Application of genomics to early clinical development planning in translational medicine

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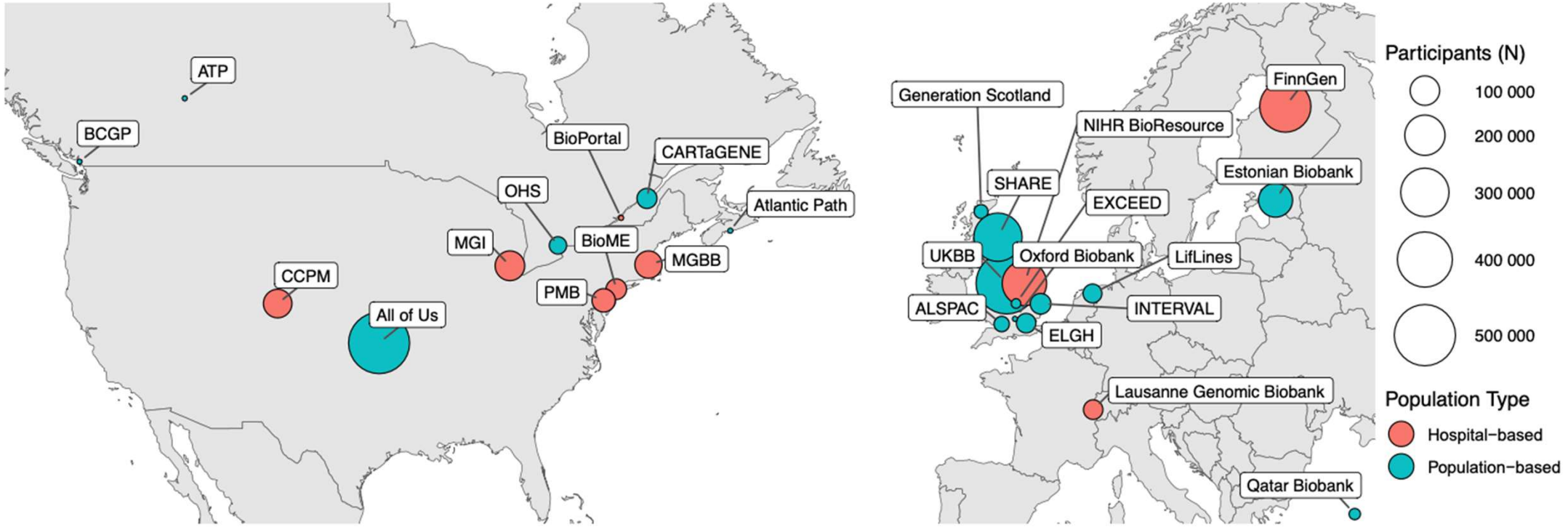
Cardiovascular health and genomic data

Immense datasets generated and growing



Non-exhaustive overview of population and hospital based cohorts with genotype and health outcomes with potential for genotype-based recall of participants (Delabays B et al. *Ann Rev Pharm Tox*. 2024)

Cardiovascular health and genomic data

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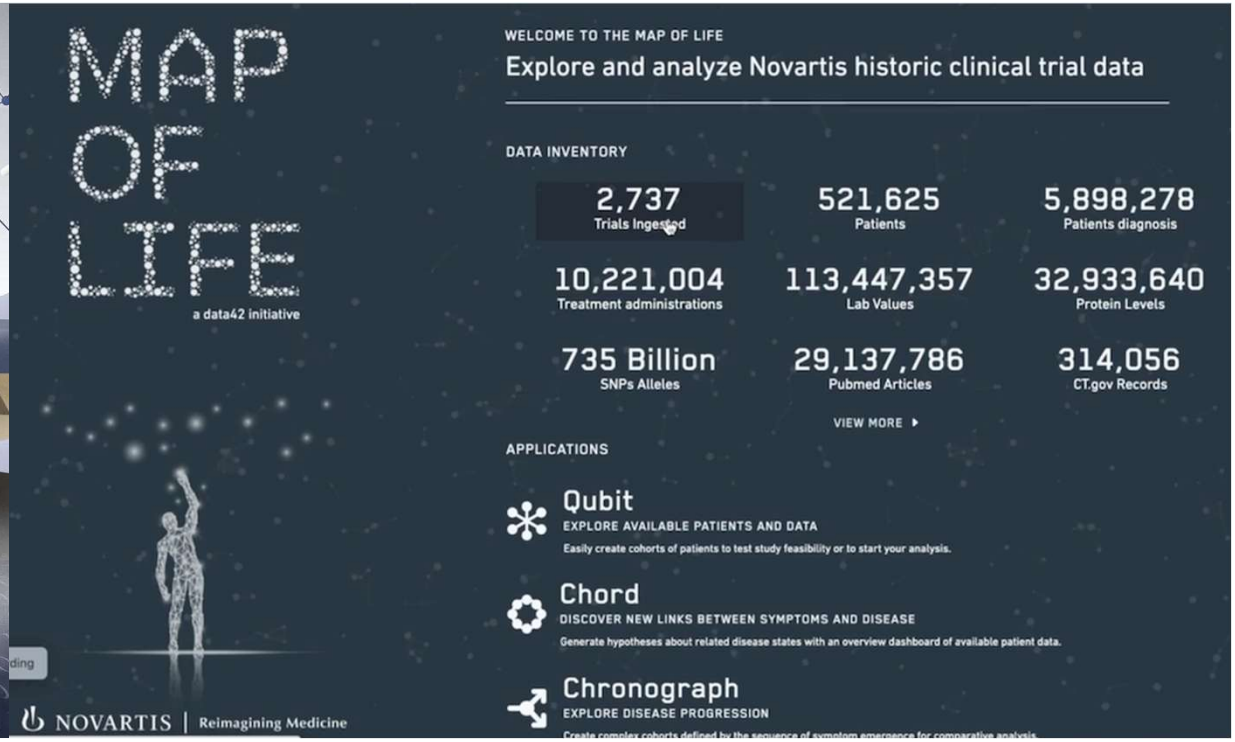


Novartis Live.Magazine, September 2021
https://live.novartis.com/article/a-hitchhikers-guide-to-pharmas-digital-universe

Case study:
Genomic-based patient selection in cardiovascular medicine

Genomic-based patient stratification strategies for individualized treatments have been proposed as a transformative approach for cardiovascular medicine

However, utilization of clinical genetic biomarkers across cardiovascular medicine is limited

