Getting risk stratification right: research perspective

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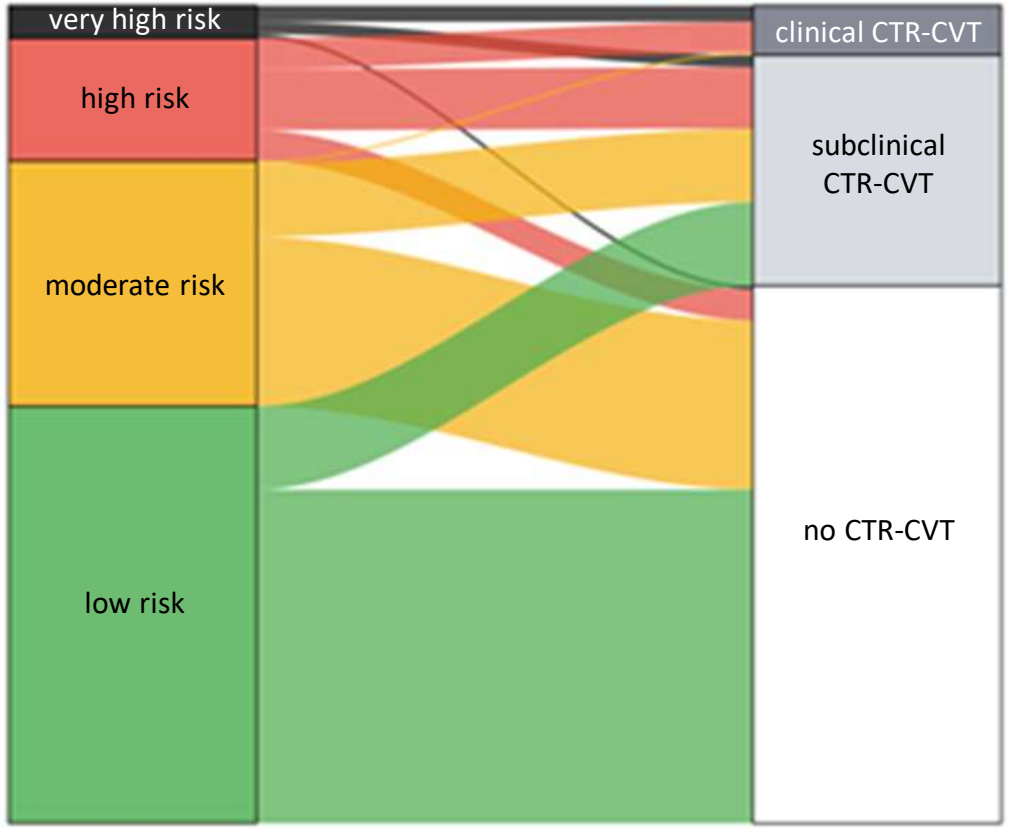
Speaker and/or advisory board from Bayer, Daiichi Sankyo, MSD, Janssen, and Gossamer Bio
Scientific consultancy agreement between Bayer and the Department of Internal Medicine, University of Genova

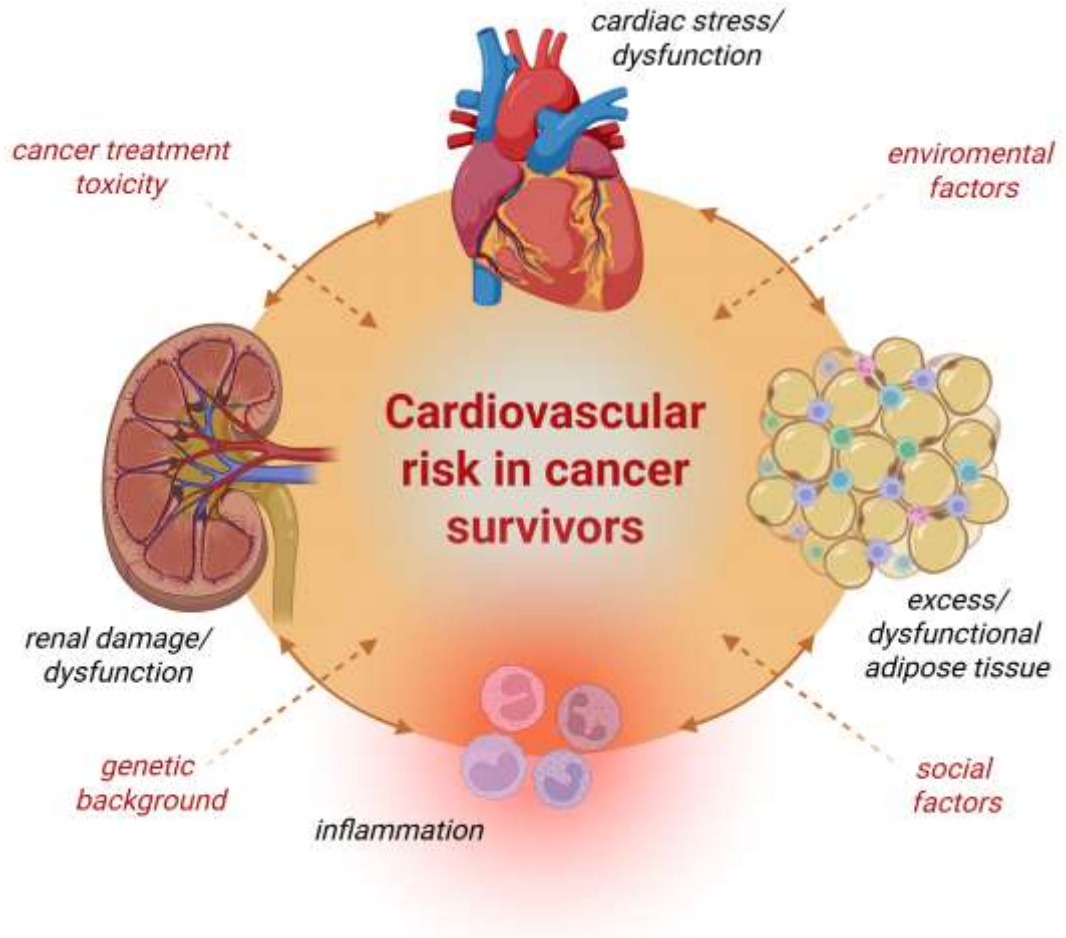
Cardiovascular risk assessment in cardio-oncology



Cancer treatment-related cardiovascular toxicity (CTR-CVT)

- cancer treatment is the main determinant of the risk
- need for specific risk prediction models
- current approaches are relatively precise

