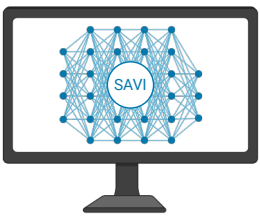
Supplemental Figure S1: Variant Annotation and curation workflow.
Whole-genome sequencing (WGS) data from All of Us participants were processed into a meta-level Variant Annotation Table (VAT). Variants were restricted to a predefined set of 22 ACMG cardiomyopathy-associated genes and prioritized for potential reportability using the internally developed and validated Semi-Automated Variant Interpretation (SAVI) software. Prioritized variants underwent manual review and confirmation of classification using the SAVI user interface. Clinical phenotypes were ascertained through linked electronic health record (EHR) data using International Classification of Diseases, Ninth and Tenth Revision (ICD-9/10), and Current Procedural Terminology (CPT) codes. Curated genetic variants were subsequently correlated with cardiac phenotypes in variant carriers.

All of Us
Participants with WGS data
(n = 414,830)

Meta-level Variant Annotation Table (VAT)

Subset with Genes of Interest
(22 ACMG Cardiomyopathy-related genes and variants)

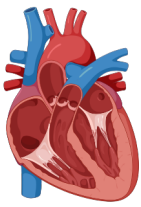


Potentially reportable variants prioritized by the SAVI software

Manual curation of prioritized variants by SAVI-UI to confirm classification

EHR

Clinical phenotype: ICD 9/10 and CPT codes*



Identification of clinical phenotypes in participants with curated reportable variants

Correlation of P/ LP variants with clinical phenotypes