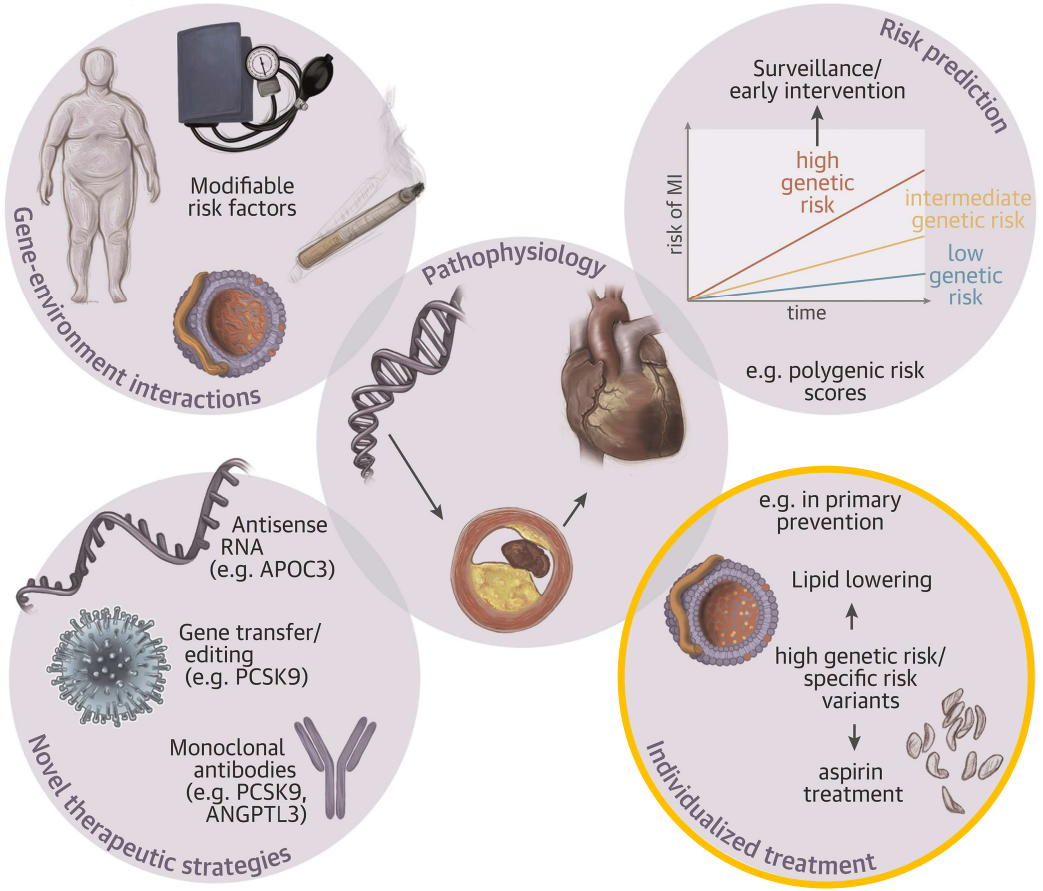
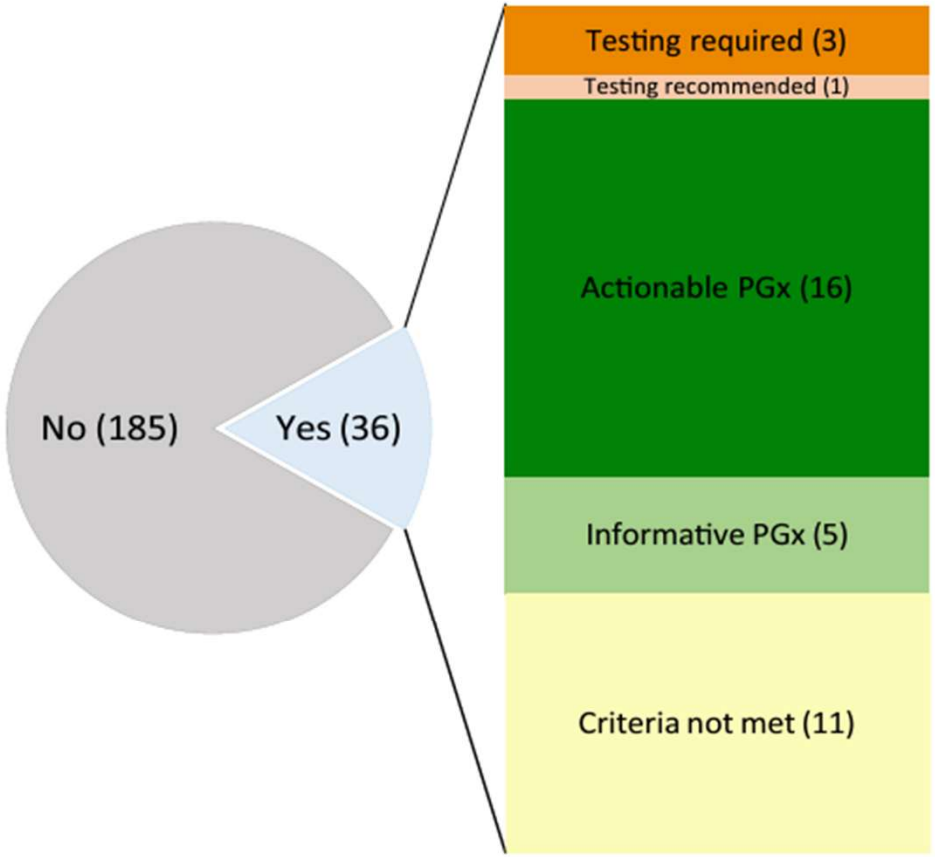
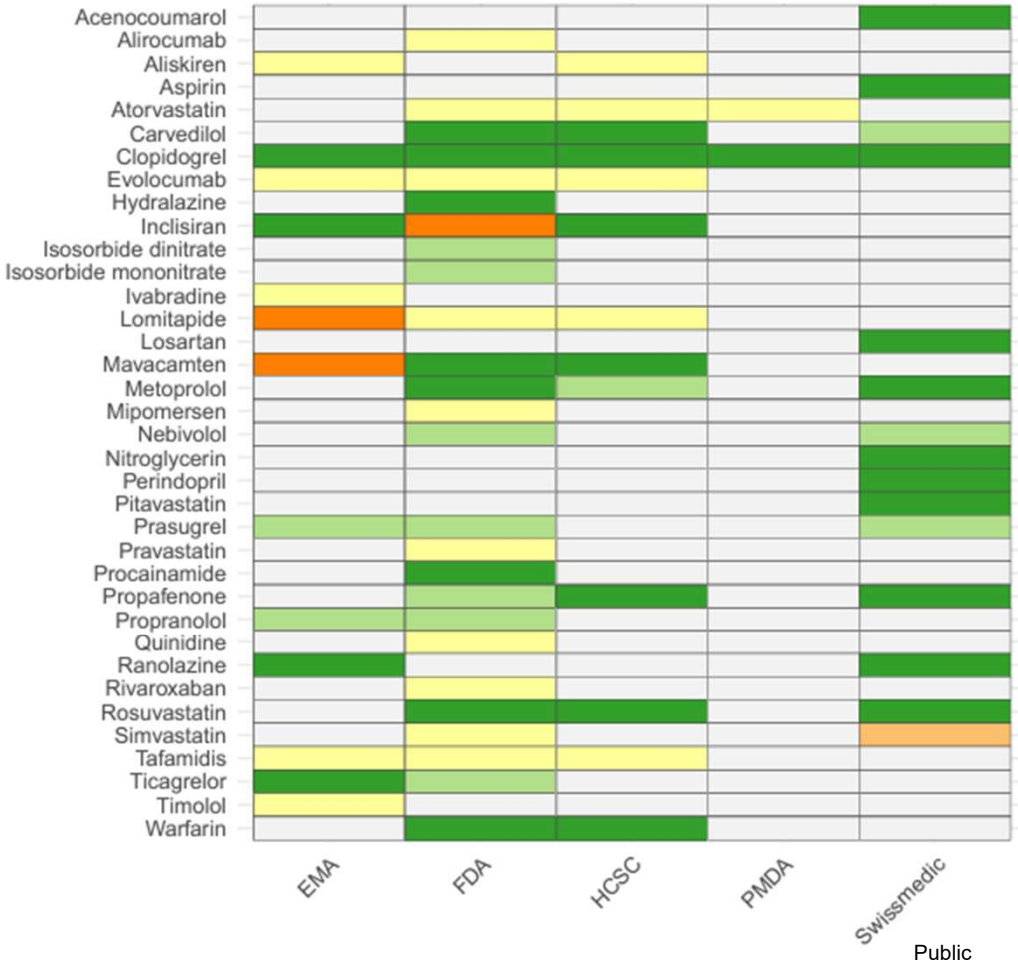