Cardiovascular risk assessment in cardio-oncology



Cardiovascular disease

- wider range of factors accounting for the risk
- risk prediction models used for the general population do not incorporate cancer and cancer treatments
- need for refined or new models

Ameri P et al. Eur Heart J Qual Care Clin Outcomes. 2026

1. Genetic susceptibility

common
genetic variants
(polygenic risk scores)

cancer treatment-related
(CTR) cardiomyopathy

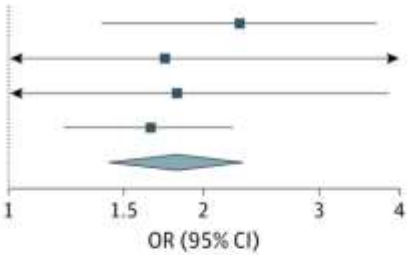
polygenic risk scores
for primary cardiomyopathies

rare
genetic variants
(primary cardiomyopathies)

Mass General Brigham (MGB) Biobank, UK Biobank, FinnGen, and Veterans Affairs Million Veteran Program (MVP)

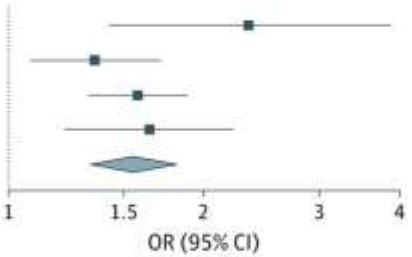
A PPCM phenotype

Biobank	Population	Control	OR (95% CI)	*P* value
MGB	21	42024	2.26 (1.39-3.67)	<.001
UK	2	295055	2.47 (0.62-9.85)	.2
FinnGen	7	417753	1.82 (0.77-3.55)	.2
MVP	40	513067	1.65 (1.22-2.22)	.001
Meta	70	1267899	1.82 (1.43-2.30)	<.001



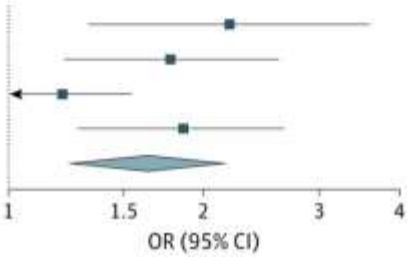
B ACM phenotype

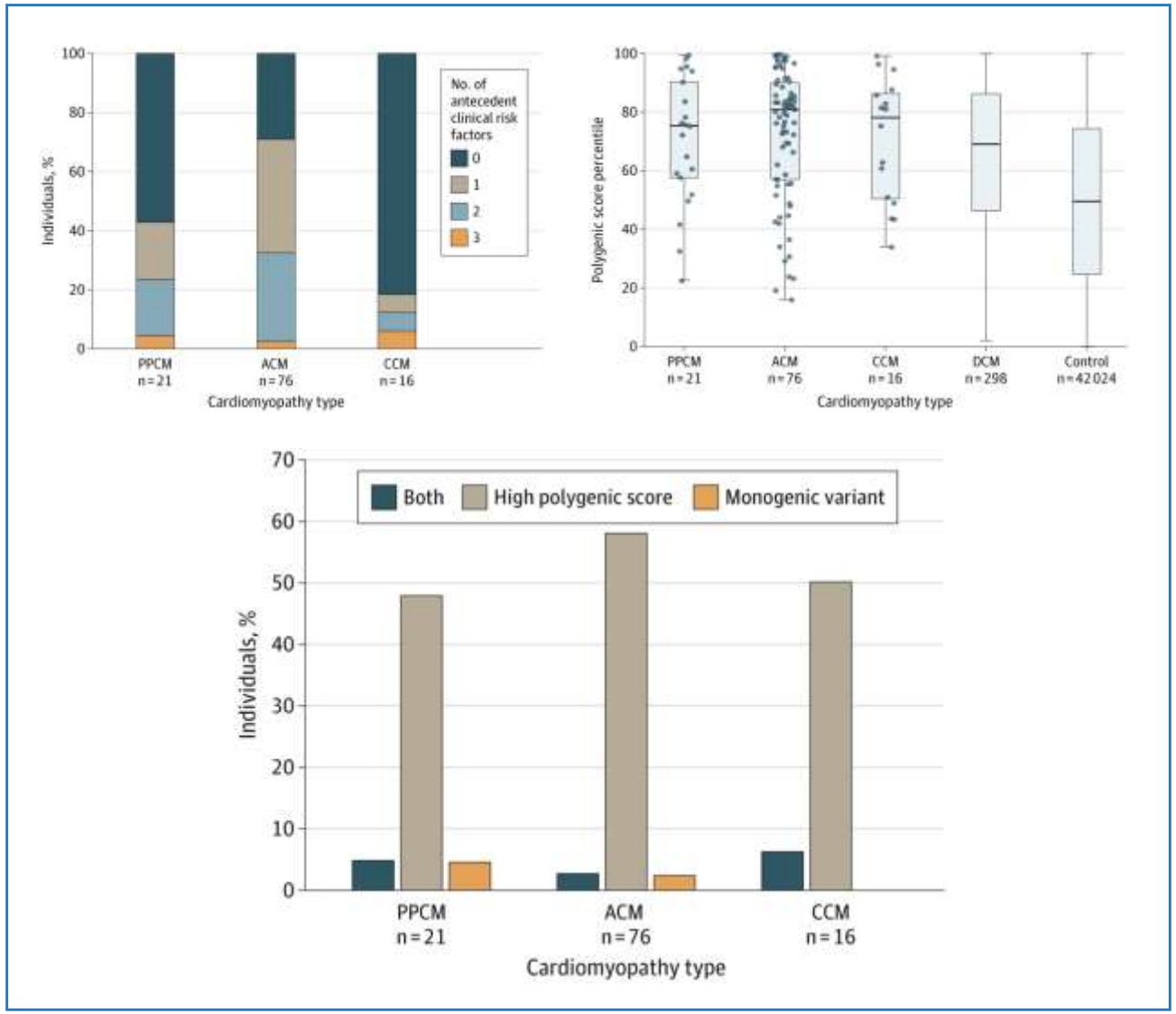
Biobank	Population	Control	OR (95% CI)	*P* value
MGB	76	42024	2.34 (1.41-3.88)	<.001
UK	74	295055	1.3 (1.08-1.72)	.01
FinnGen	125	417753	1.58 (1.05-1.48)	.01
MVP	2006	513067	1.65 (1.22-2.22)	<.001
Meta	2281	1267899	1.56 (1.34-1.82)	<.001



C CCM phenotype

Biobank	Population	Control	OR (95% CI)	*P* value
MGB	16	42024	2.19 (1.33-3.60)	.002
UK	29	295055	1.78 (1.22-2.61)	.003
FinnGen	65	417753	1.21 (0.95-1.54)	.001
MVP	953	513067	1.85 (1.28-2.67)	<.001
Meta	1063	1267899	1.64 (1.24-2.15)	<.001





