Phenome-Wide Association Study of Echocardiographic Measures of Cardiac Structure and Function in the Penn Medicine BioBank

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Motivation

Problem:

- Quantitative echocardiographic measures are critical for assessing cardiac structure and function
- But, interpreting Echocardiograms (echos) are resource-intensive
- Models have been developed to automatically derive quantitative measures from echos
- But, the validity and robustness of these models are not well understood

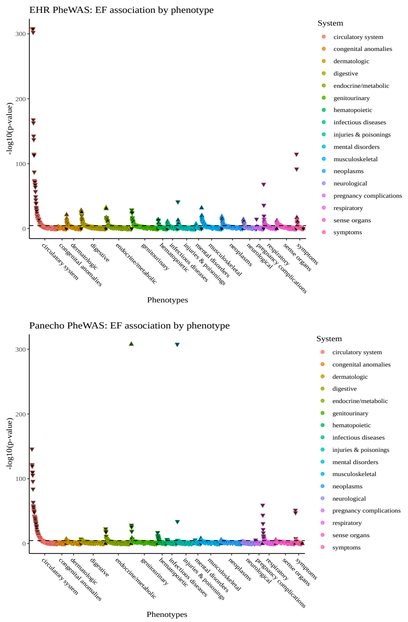
Objective: Use **PheWAS** to evaluate whether a **Deep Learning (DL) Approach** for reading echos effectively recapitulates echo-disease/phenotype associations observed with manually-derived echo variables

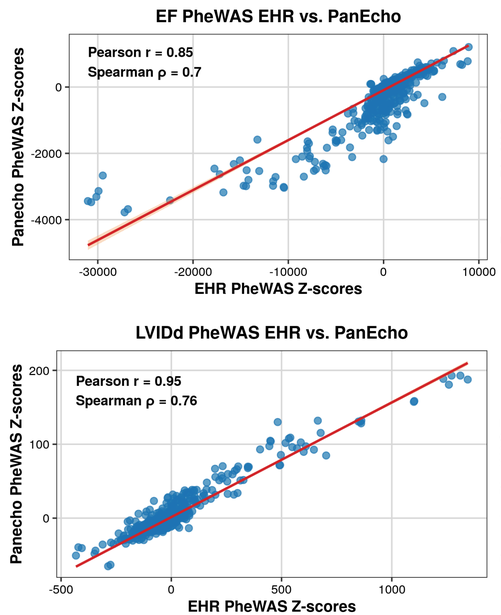
Novel Associations from PheWAS can also be discovered

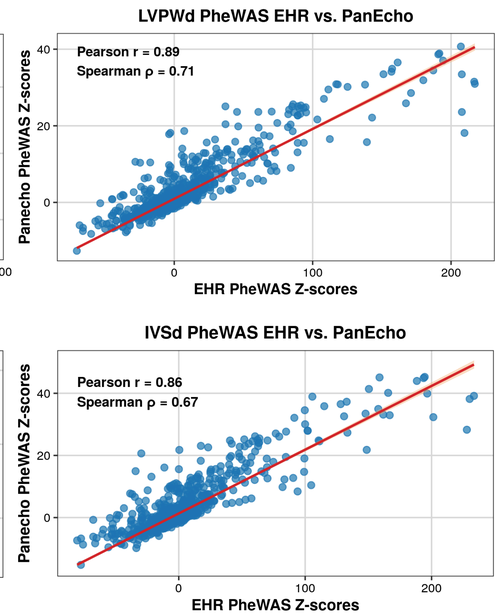
Solution: If PheWAS associations from DL-derived echo measures **mirror PheWAS associations** from electronic health record (EHR)-derived echo measures, we can **demonstrate robustness**

We use PanEcho (Holste et al., 2025) as the DL approach and EF, LVIDd, IVSd, and LVPWT as the echo measures