image: Kessler and Schunkert, *JACC BTS*, 2021

Cardiovascular pharmacogenomics

Primarily focused on drug metabolism



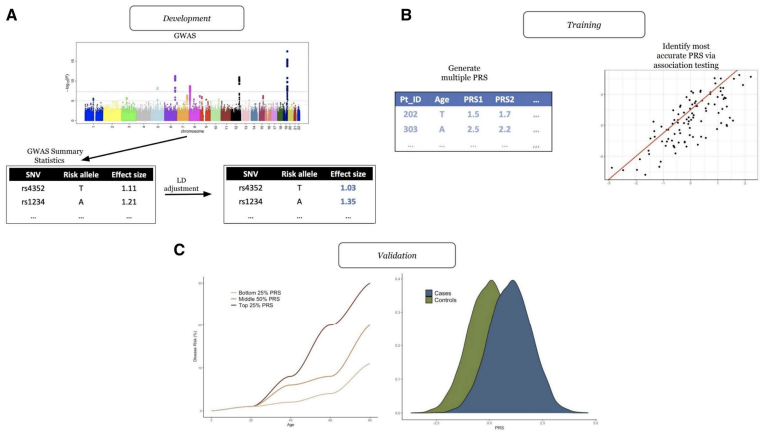


Delabays B et al. *Pharm Rev*, 2024

Cardiovascular polygenic risk scores (PRS)

Area of substantial research activity

- Intense research focus
- Growing public awareness
- No widespread clinical use



The New York Times

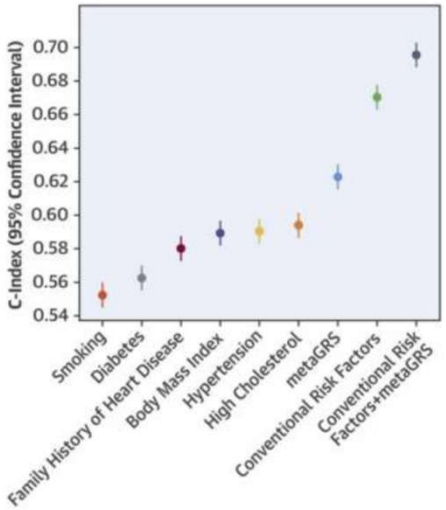
To Prevent Heart Attacks, Doctors Try a New Genetic Test

Polygenic risk scores could help patients, including younger ones, understand whether they really need early treatment for heart disease.

By Gina Kolata

Gina Kolata has been reporting on heart disease prevention for decades and visited patients and doctors at the University of Pennsylvania lipid clinic to report this article.

May 30, 2023



Evidence gap needs to be addressed with prospective clinical trials

Evolution of PRS in cardiovascular trials

First generation
Intervention: none
Outcome: post-hoc subgroups (difference in relative risk reduction)

Second generation
Intervention: prospective disclosure \ counselling
Outcome 1: surrogate outcomes (eg. change in LDL cholesterol)
Outcome 2: indirect effect on treatment

Third generation
Intervention: prospective PRS-guided therapy with established medicines
Outcome: clinical outcomes (eg. major adverse cardiovascular events)

Evolution of PRS in cardiovascular trials

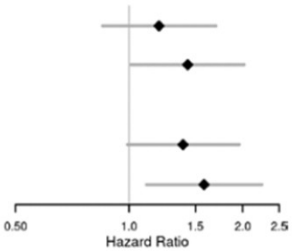
First generation
Intervention: none
Outcome: post-hoc subgroups (difference in relative risk reduction)

Example: *Post-hoc* PRS analyses in CANTOS trial

CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

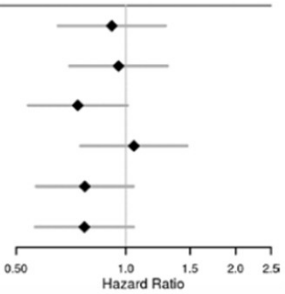
B Comparing to T1 for MACE+ in Placebo

PRS Group	Events/Total	HR (95% CI)	P-value
CAD T1	63/394	Ref.	
CAD T2	74/378	1.2 (0.85,1.7)	0.29
CAD T3	74/365	1.43 (1.01,2.02)	0.043
MetaCAD T1	62/405	Ref.	
MetaCAD T2	76/373	1.39 (0.99,1.96)	0.058
MetaCAD T3	73/359	1.58 (1.11,2.25)	0.011



C Canakinumab 150/300mg vs Placebo for MACE+

PRS Group	Events/Total (Canakinumab)	Events/Total (Placebo)	HR (95% CI)	P-value
CAD T1	82/514	63/394	0.91 (0.65,1.28)	0.61
CAD T2	101/537	74/378	0.95 (0.7,1.3)	0.77
CAD T3	89/525	74/365	0.74 (0.54,1.01)	0.058
MetaCAD T1	82/495	62/405	1.05 (0.75,1.47)	0.77
MetaCAD T2	96/553	76/373	0.77 (0.57,1.05)	0.097
MetaCAD T3	94/528	73/359	0.77 (0.56,1.05)	0.098



Tertile 3 (high PRS) vs Tertile 1 (ref – low PRS): ~40-60% increase risk of CV events (p <0.05)

Tertile 3 (high PRS) vs Tertile 1 (ref – low PRS): ~25% RRR of MACE with IL-1b mAb (not statistically significant p = 0.05-0.10)

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Xu et al. *Circ Genom Prec Med.* 2021

Evolution of PRS in cardiovascular trials

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Second generation
Intervention: prospective disclosure \ counselling
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Intervention: prospective PRS-guided therapy with established medicines
Outcome: clinical outcomes (eg. major adverse cardiovascular events)

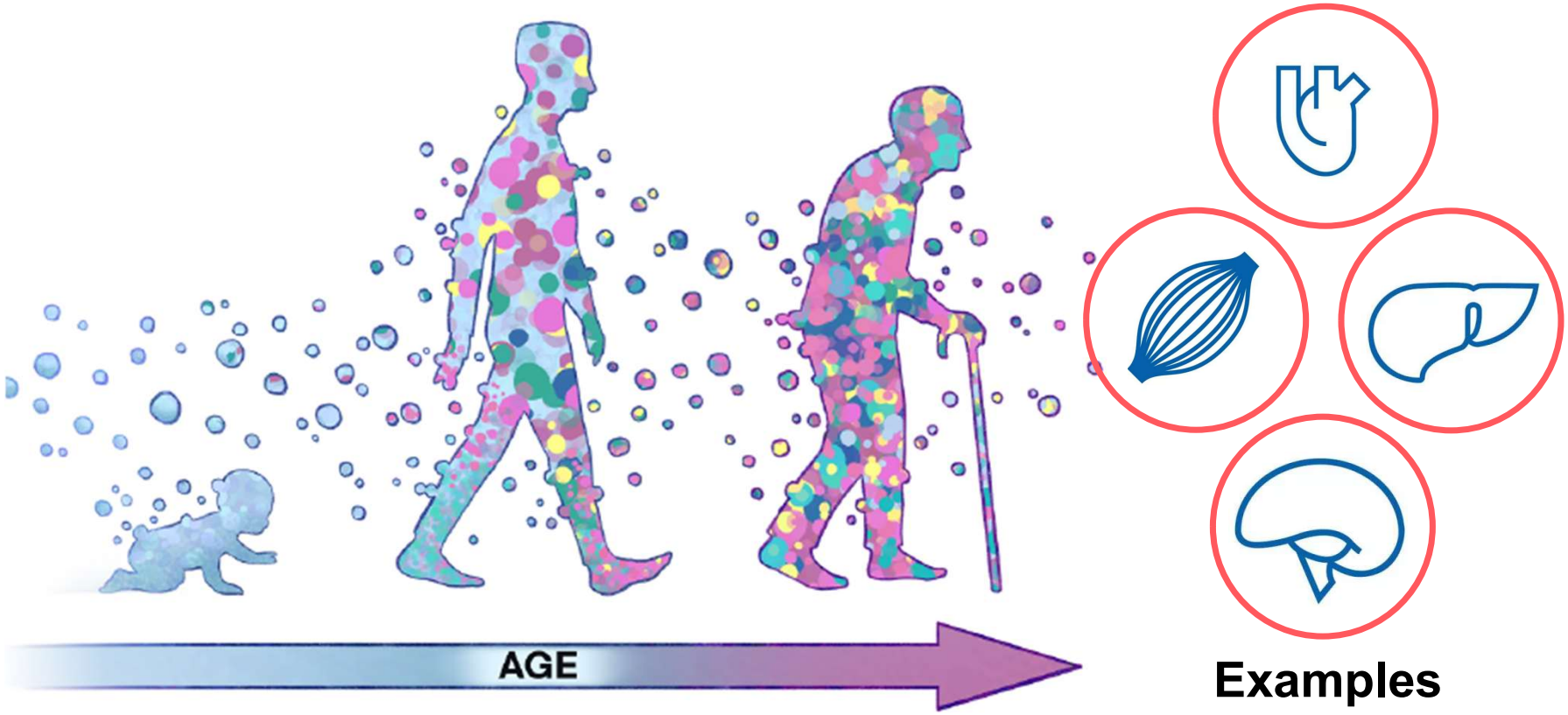
Fourth generation? Integration in drug development

