Risk prediction to prescribe a life-long personalized screening program, including age to start and frequency

Ulrike Peters
Fred Hutchinson Cancer Center
University of Washington

Li Hsu,
Professor at Fred Hutchinson Cancer Center

Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO)

A growing resource

- 80+ studies
  - CCFR and CORECT
- 150,000+ participants with genetic, clinical, epidemiologic & lifestyle data
- 3,000 participants with whole genome sequencing data
- 30,000+ patients with extended clinical and survival data
- 15,000+ patients with tumor characteristics data
- 7,000 patients with tumor sequencing data

R01-CA059045, U01-CA137088, U19-CA148107, U01-CA164930, R01-CA176272, U01-CA185094, R01-CA201407, R01-CA206279 , R21-CA230486
X01-HG006196, X01-HG006662, X01-HG007585, X01HG009781, JUNO Therapeutics, R01-CA244588, R01-CA248857, R01-CA273198, R01-CA276306

Heritable and Environmental Contributions in Common Cancers

Cancer Site	Heritable Factors	Environmental Factors	
		Shared	Non-shared
Prostate	0.42 (0.29-0.50)	0 (0-0.09)	0.58 (0.50-0.67)
Colorectal	**0.35 (0.10-0.48)**	**0.05 (0-0.23)**	**0.60 (0.52-0.70)**
Bladder	0.31 (0.00-0.45)	0 (0-0.28)	0.69 (0.53-0.86)
Breast	0.27 (0.04-0.41)	0.06 (0-0.22)	0.67 (0.56-0.76)
Lung	0.26 (0.00-0.49)	0.12 (0-0.34)	0.62 (0.51-0.73)

Scandinavian Twin Registry, Lichtenstein et al. 2000, *New Engl J Med*

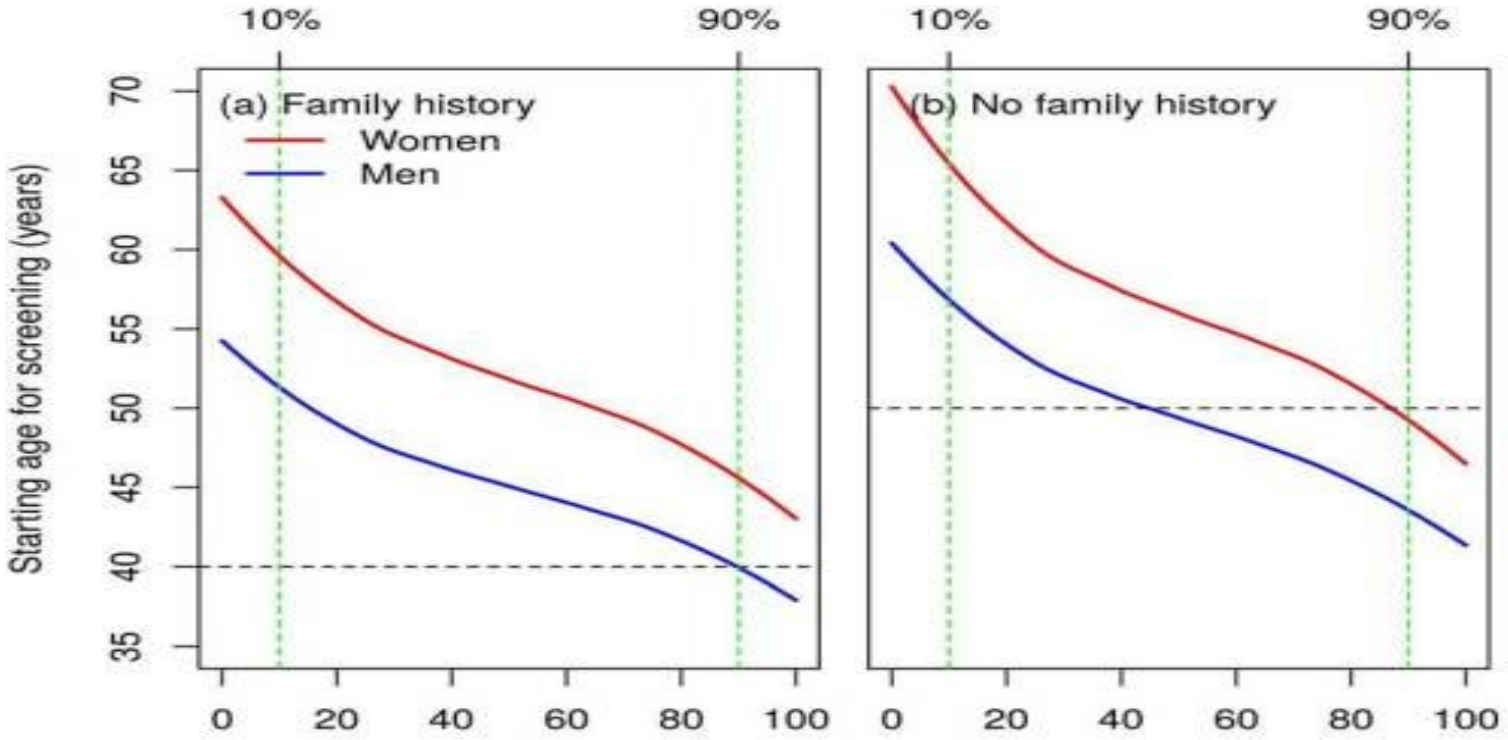
Risk Prediction of Colorectal Cancer using Environmental and genetic risk factors

