

## **Breakout Session 7:**

# **Development of a Cloud-based Analytical Tool for Polygenic Risk Score and its Implication in Heart Failure Research**

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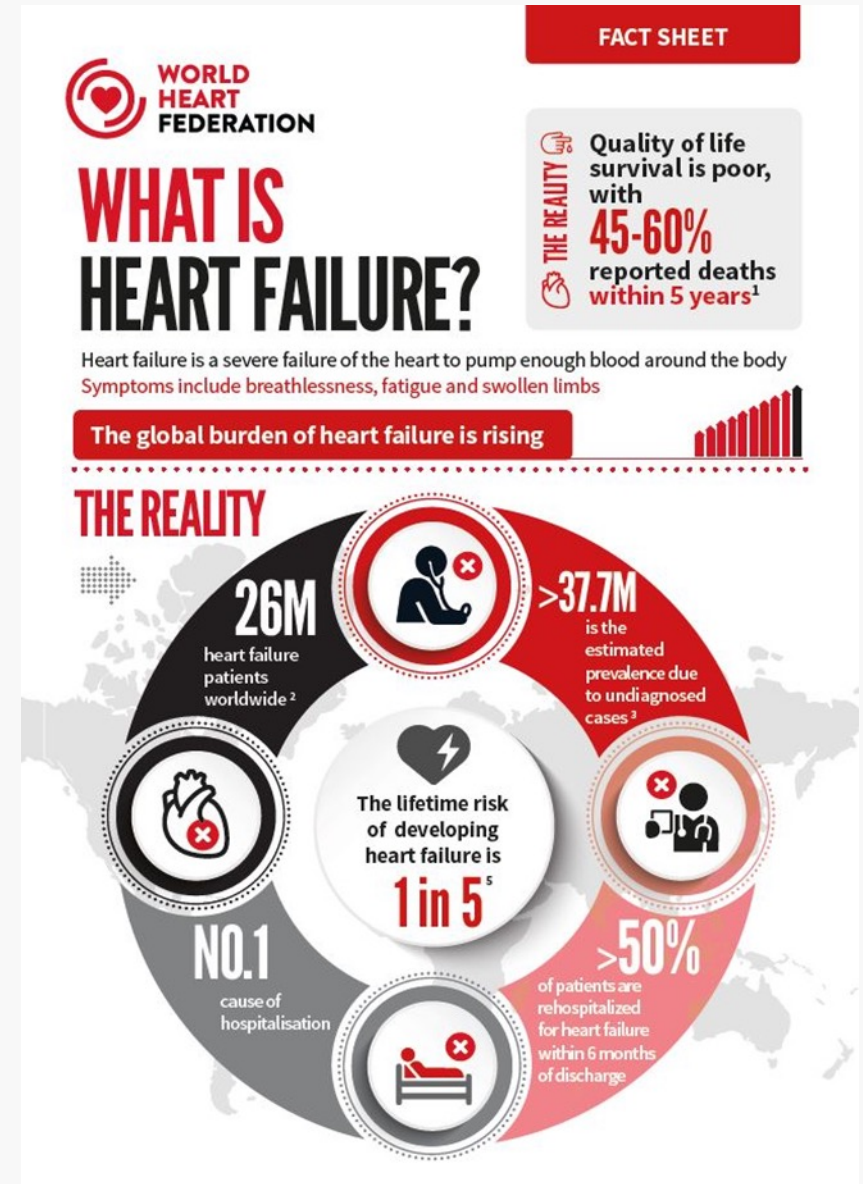
# DEVELOPMENT OF A CLOUD-BASED ANALYTICAL TOOL FOR POLYGENIC RISK SCORE AND ITS IMPLICATION IN HEART FAILURE RESEARCH