Applications for cardio-immunology

Genetic subgroup	Higher CVD risk in CANTOS	Higher CVD risk in external cohorts	Increased benefit with IL-1b inhibition in CANTOS	External validation of enhanced CVD benefit with immune-modulatory therapies	Mechanistic link to greater response to immune-modulatory therapies	Potential size of population	Utility to guide treatment across race/ethnicity	Current adoption of testing
CAD PRS	~40-60%	Yes, magnitude varies	~25% RRR (ns)	No	No	Arbitrary threshold ~33%? (top tertile)	Severely limited in non-White populations	Limited

… are there other clinical genomic biomarkers of elevated residual risk and greater treatment response?

Somatic mosiacism is emerging as a potential driver of many chronic diseases of aging



Evans and Walsh, *Phys Rev.* 2022

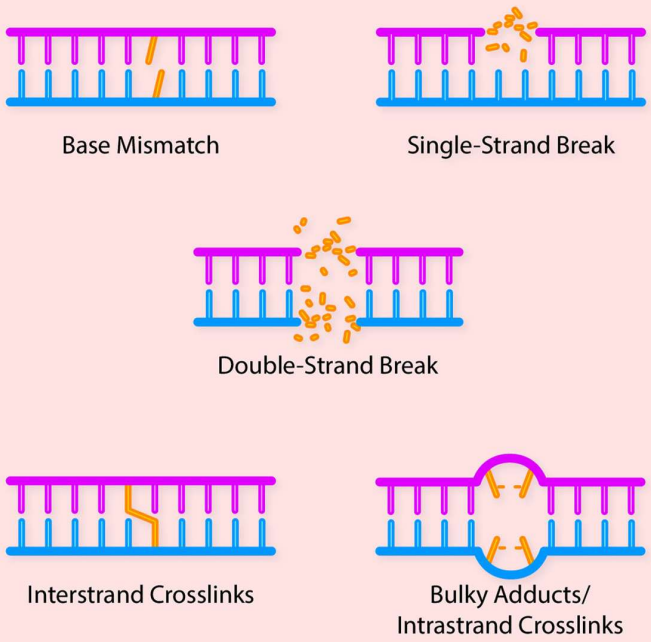
Clonal hematopoeisis of indeterminate potential (CHIP)