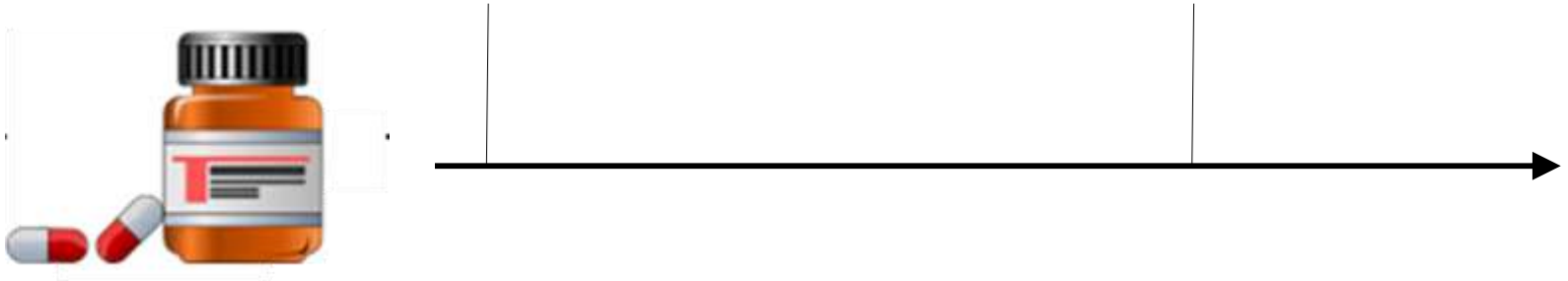
Maamari DJ et al. JAMA Cardiol. 2025;10:1138-46

	Genetic variants
CAVEATS	Most studies assessed a *cardiomyopathy* endpoint Key criteria: rigorous analytical flow; confirmation across different cohorts; functional validation
PROS	One-timepoint, lifelong information Cheap and easy (single gene seq, gene panel seq)
CONS	Costly and difficult to interpret (whole-exome seq, whole-genome seq) Evolving knowledge about P/LP rare genetic variants Implications of positive testing

2. (Circulating) biomarkers

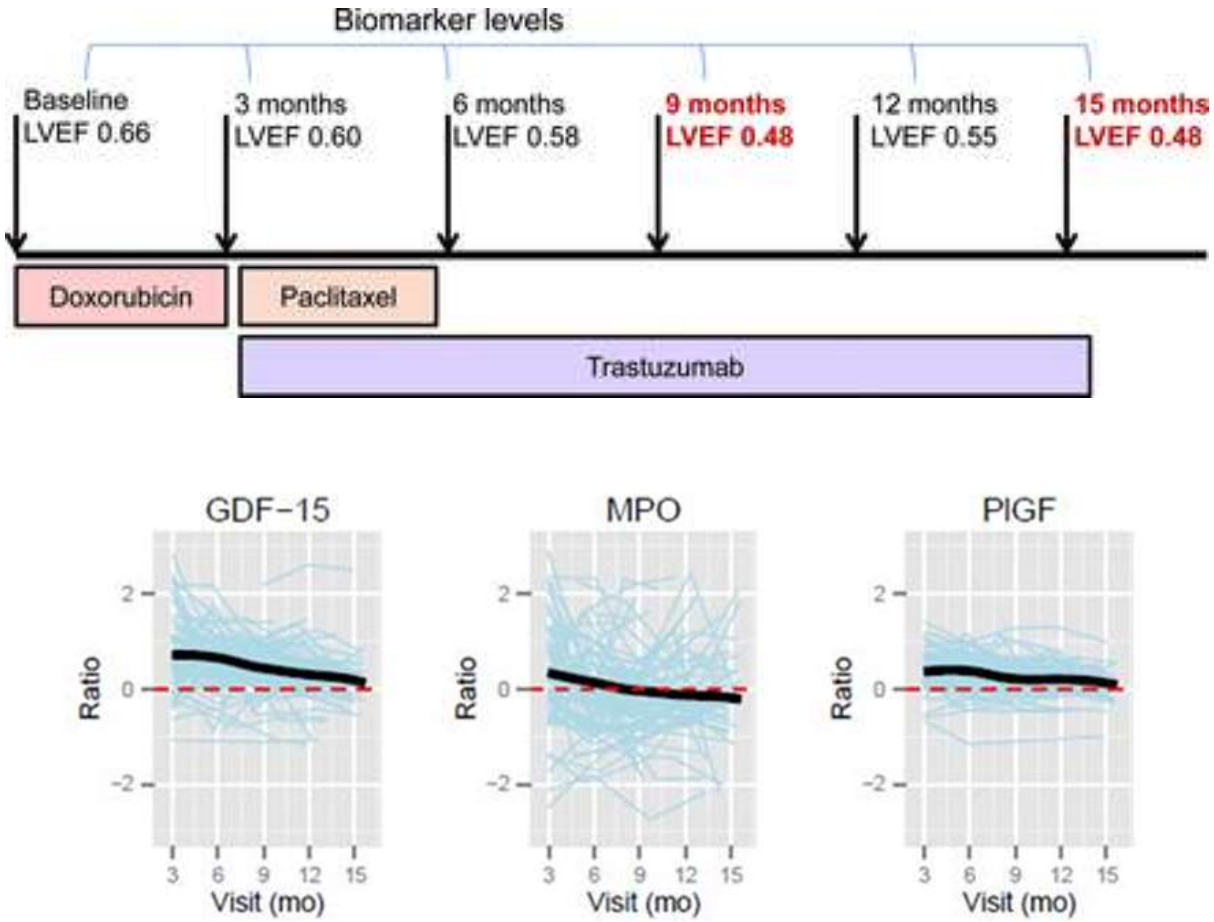
increased (or decreased) concentrations of biomarker X

