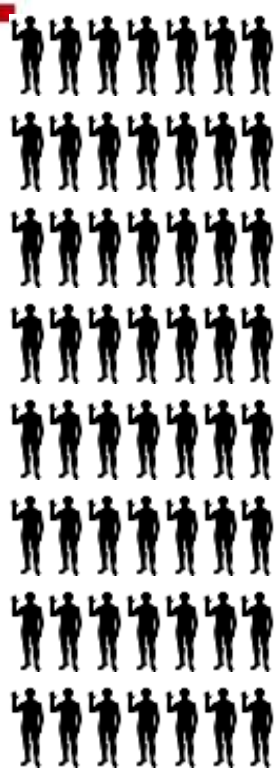
Environmental Exposures

Mental Health

Air pollution exposure and cardiometabolic risk



Longitudinal Personal Omics Profiling



109 Individuals

Omics Measurements

Genome

Epigenome

Transcriptome

Proteome

Cytokines

Metabolome
Lipidomics

Autoantibody-ome

Microbiome (Gut, Urine, Nasal, Tongue, Skin)

Billions of Measurements

Clinical Tests
Questionaires

Stress Echos
Glucose Control

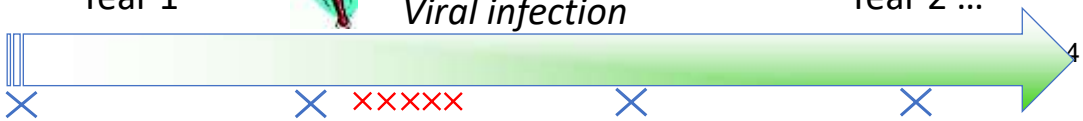
Biosensors

Year 1

Viral infection

Year 2 …

>11 yrs!



Zhou, … Snyder Nature 2019

44

Remote Monitoring Using Microsampling

Mitra Microsampling Collection

Overnight Delivery

Lab Processing

Measure >2200 analytes

Lab Analysis

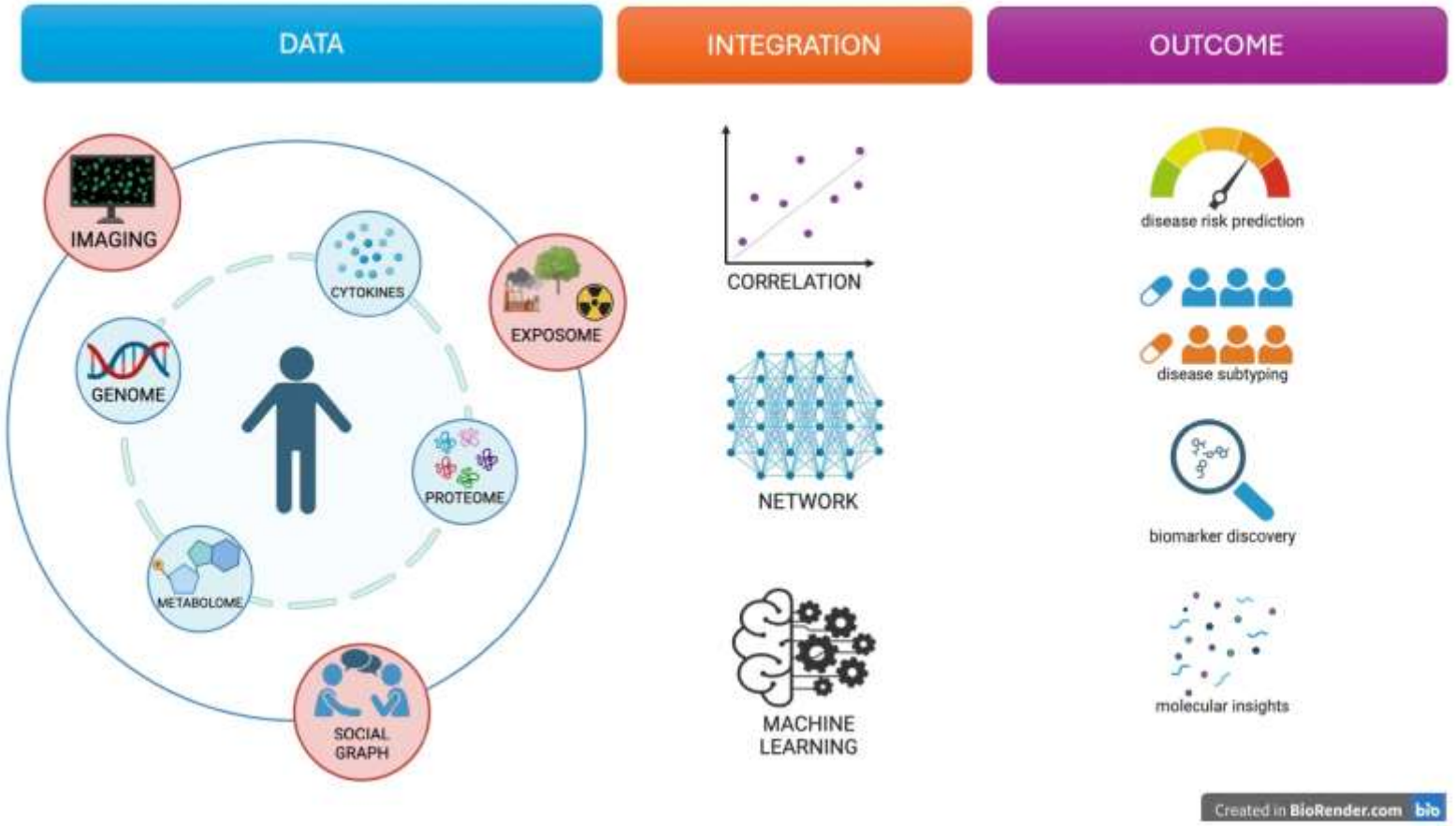
Lipidomics

Metabolomics

Proteomics

Cytokine
Cortisol
Total protein
Hormone

Genomic and Exposomic Analyses to Elucidate Environmental and Molecular Drivers of Chest Pain and Cardiovascular Disease Risk



Tor Vergata, Yale, Abano Terme hospital, in progress

Clinical Applications & Future Directions

Precision Medicine: Integrating multi-OMICS data for tailored therapies.

Early Disease Detection: Liquid biopsies for circulating biomarkers.

Drug Development: Targeting OMICS-identified pathways (e.g., PCSK9 inhibitors from genomics).

“La biologia moderna è diventata così genocentrica che abbiamo dimenticato che le vere unità di funzione e struttura in un organismo sono le cellule e non i geni”.

Sydney Brenner (2002)

Nobel Prize in Physiology or Medicine 2002