Tamar Sofer, PhD & Bing Yu, PhD

Jan 17<sup>th</sup> - 18<sup>th</sup>, 2024

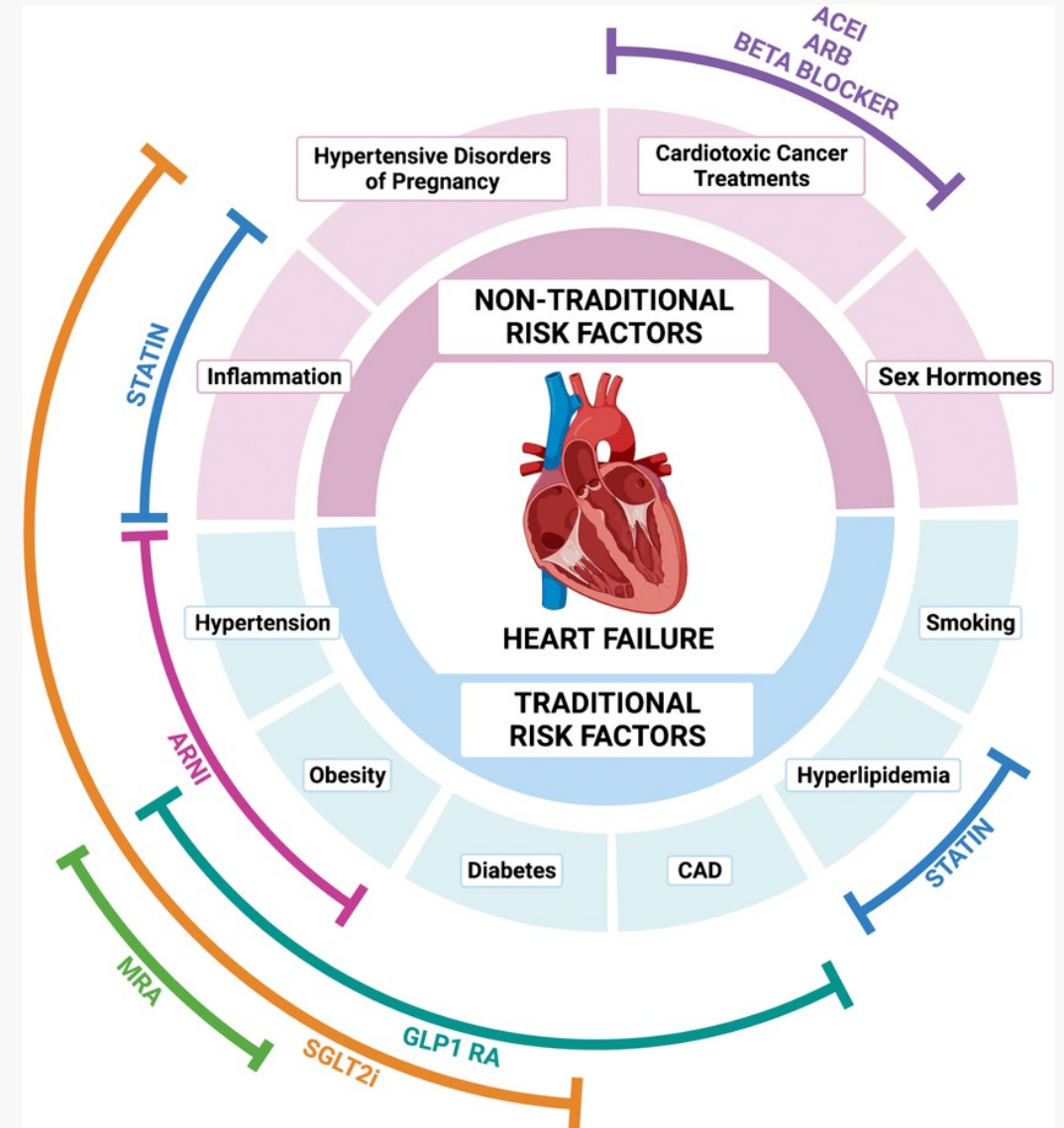
# Heart Failure

- Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.
- HF is common, affecting more than 6 million American Adults.
- Lifetime risk of developing HF is 1 in 5.
- 5-year survival rate of HF is around 50%.