70-80% are somatic mutations in *DNMT3A* or *TET2*

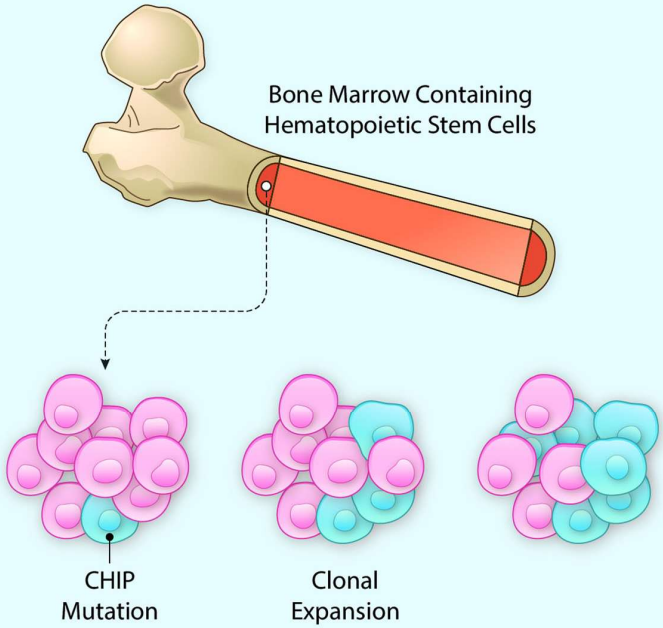
Risk factors for clonal hematopoiesis

Aging, environmental triggers, genotoxic stress, germline predisposition

DNA Damage



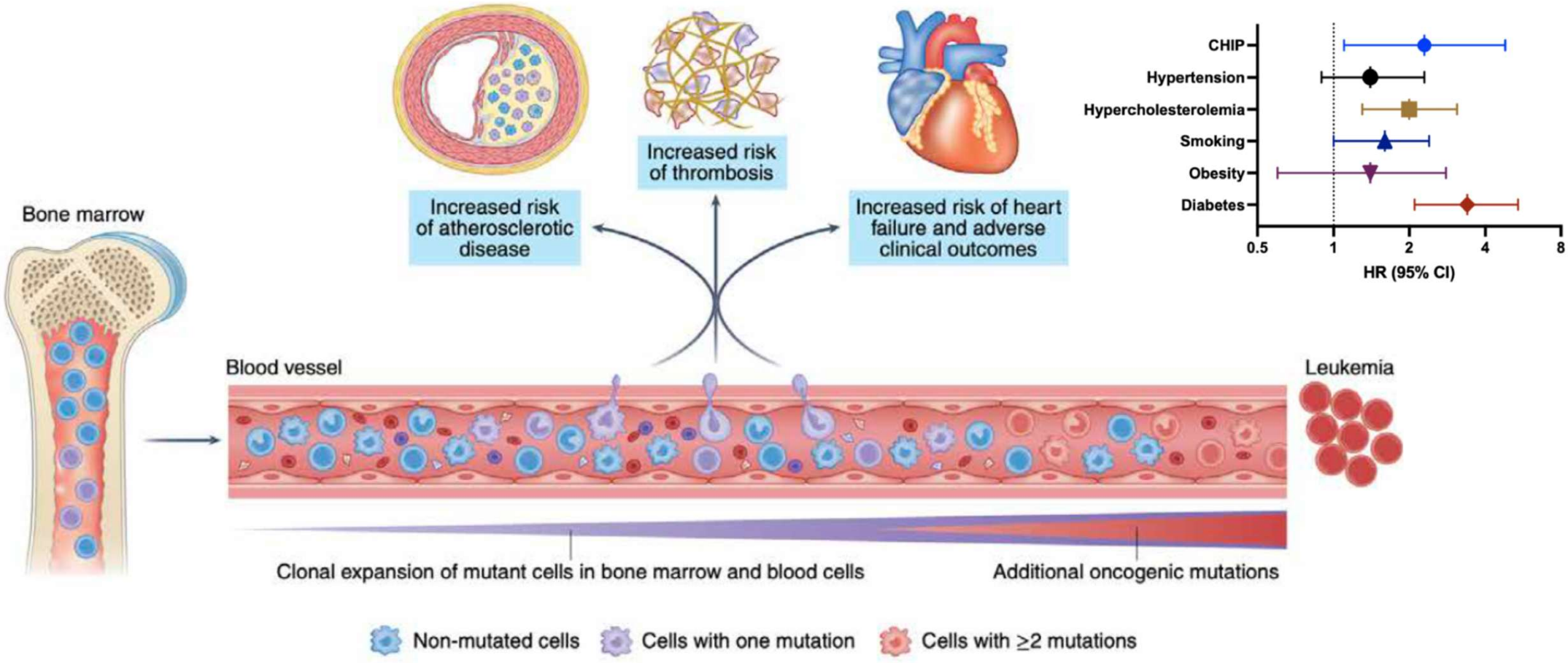
Clonal Hematopoiesis



It is projected that by the time a person reaches the age of 70, they may have up to 1.4 million protein-coding variations in their HSC reservoir. Any mutation that leads to a fitness advantage of the impacted cell may initiate clonal expansion.

Heimlich and Bick, *Circ Res.* 2022

CHIP + cardiovascular disease (CVD)

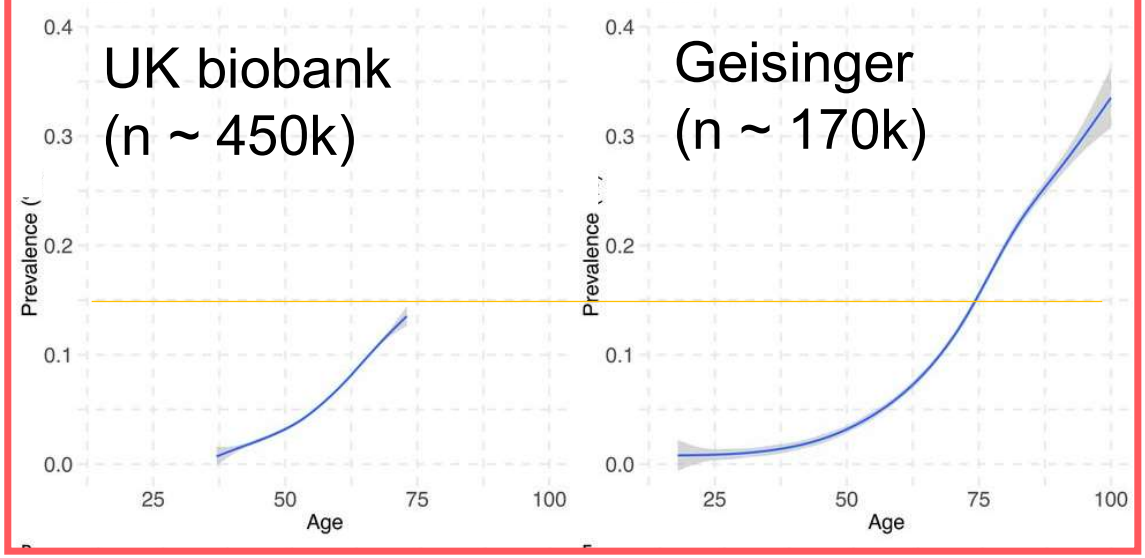


Tall and Fuster, *Nature CV Res.* 2022

Increasing awareness due to high prevalence in select CVD populations

General population

Prevalence ~15% at 75 years of age



CVD populations

New CHIP + CVD data consistently emerging.

Examples:

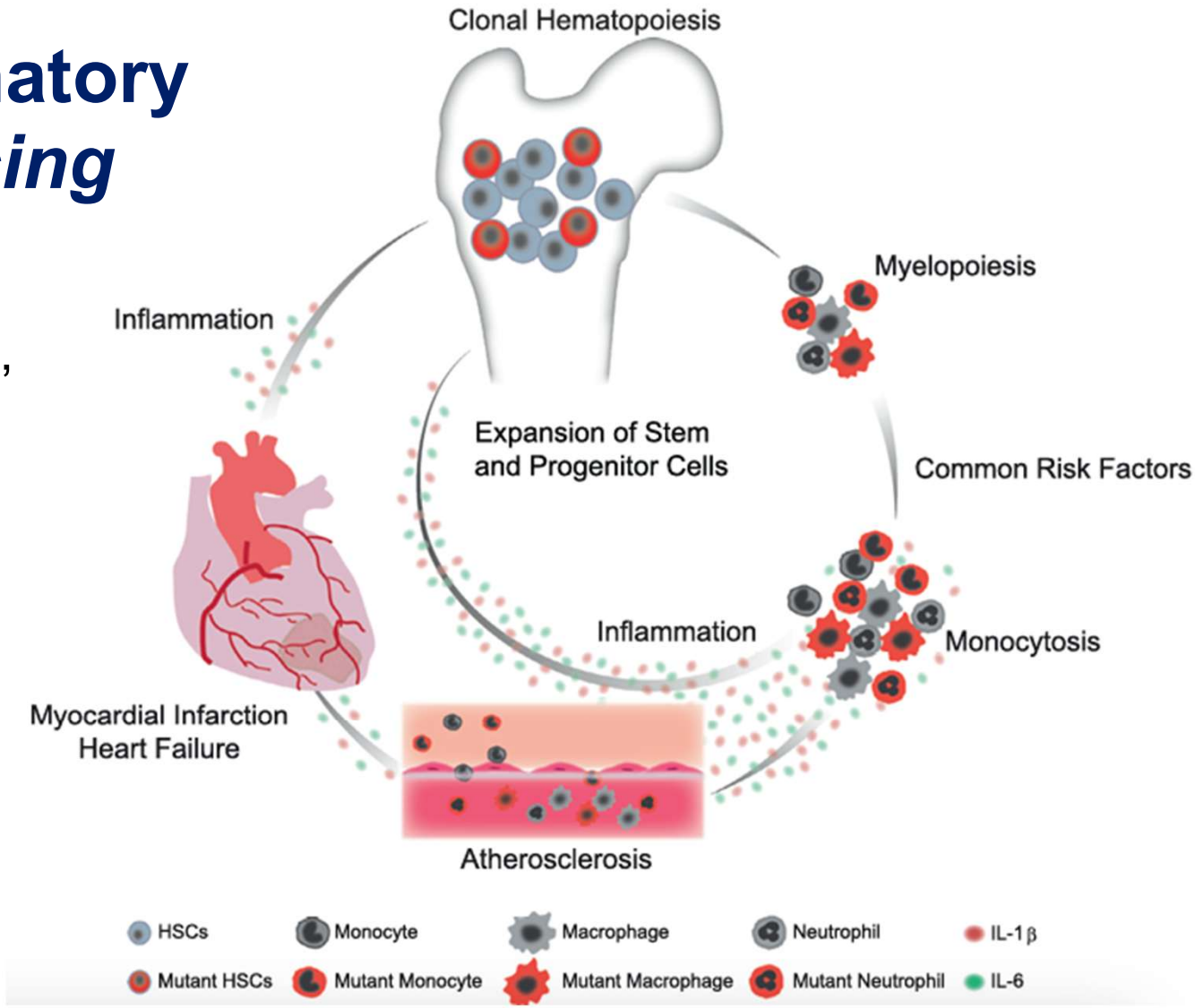
- 18% (~1 in 5; n~1500) in VUMC cath population + more left main coronary stenosis with *TET2* CHIP
- 29% (n~130) post-ACS / cardiogenic shock + worse 30d outcomes

Absolute burden to increase with demographic shifts to an aging population

Kessler et al. *Nature* 2022. Heimlich et al. *Circ Genom Precis Med* 2023; Bohme et al *JACC* 2022

Pro-inflammatory *self-reinforcing*

Linked to higher NLRP3, IL-1β, IL-6, etc.