	Male (N=4666)	Female (N=5500)
	OR (95% CI)	OR (95% CI)
Environmental risk score (ERS, **quartile**)	1.36 (1.29 to 1.44)	1.35 (1.28 to 1.42)
Polygenic risk score (PRS, **quartile**)	1.34 (1.27 to 1.42)	1.30 (1.23 to 1.36)
Fam Hx	1.67 (1.38 to 2.03)	1.46 (1.24 to 1.72)
Endoscopy Hx	0.29 (0.24 to 0.34)	0.53 (0.47 to 0.61)

- Environmental risk score: height, BMI, education, type 2 diabetes, smoking, alcohol, aspirin, NSAIDS,
- HRT, dietary intake physical activity
- Polygenic risk score (PRS): 63 genetic variants

Jeon et al. 2018, *Gastroenterology*

Environmental and Polygenic Risk Score can inform the Starting age of CRC Screening



Screening age

		Men	Women
RS	1%	55	64
	10%	51	59
	50%	45	52
	90%	40	46
	99%	38	43

Screening age

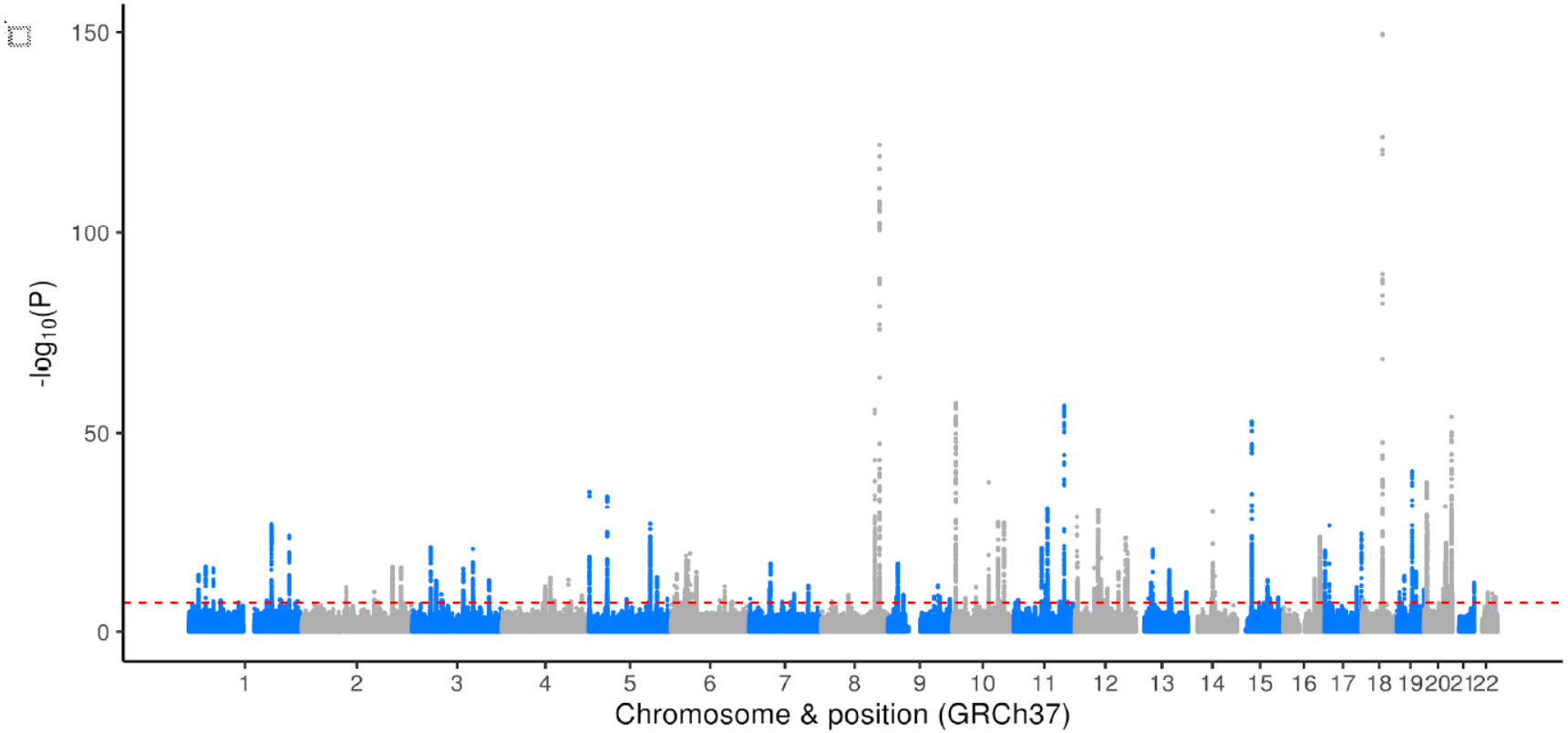
		Men	Women
RS	1%	61	71
	10%	56	64
	50%	49	56
	90%	44	50
	99%	41	46

Jeon et al. 2018, *Gastroenterology*

Genome-wide Association Study Suggests More Genetic Variants Contribute to Risk Prediction of Colorectal Cancer

Genome-wide association testing including >100,000 CRC cases and 150,000 CRC controls

Manhattan plot (each dot is one genetic variants we tested >1M genetic variants)