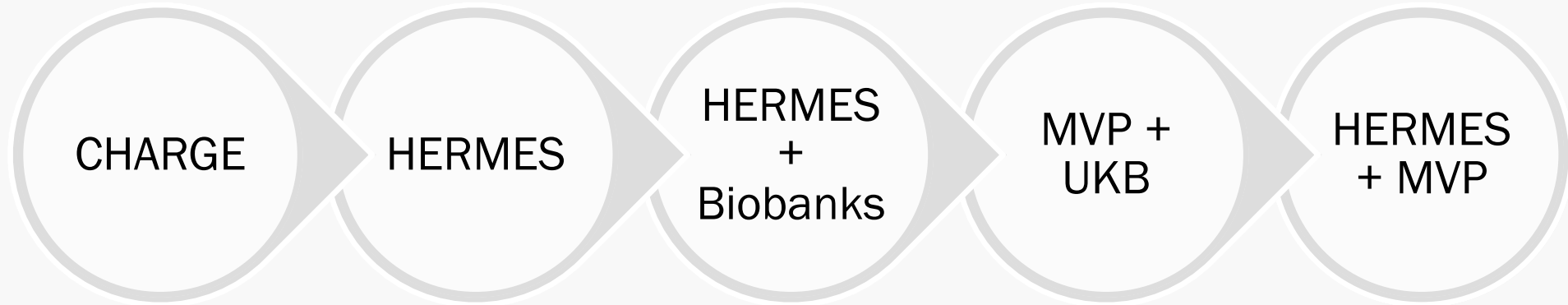


# Clinical Risk Factors

- Age
- Smoking
- Hypertension (HTN)
- Coronary heart disease (CHD)
- Obesity
- Type 2 Diabetes (T2D)
- Atrial Fibrillation (AF)
- Genetics



# Genome-wide Association Studies on Heart Failure



Smith, 2010  
N = 20,926  
# loci = 2

Shah, 2020  
N = 977,323  
# loci = 12

Levin, 2022  
N = 1.7 millions  
# loci = 47

Joseph, 2022  
N = 690,302  
# loci = 20

Rasooly, 2023  
N = 1.3 millions  
# loci = 18

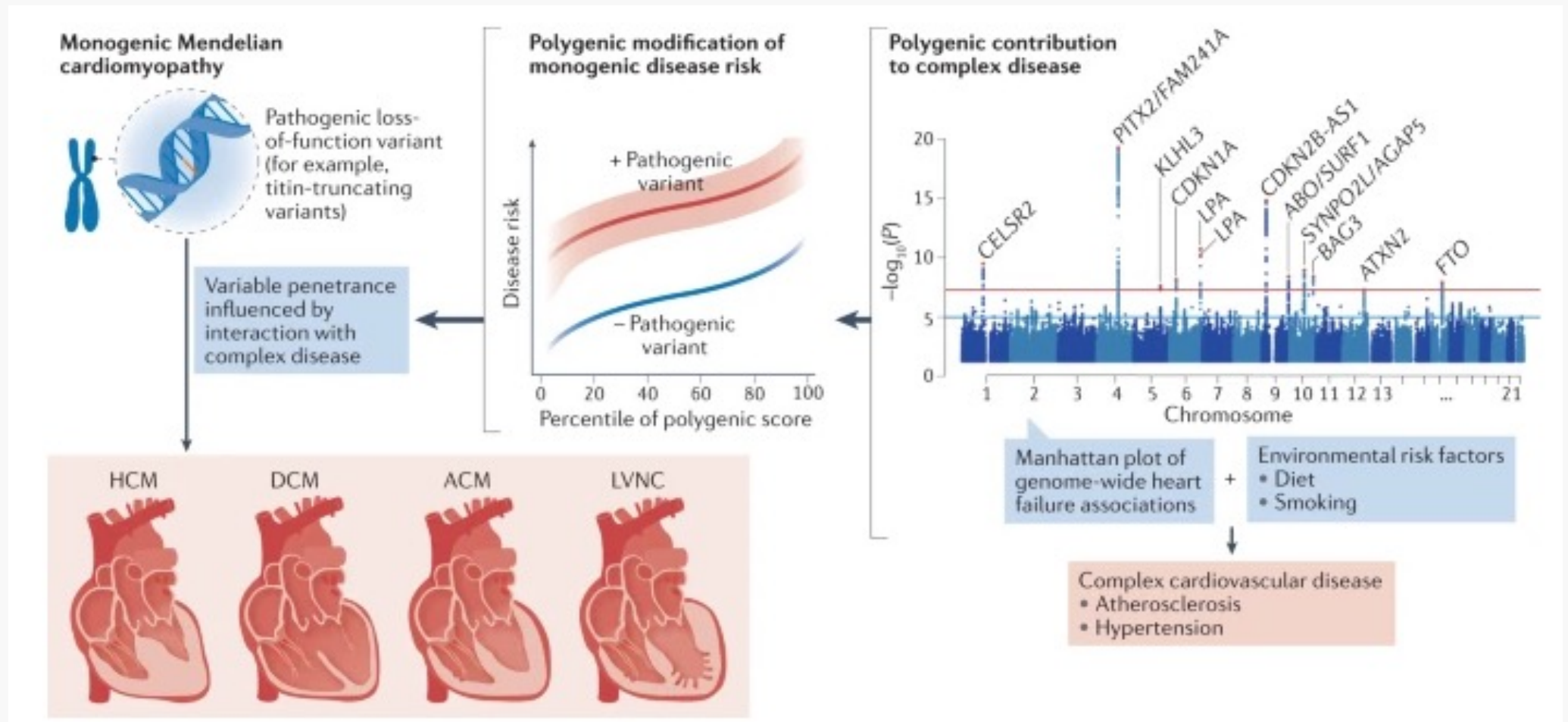
*CHARGE: the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium*