change in the concentrations of biomarker X

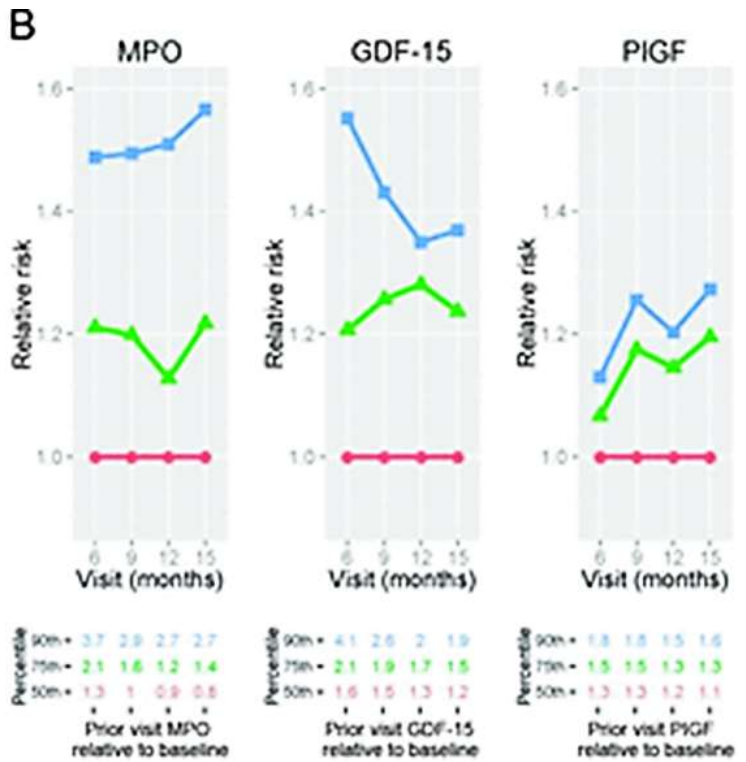


cancer treatment-related cardiac dysfunction

- 78 patients with HER2-positive breast cancer receiving anthracycline and cyclophosphamide followed by taxanes and trastuzumab
- 23 (24%) patients experienced 39 cardiotoxicity events, defined as a reduction in LVEF of ≥5% to <55% with HF symptoms or an asymptomatic reduction of LVEF of ≥10% to <55%



risk of cardiotoxicity at the subsequent 3-month visit



▲ 75th percentile
■ 90th percentile
● median

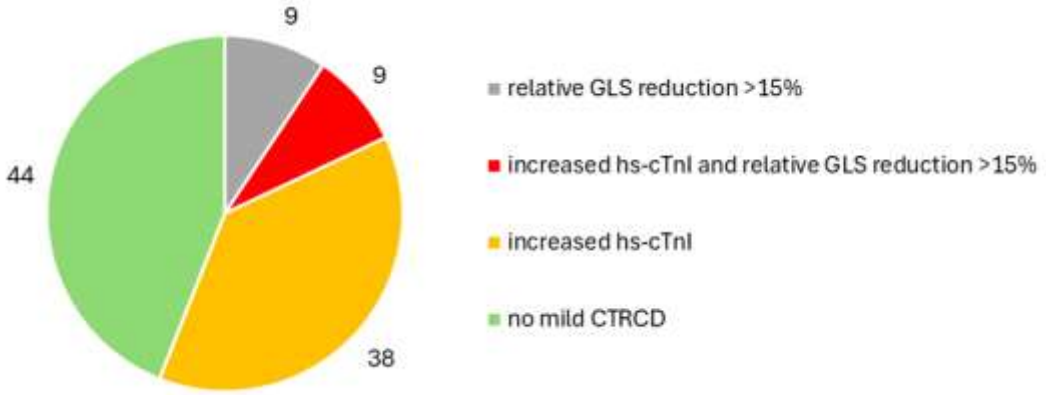
Putt M et al. Clin Chem. 2015;61:1164-72