Fernandez-Rozadilla et al. *Nat Genetics* 2023

Polygenic Risk Score Using Genome-wide Scan Data and Machine Learning Methods

- Training
  - *55,105 cases and 65,079 controls*
- Validation
  - *2,300 cases and ~140,000 controls*
- Analysis limited to non-Hispanic White study participants

Thomas, et al. 2020, *Am J Hum Genet*

Genome-wide Data Improve Performance of Polygenic Risk Score (Results from Independent Validation)

Approaches	# Variants	AUC (95% CI)
Known variants	140	**0.615** (0.600-0.615)
Selection + Machine Learning	10,000	**0.621** (0.606-0.636)
LDpred (Machine Learning)	1,180,765	**0.640** (0.628-0.656)

Thomas, et al. 2020, *Am J Hum Genet*

Inclusion of Asian Genome-wide Scan Data in Polygenic Risk Score Development

- **Training**
  - *Non-Hispanic White* ***(78,473 cases and 107,143 controls)***
  - ***Asian (21,731 cases and 47,444 controls)***

- **Validation**
  - *Asian (3,651 cases and 115,105 controls)*
  - *Black/African American (1,954 cases and 11,869 controls)*
  - *Hispanic (1,681 cases, 8,696 controls)*
  - *Non-Hispanic White (1,954 cases and 11,869 controls)*

Thomas, …, Peters, Hsu (2022, Nature Comm)