*HERMES: the Heart Failure Molecular Epidemiology for Therapeutic Targets Consortium*

*UKB: UK Biobank*

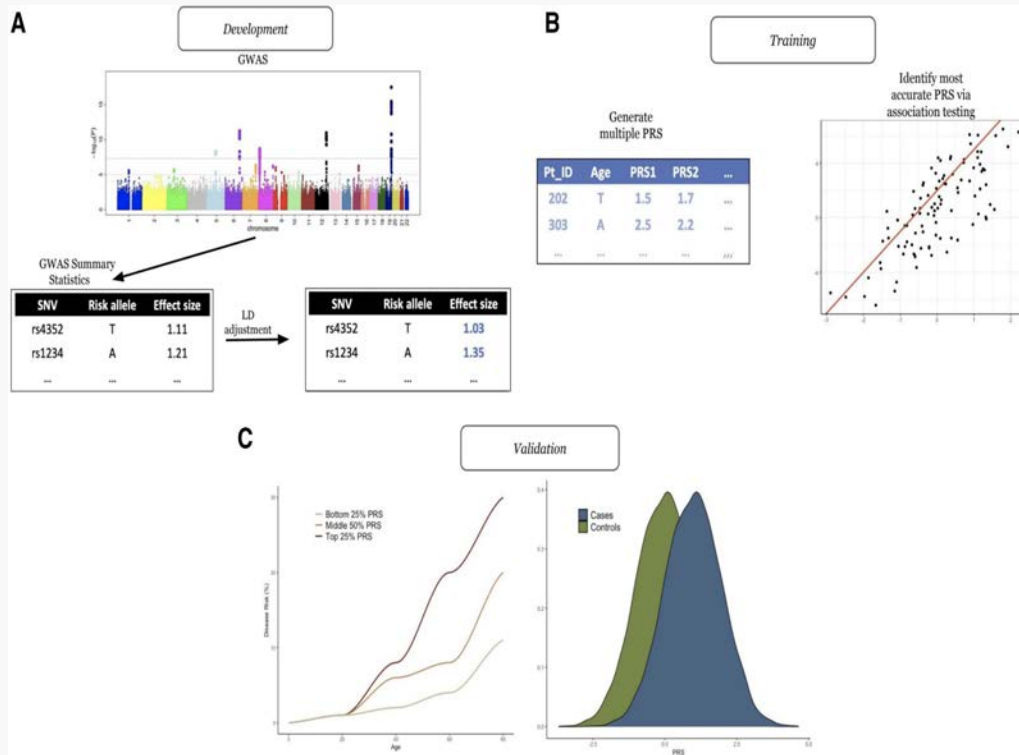
*MVP: Million Veteran Program*

# From Mendelian to Complex Disease in Heart Failure



# Polygenic Risk Score

Development of a PRS

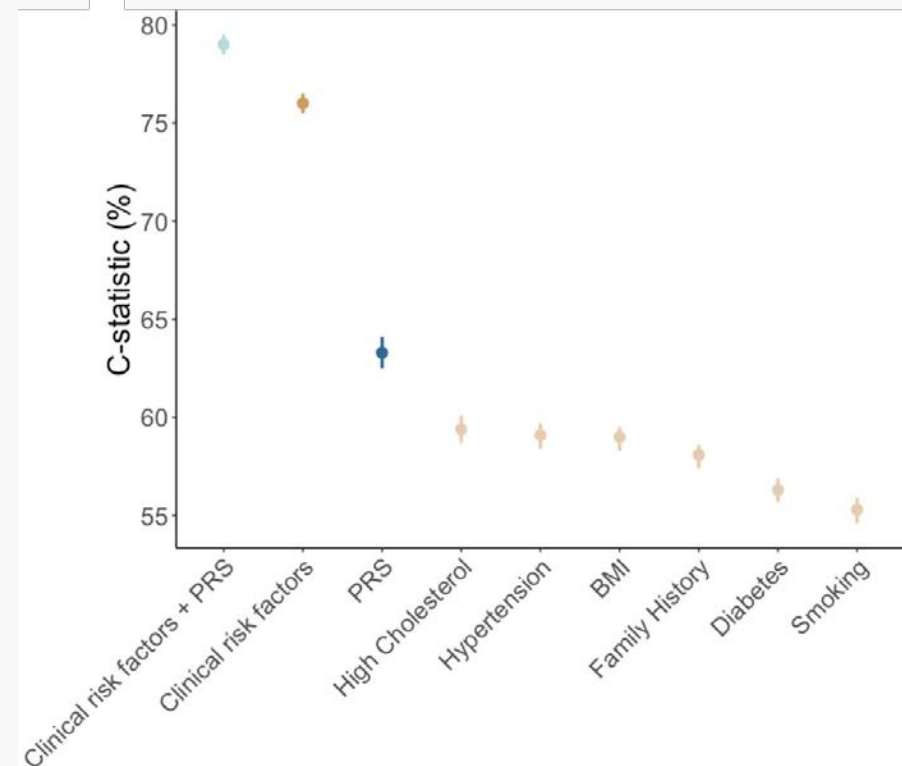


O'Sullivan, Circulation. 2022

## AHA SCIENTIFIC STATEMENT

### Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association

Predictive ability of PRS for coronary artery disease



# Goal of Our Supplement

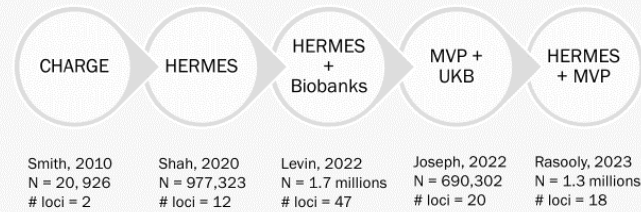
- **Aim 1: Develop a PRS construction and analyses tool on BDC Seven Bridges.** We hypothesize that a cloud-based PRS tool expedite PRS construction and performance testing. This tool can easily leverage existing GWAS summary data and genetic data on BDC. It will facilitate non-expert use of PRS software and procedures, as well as promote collaboration between researchers with appropriate access in multiple institutions.
- **Aim 2: Construct PRS of HF and assess its impact on the risk of HF.** We hypothesize that high PRS of HF is associated the increased risk of HF and improves HF prediction. Utilizing the tool built on BDC, we will construct a series of PRS using HF GWAS summary data and validate its performance. We will examine the association, as well as predictive utility of PRS for HF by leveraging data from the parent award.



# Work Environment

## Aim 1

### Genome-wide Association Studies on Heart Failure



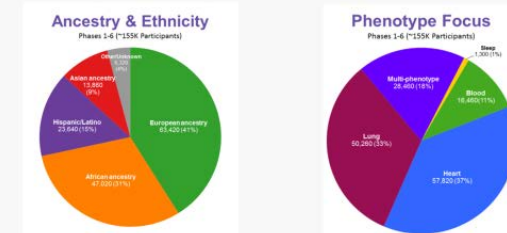
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## Aim 2

### The TOPMed Program

Trans-Omics for Precision Medicine (TOPMed) program: sponsored by the National Institutes of Health (NIH) National Heart, Lung and Blood Institute (NHLBI), is part of a broader Precision Medicine Initiative, which aims to provide disease treatments tailored to an individual's unique genes and environment.