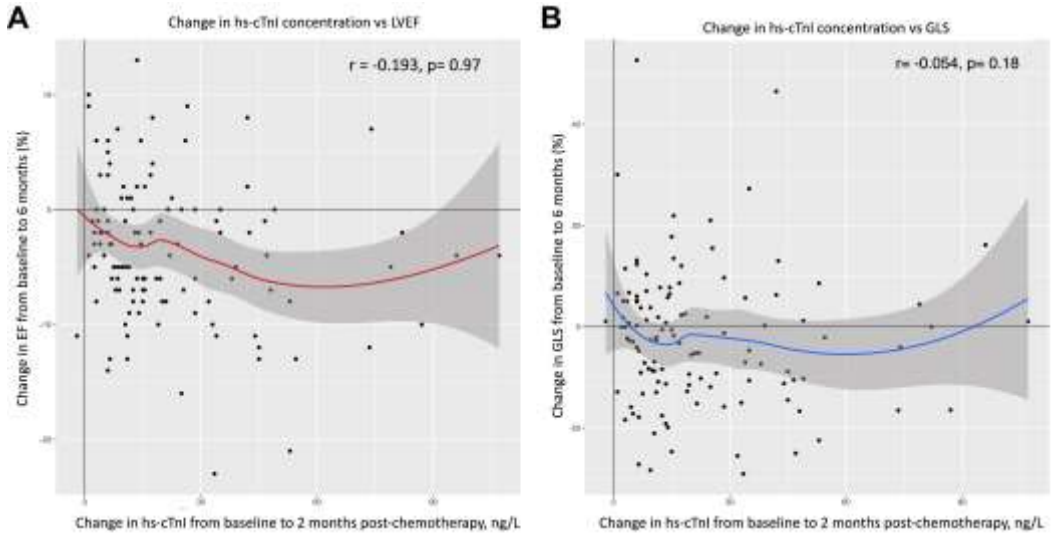
Biomarkers of cardiac injury

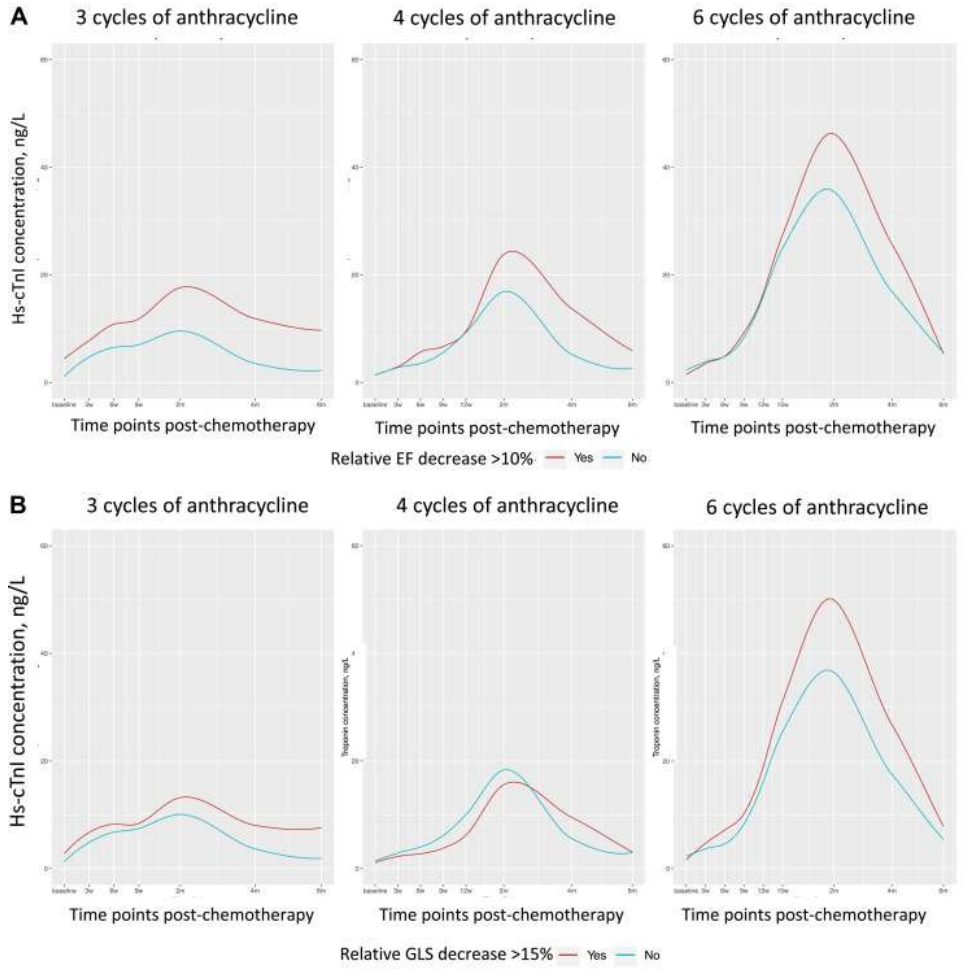
- ✓ Cardiac injury does not always entail cardiac dysfunction

Cardiac CARE trial

- Patients with breast cancer or non-Hodgkin lymphoma receiving anthracycline (cumulative epirubicin-equivalent dose <300 mg/m^2)
- CMR before and 6 months after completing chemotherapy
- hs-cTnI before each chemotherapy cycle and at 2, 4, and 6 months following treatment completion







Loganath K et al. JACC CardioOncol. 2025;7:725-35

Biomarkers of cardiac injury

✓ Cardiac injury does not always entail cardiac dysfunction

Biomarkers of pathways related to CTR-CVT

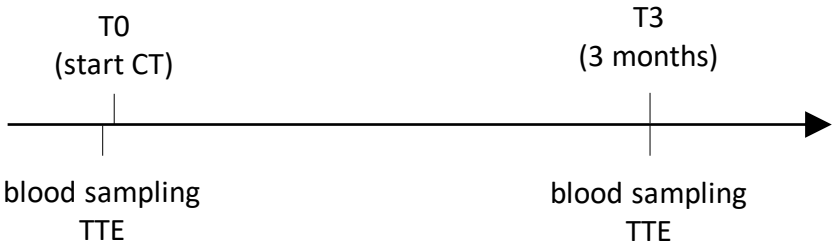
✓ Known or at least plausible pathophysiology for biomarker release/production, clear link with CTR-CVT

To which extent is the candidate biomarker released by non-CV tissues?

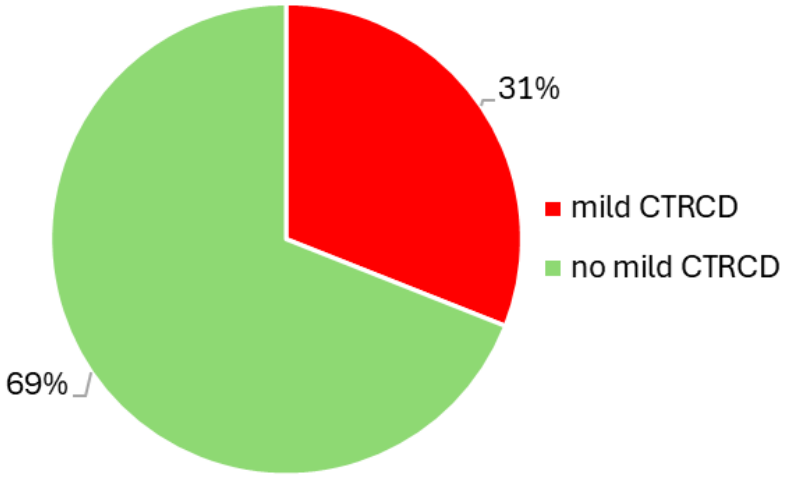
To which extent is it released in response to triggers other than CTR-CVT?

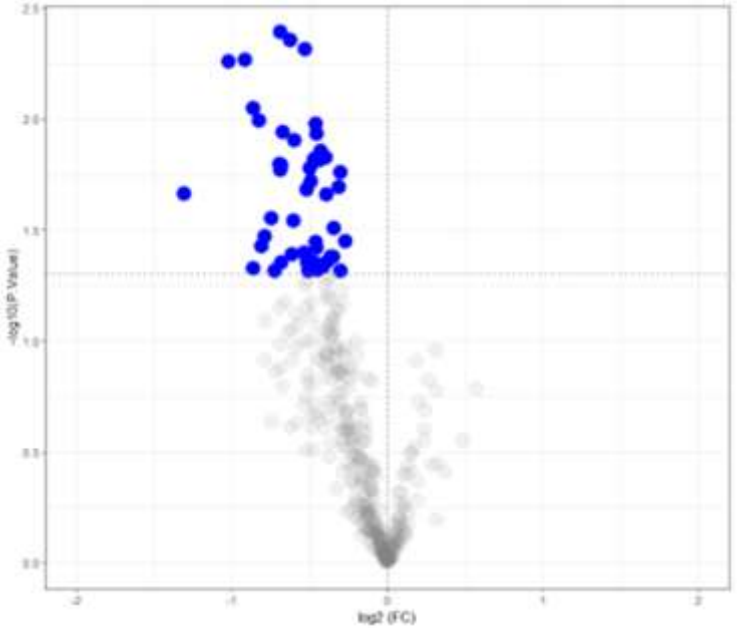
✓ Consider the presence of the tumor and the effects of treatments on it

Mueller C et al. Eur Heart J. 2023;44:301-3; Pudil R et al. Eur J Heart Fail. 2020;22:1966-83