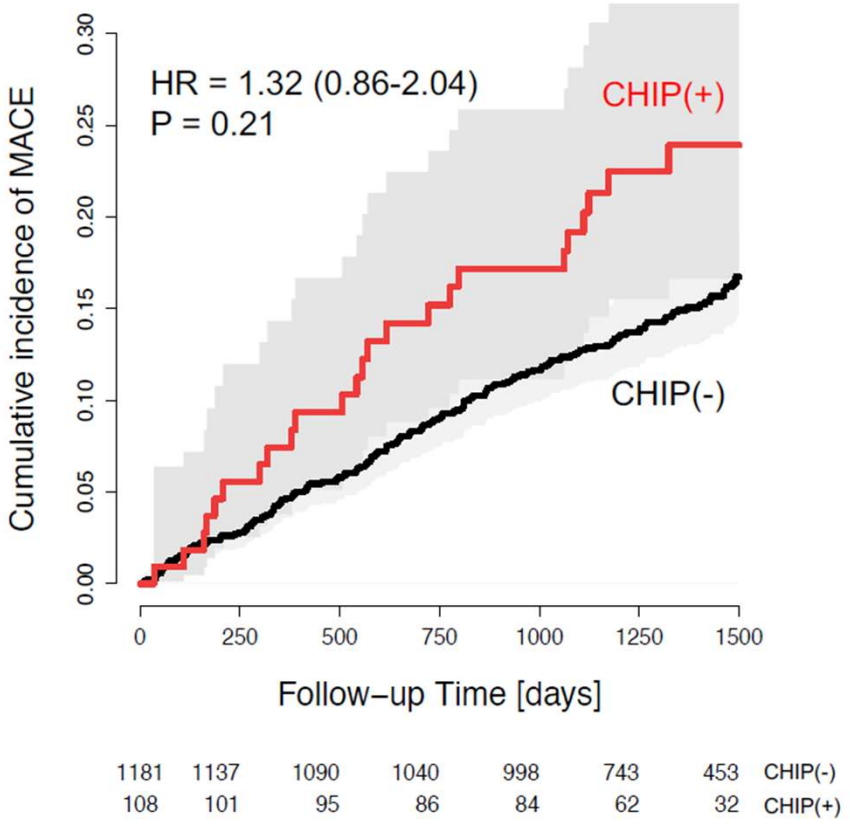


Pardali et al. *Exp Heme.* 2020

CHIP(+) patients have a higher CVD risk in CANTOS

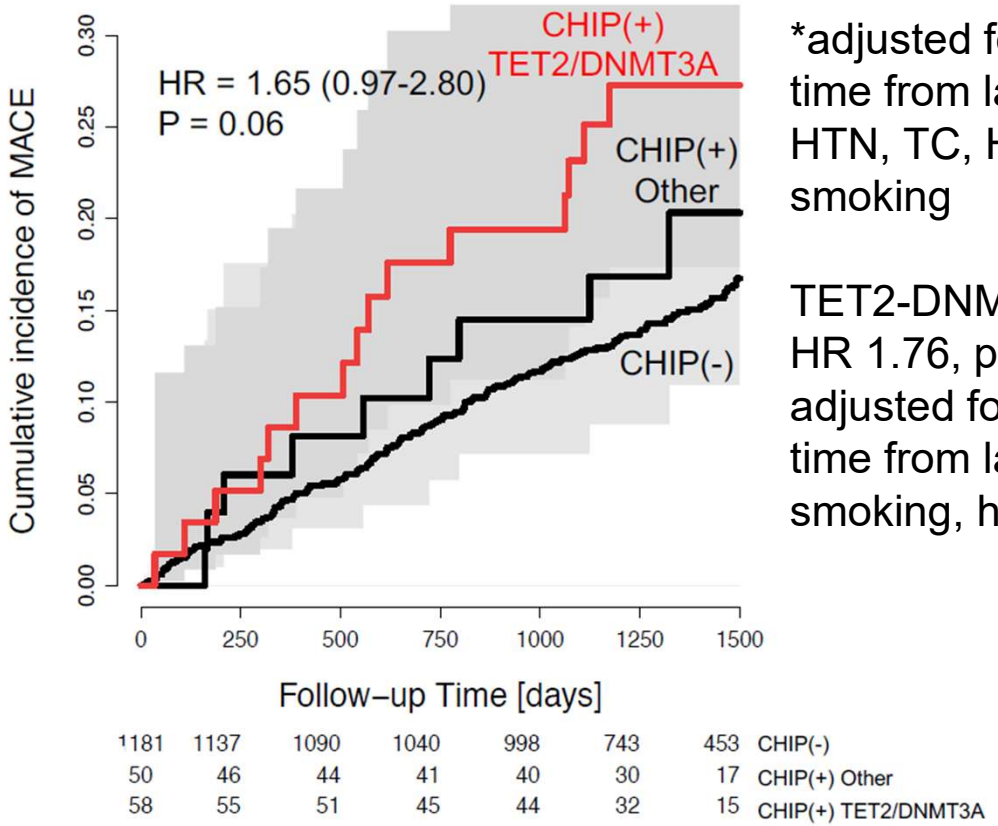
A CHIP(+)

n = 1284, 213 total events



B TET2-DNMT3A CHIP(+)

n = 1284, 213 total events



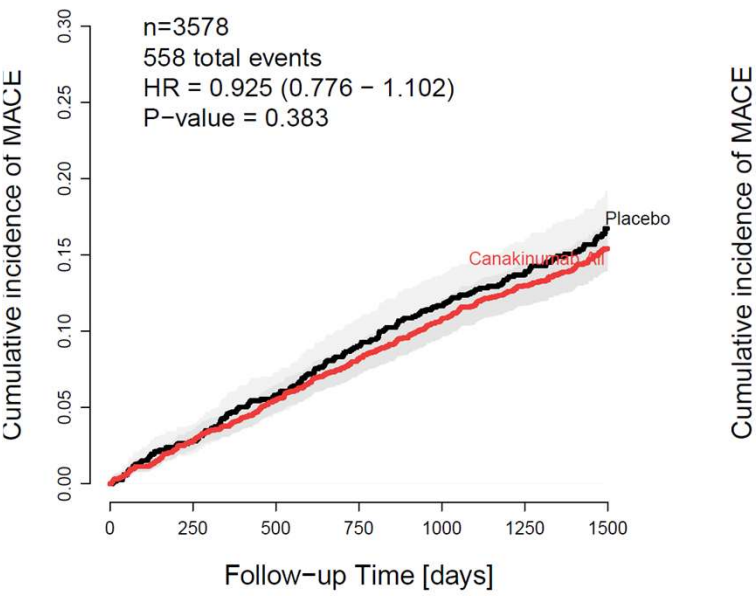
*adjusted for age, sex, time from last MI, T2D, HTN, TC, HDL, hsCRP, smoking

TET2-DNMT3A CHIP(+)
HR 1.76, p=0.04
adjusted for age, sex, time from last MI, T2D, smoking, hsCRP