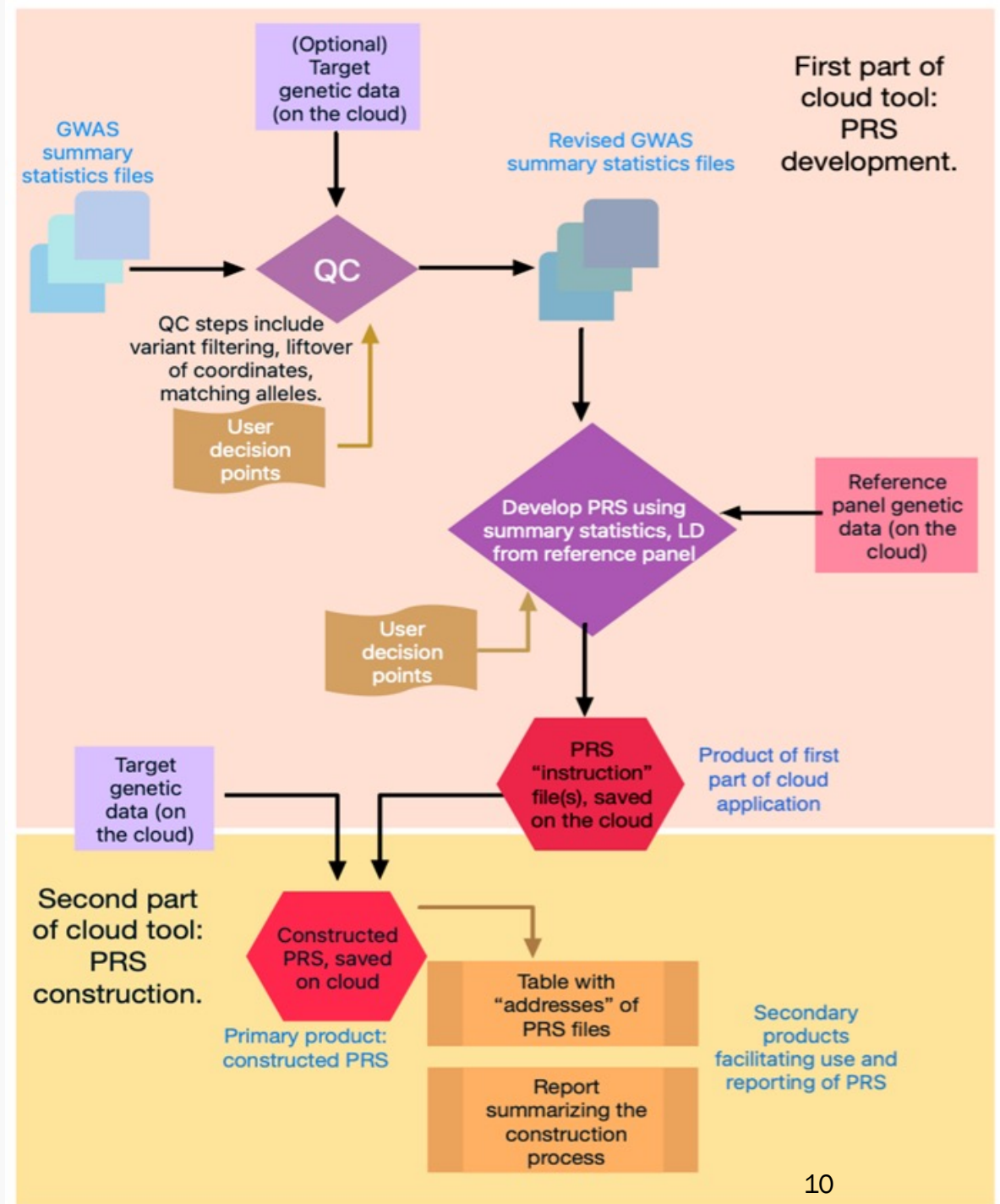


<https://www.nhlbiwgs.org/>

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# Proposed Workflow

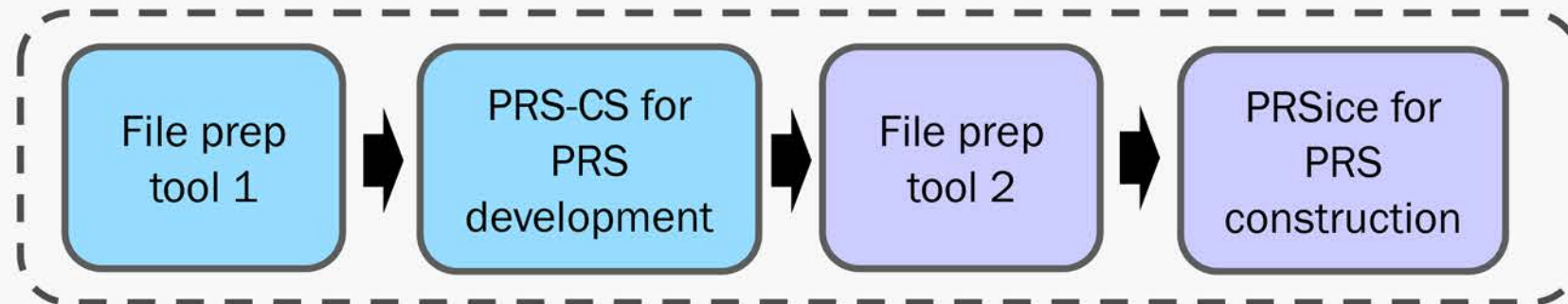
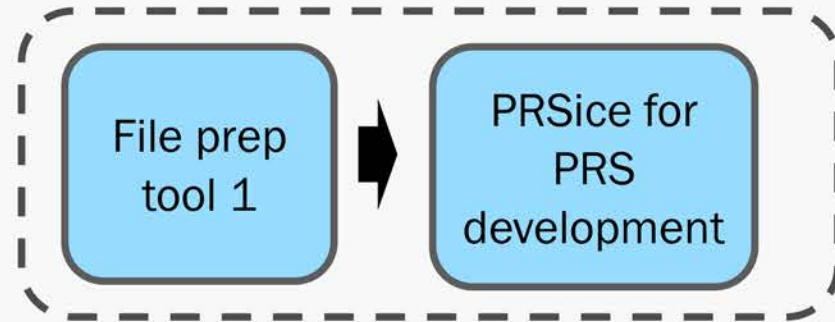
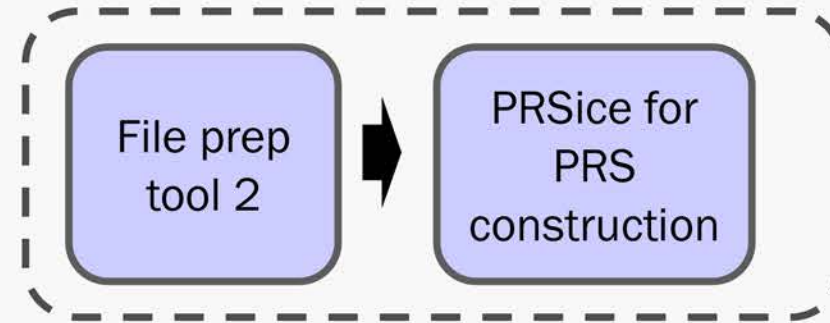
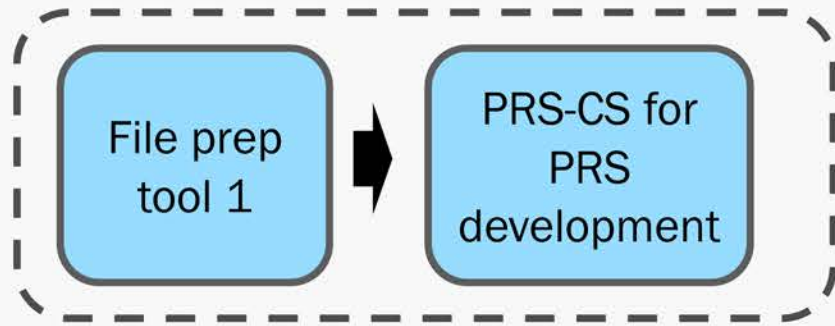
- PRSs need to be **developed**, and **constructed**.
- Development process:
  - Use summary statistics from GWAS, reference panel for linkage disequilibrium (correlation between genetic variants), and software.
  - Result: set of genetic variants, alleles, and weights ["PRS instructions"].
- Construction process:
  - Use "PRS instructions", "target" genetic data, and build PRS as a weighted sum of alleles.



# Cloud Implementation

- We plan to use the Seven Bridges platform.
- PRS development:
  - *Multiple potential software/methods. We are planning to use three.*
    - One "tool" per PRS software.
- PRS construction:
  - *One tool.*
- Both PRS development and PRS construction steps may need to use "data preparation" tools.
  - *E.g. genomic coordinates "lift over".*
- Workflow:
  - *Connect multiple tools.*
  - *Currently: we plan to create multiple workflows to limit the number of parameters that the users has to set.*

# Planned workflows (examples)



# Acknowledgements

- ❖ NIH/NHLBI
- ❖ The TOPMed program
- ❖ The participating studies and participants
- ❖ Investigators at UTHealth Houston and Beth Israel Deaconess Medical Center (BIDMC)

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