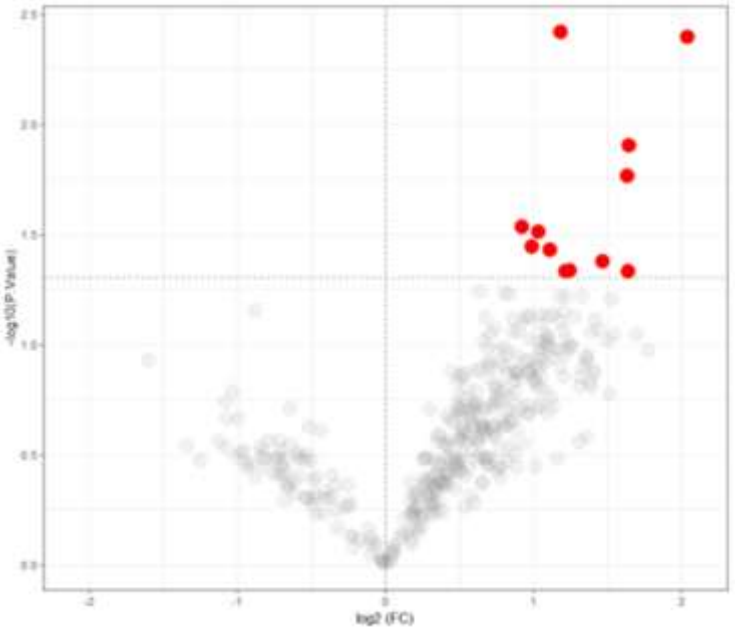
- 48 patients with breast cancer or lymphoma receiving anthracycline
- median age 48.0 (39.8-57.5) years old, 25% male





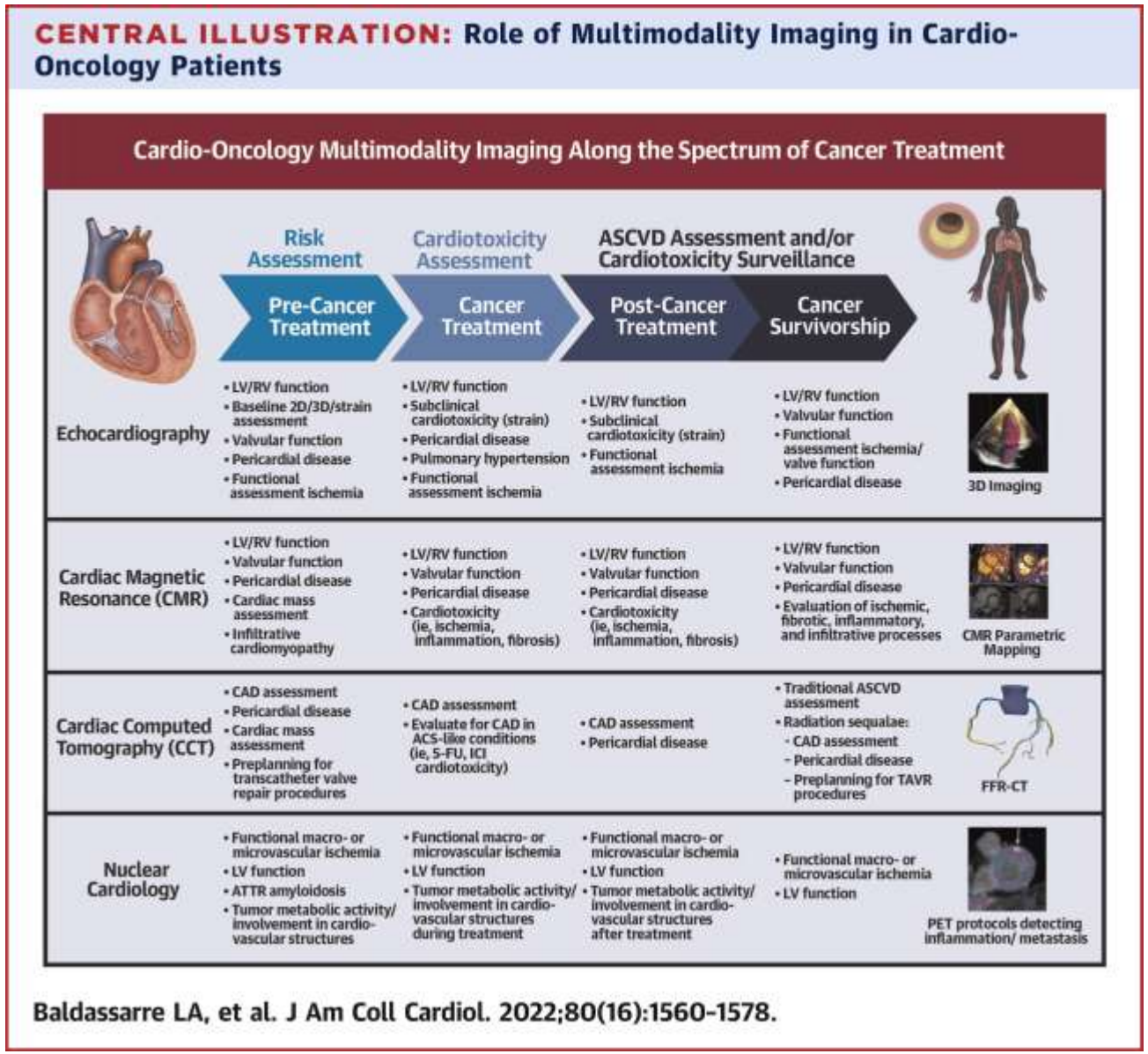
baseline

3 months



	Genetic variants	Biomarkers
CAVEATS	Most studies assessed a *cardiomyopathy* endpoint Key criteria: rigorous analytical flow; confirmation across different cohorts; functional validation	Most studies assessed surrogate endpoints (hsTn/BNP, GLS, LVEF) Key criteria: objectivity, reproducibility, defined normal ranges; strong causal association with CTR-CVT
PROS	One-timepoint, lifelong information Cheap and easy (single gene seq, gene panel seq)	Cheap and easy, even when assessed at multiple timepoints
CONS	Costly and difficult to interpret (whole-exome seq, whole-genome seq) Evolving knowledge about P/LP rare genetic variants Implications of positive testing	Predictive performance may vary over time