Svensson et al. *JAMA Cardiology*. 2022

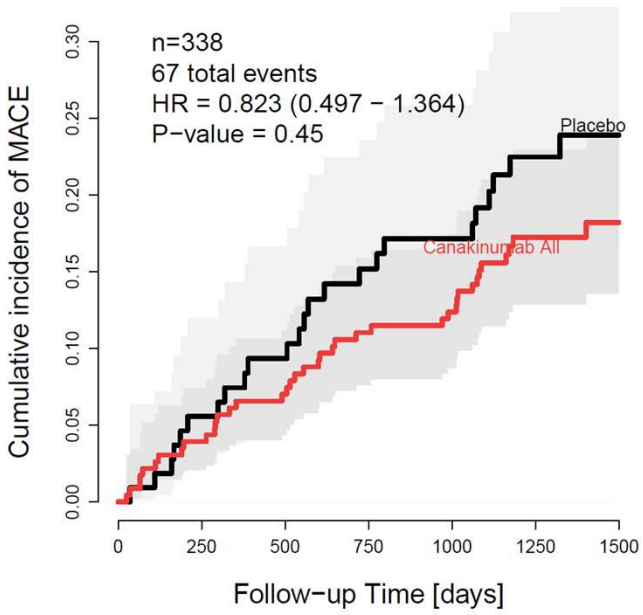
CHIP(+) participants demonstrated a larger reduction in CVD events with canakinumab

CHIP (-)



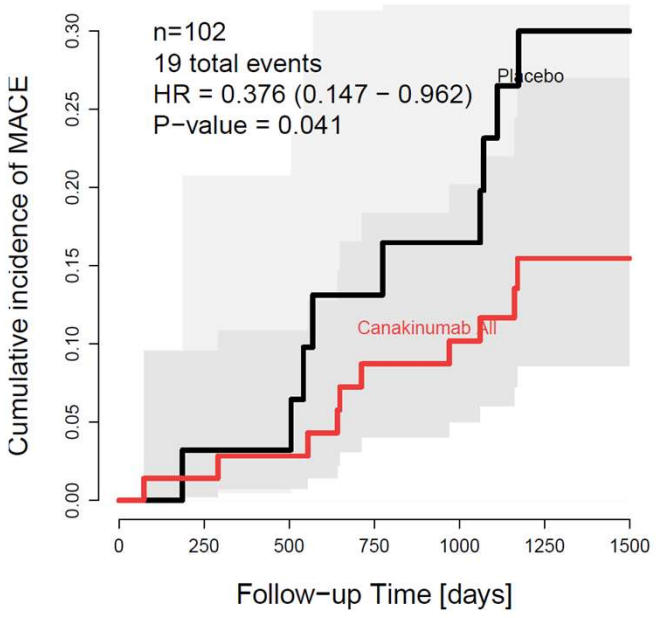
1181	1137	1090	1040	998	743	453	Placebo
2404	2314	2227	2142	2062	1521	933	Canakinumab

CHIP (+)



108	101	95	86	84	62	32	Placebo
230	219	209	198	195	129	72	Canakinumab

TET2-CHIP (+)



31	30	30	26	25	19	11	Placebo
71	69	67	62	61	37	14	Canakinumab

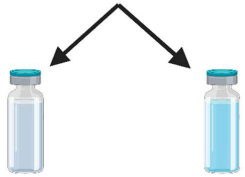
Svensson et al. *JAMA Cardiology*. 2022

Multiple lines of supporting evidence

Experimental Randomization

Atherogenic Mice

Ldlr-/- 10% WT BM vs *Ldlr-/-* 10% *Tet2-/-* BM



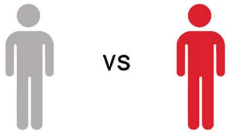
Placebo NLRP3i

↓20% ↓50%

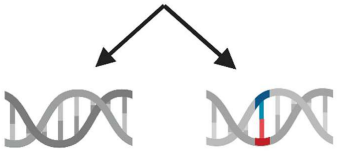
Fuster JJ, et al, Walsh K. *Science* 2017

Mendelian Randomization

Humans without CAD

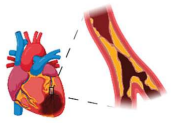


No CHIP vs *TET2/DNMT3A* CHIP



WT *IL6R* p.Asp358Ala

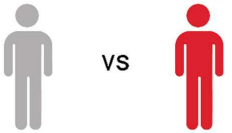
↓5% ↓54%



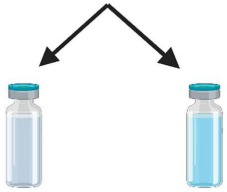
Bick AG*, Pirruccello JP*, et al, Natarajan P. *Circulation* 2020

Randomized Controlled Trial Post hoc exploratory analysis

Humans with CAD + ↑hsCRP

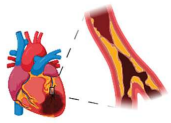


No CHIP vs *TET2* CHIP



Placebo IL-1β mAb

↓15% ↓62%



Svensson EC, et al, Basson CT. *JAMA Cardiol* 2022

CANTOS

Canakinumab Anti-inflammatory Thrombosis Outcomes Study

Increased risk of MACE

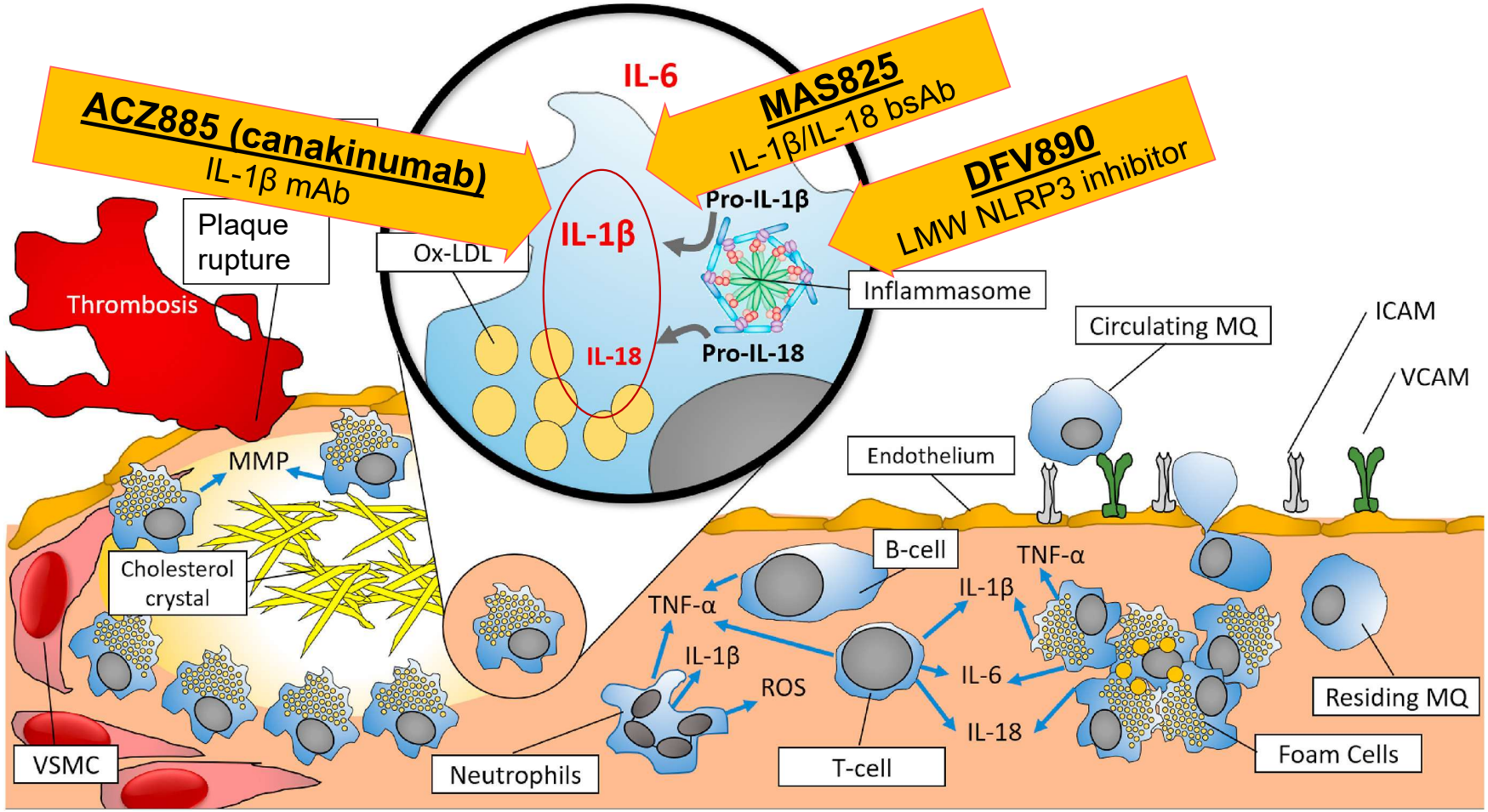
↑ 30% all-CHIP
70% *TET2/DNMT3A*-CHIP
as compared to CHIP (-)