Results

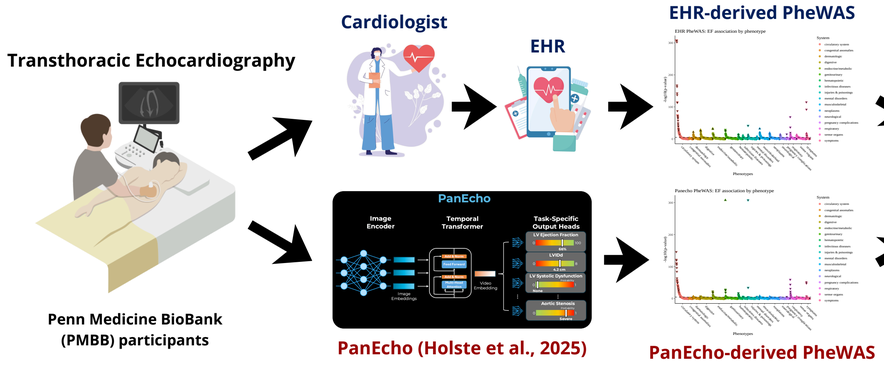






Quantitative Echo Measure	EHR-derived Significant PheWAS Associations (n = 19,079)	PanEcho-derived Significant PheWAS Associations (n = 4679)
Ejection Fraction (EF)	Heart failure with reduced ejection fraction (OR = 0.92, p <1E-300)	Heart failure with reduced ejection fraction (OR = 0.81, p <1.33E-146)
	Ventricular tachycardia (OR = 0.94, p <1E-300)	Paroxysmal ventricular tachycardia (OR = .88, p = 2.4E-106)
	Mitral valve disorders (OR = 0.98, p = 8.37E-58)	Heart valve disorders (OR = 0.94, p = 1.9E-33)
Left Ventricular Internal Diameter in end Diastole (LVIDd)	Cardiomyopathy (OR = 2.81, p = 5.06E-296)	Cardiomyopathy (OR = 7.26, p = 3.54E-85)
	Hypertensive heart disease (OR = 1.73, p = 3.59E-59)	Hypertensive heart disease (OR = 3.72, p = 5.02E-39)
	Arrhythmias (OR = 1.49, p = 3.25E-63)	Atrial fibrillation (OR = 2.63, p = 2.93E-29)
Interventricular Septal Thickness (IVSd)	Hypertrophic cardiomyopathy (OR = 415, p = 3.05E-125)	Hypertension (OR = 4750, p =2.9E-72)
	Hypertension (OR = 8.52, p =3.13E-109)	Cardiomegaly (OR = 398, p =6.56E-54)
	Aortic valve disorders (OR = 7.60, p = 1.64E-102)	Heart valve replaced (OR = 2.65, p = 5.6E-32)
Left Ventricular Posterior Wall Thickness (LVPWd)	Heart failure with preserved ejection fraction (OR = 13.3, p = 3.38E-96)	Heart failure with preserved ejection fraction (OR = 10500, p = 4.89E-54)
	Heart valve replaced (OR = 8.35, p = 8.27E-54)	Heart valve replaced (OR = 1380, p = 7.92E-28)
	Endocarditis (OR = 4.72, p = 3.82E-13)	Carditis (OR = 110., p = 7.11E-14)

Methodology



Discussion

Expected and novel associations between EHR-derived echo measurements and clinical phenotypes were observed. Results were **well-recapitulated** using PanEcho-derived measurements. Limitations include **selection bias** in who received echo and **reverse causality**; directionality of associations should be **interpreted cautiously**. Future work will leverage genotype data to investigate potentially causal associations using Mendelian randomization.

Notes:

- PheWAS significance assessed via Bonferroni correction (α = 0.05) after adjusting for age, sex, and 10 genetic principal components
- For EHR-derived analysis, average age was 55.2 years, 50% were female, and 69.3% had European (EUR) genetic ancestry
- For PanEcho-derived analysis, average age was 59.8 years, 47% were female, and 65.0% had European (EUR) genetic ancestry

References

Holste G, Oikonomou EK, Tokodi M, Kovács A, Wang Z, Khera R. Complete AI-Enabled Echocardiography Interpretation With Multitask Deep Learning. JAMA. 2025;334(4):306–318. doi:10.1001/jama.2025.8731

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