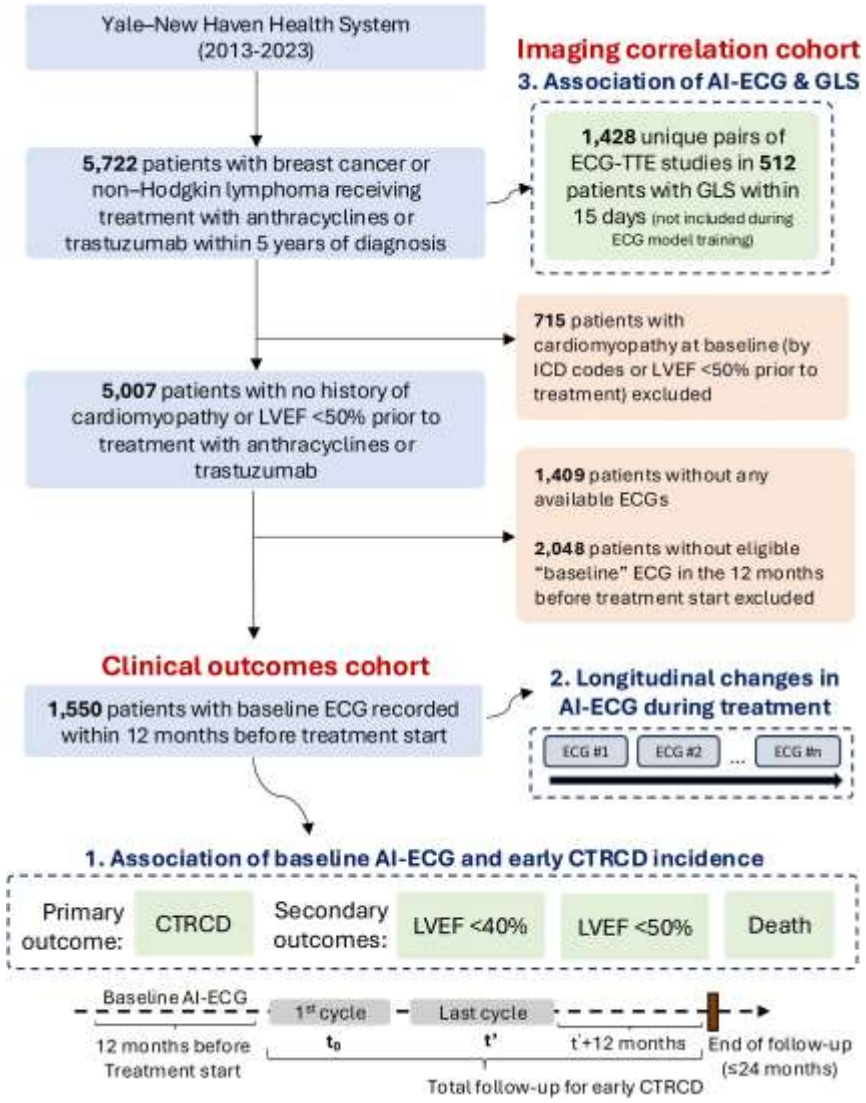
3. Imaging

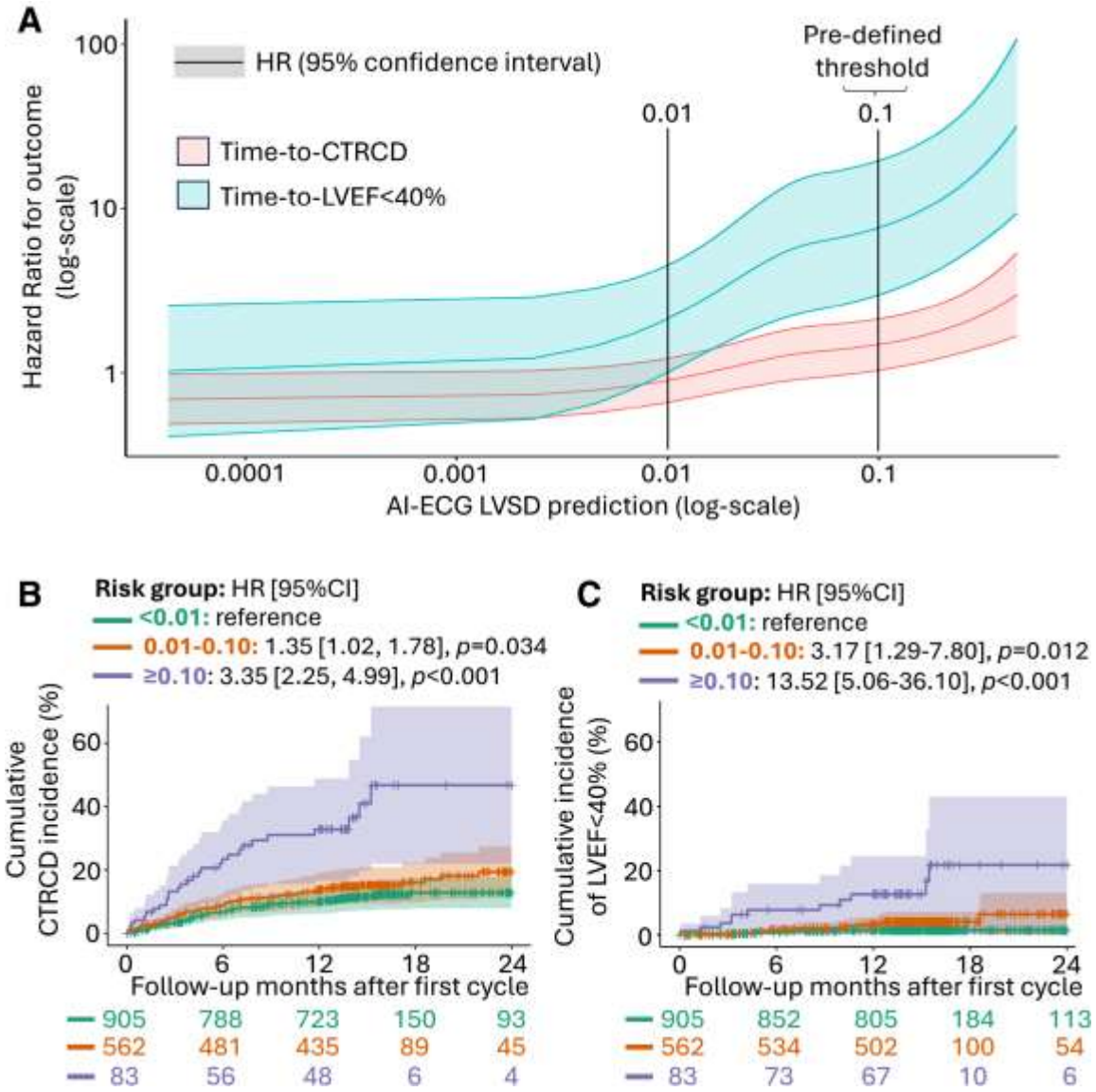


Baldassarre LA, et al. J Am Coll Cardiol. 2022;80(16):1560-1578.