Natarajan P, *ATVB* 2023

CVD risk reduction in CHIP vs PRS-defined strategies

Genetic subgroup	Higher CVD risk in CANTOS	Higher CVD risk in external cohorts	Increased benefit with IL-1b inhibition in CANTOS	External validation of enhanced CVD benefit with immune-modulatory therapies	Mechanistic link to greater response to immune-modulatory therapies	Potential size of population	Utility to guide treatment across race/ethnicity	Current adoption of testing
CHIP	60-75%	~100%	Up to >60% RRR	Yes, with human genetics but conflicting data	Yes	~3-30% (depending on pop. and mutation)	Yes	Limited
CAD PRS	~45%	Varies	~26% RRR	No	No	Arbitrary threshold ~33%? (top tertile)	Severely limited in non-White populations	Limited

Immunomodulatory therapies + atherosclerosis



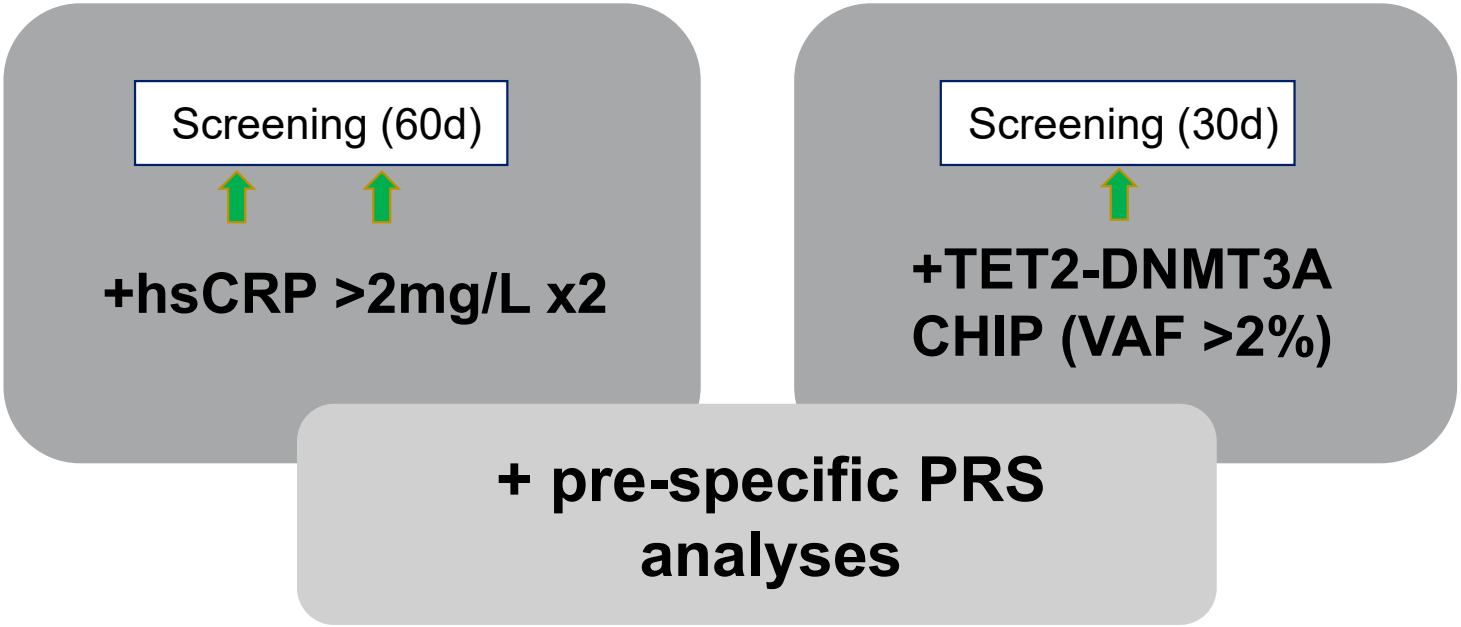
Alfaddagh et al. *AJPC* 2020

Cytokine response across various enrichment strategies for residual inflammatory CV risk

Two Phase 2a trials evaluating varied patient enrichment approaches

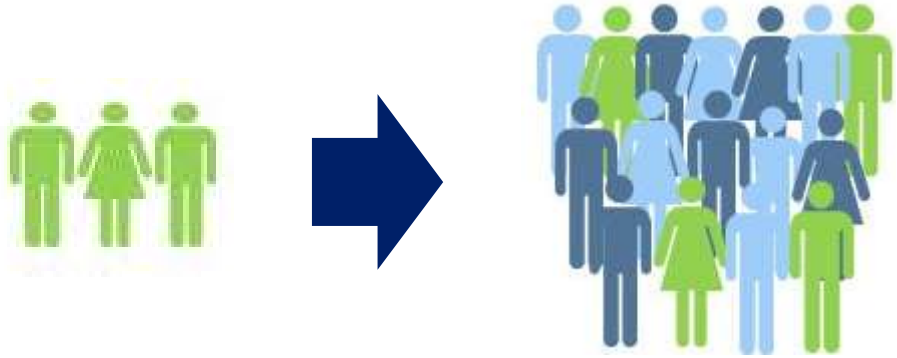
NCT06097663
NCT06031844

Stable post-myocardial infarction

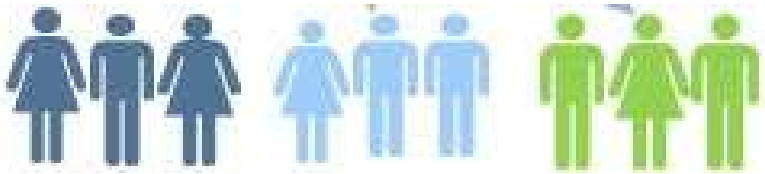


Additional potential CV applications for PRS in TM trials and/or clinical development programs

Selection for enhanced event rate for shorter, faster, early trials
Extrapolate effect to unselected population for further development



Expand potential eligible patient population (eg. additional factor to qualify for high-risk primary prevention trials)



Summary and conclusions

- Genotype-guided pharmacotherapy approaches hold promise in cardiovascular medicine
- Translational medicine and early clinical development programs offer opportunities to evaluate various approaches
- Pros and Cons of various approaches must be carefully weighed
- Immense genetic datasets + cardiometabolic health outcomes continue to grow, with opportunities to evaluate enhanced treatment response / greater benefit-risk ratio with therapy
- Well designed rigorous prospective clinical trials are needed to demonstrate clinical benefit

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Thank you

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