Opportunistic use of imaging data to stratify the risk of CTR-CVT

- ✓ ECG (!)
- ✓ 18F-FDG PET/CT
- ✓ CT myocardial extracellular volume
- ✓ …



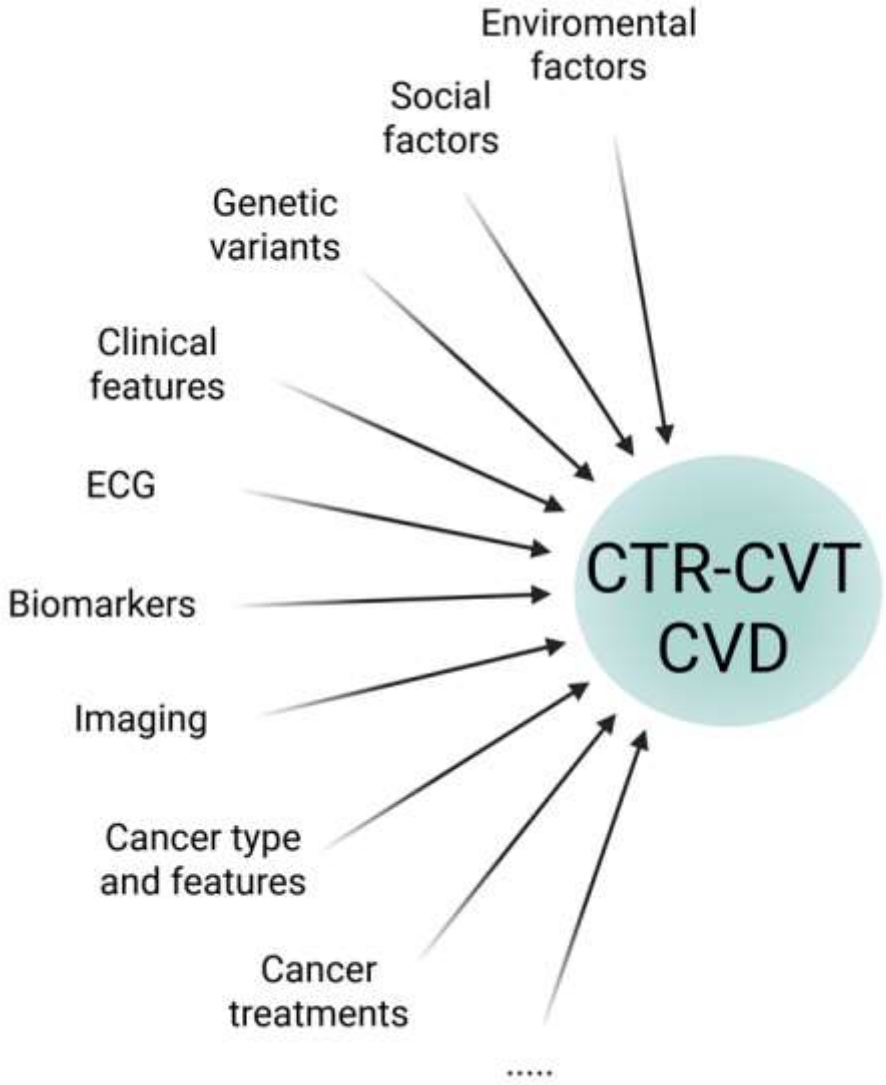


CTRCD = LVEF <50%, cardiomyopathy, or HF

Oikonomou EK et al.
Circ Cardiovasc Qual Outcomes. 2025;18:e011504

	Genetic variants	Biomarkers	ECG and imaging
CAVEATS	Most studies assessed a *cardiomyopathy* endpoint Key criteria: rigorous analytical flow; confirmation across different cohorts; functional validation	Most studies assessed surrogate endpoints (hsTn/BNP, GLS, LVEF) Key criteria: objectivity, reproducibility, defined normal ranges; strong causal association with CTR-CVT	Studies assessed various endpoints (clinical events vs surrogate imaging endpoints) Often retrospective design Key criteria: objectivity, reproducibility, normal ranges
PROS	One-timepoint, lifelong information Cheap and easy (single gene seq, gene panel seq)	Cheap and easy, even when assessed at multiple timepoints	Exploitation of data collected within clinical practice
CONS	Costly and difficult to interpret (whole-exome seq, whole-genome seq) Evolving knowledge about P/LP rare genetic variants Implications of positive testing	Predictive performance may vary over time	Reliance on specialist- or AI-guided assessment Ethical and/or practical concerns to perform additional imaging exams in cancer patients

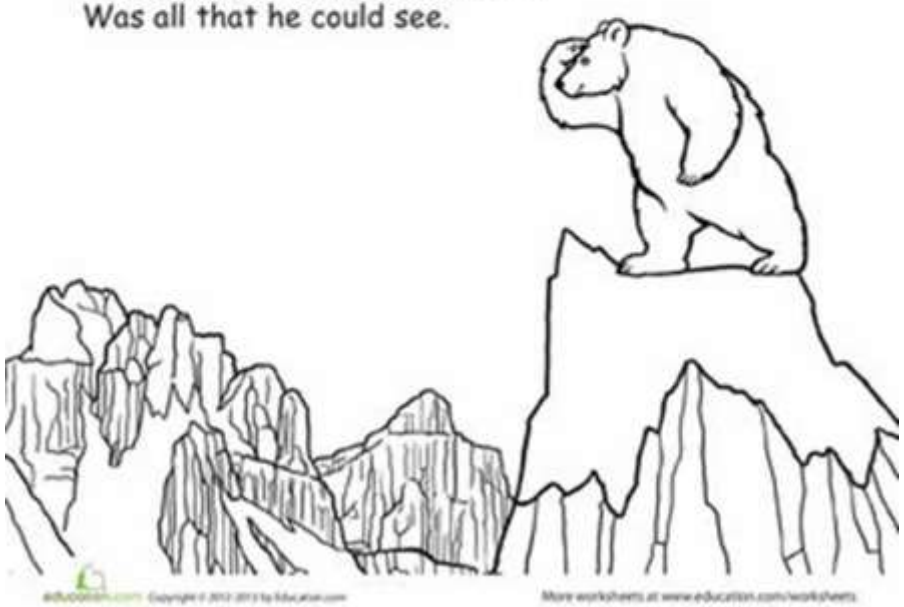
4. Artificial intelligence!

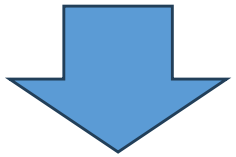


	AI-enhanced risk models
CAVEATS	The quality of input data is critical Key criteria: rigorous analytical flow; confirmation across different cohorts
PROS	Most comprehensive approach Operator independent Self-improving
CONS	Limited accessibility Costs Environmental concerns

The Bear Went Over The Mountain
(Sung to the tune of "For He's a Jolly Good Fellow")

The bear went over the mountain,
The bear went over the mountain
The bear went over the mountain,
To see what he could see.
And all that he could see,
And all that he could see
Was the other side of the mountain,
The other side of the mountain
The other side of the mountain,
Was all that he could see.





closer surveillance??
lower thresholds for starting CV medications??

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