Inclusion of Asian Genome-wide Scan Data improves performance of Polygenic Risk Score most in Asian and Hispanic people

Race/Ethnicity	AUC Euro-centric PRS	AUC Asia-Euro PRS
Asian	0.59 (0.57-0.60)	**0.63 (0.62-0.64)**
Black or African - American	0.58 (0.56-0.59)	**0.59 (0.57-0.61)**
Latinx/Hispanic	0.59 (0.57-0.61)	**0.62 (0.60-0.63)**
Non-Hispanic White	0.63 (0.62-0.64)	**0.64 (0.63-0.65)**

Thomas et al. 2022, Nature Comm

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Things to consider

Use of genetic risk prediction as early detection vs. risk stratification tool

- *Risk stratification* aims to identify high-risk individuals who can benefit from earlier and/or more frequent screening
  - Polygenic risk score (PRS) only needs to be measured once (could be at birth)

- *Early detection* aims to detect precursor or early-stage disease
  - Biomarkers usually require repeated measurements over defined time intervals close to disease onset
  - As a result, the sensitivity and specificity of early detection biomarkers need to be high for them to be effective

Family history and Polygenic Risk Score (PRS) Provide Complementary Information

- >80% of CRC patients do not have a positive family history

- Family history AUC ~0.54
- Best PRS AUC ~0.64

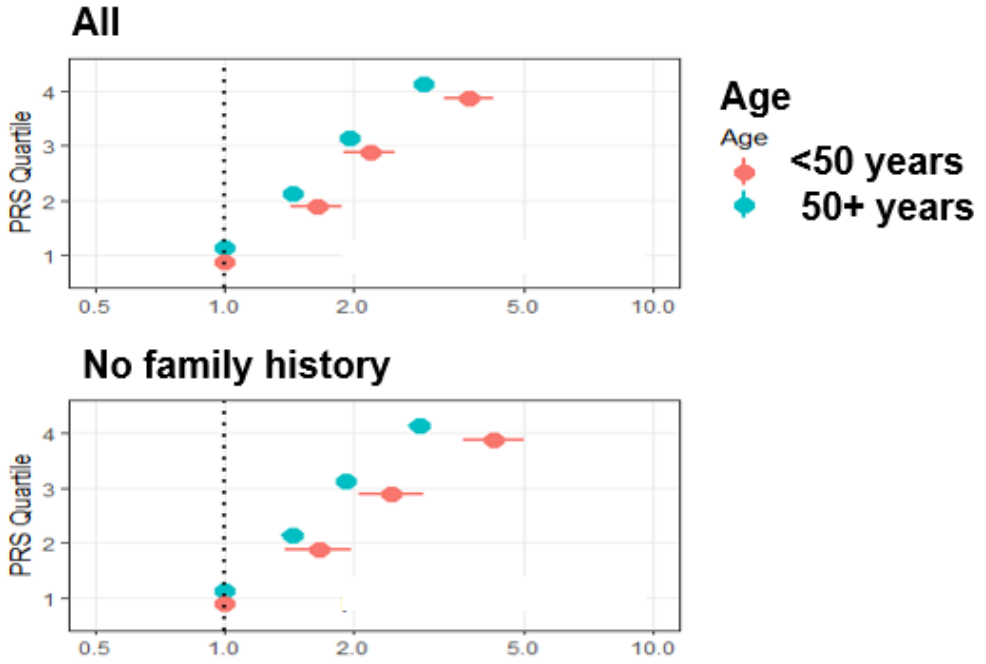
- Family history explains 3% of the PRS variation
- PRS explains 10% of the family history variation

=> Family history and PRS contributing independently to risk prediction

Polygenic Risk Score Predict Colorectal Precursor Lesions and is Most Predictive in Early-Onset Colorectal Cancer

Outcome	**AUC (95%CI)**
CRC	**0.64** (0.63-0.66)
Advanced adenoma	**0.61** (0.60-0.62)
Advanced neoplasia (CRC + advanced adenoma)	**0.62** (0.62-0.63)

- PRS is more predictive in early-onset CRC
  - Particularly those with a negative family history



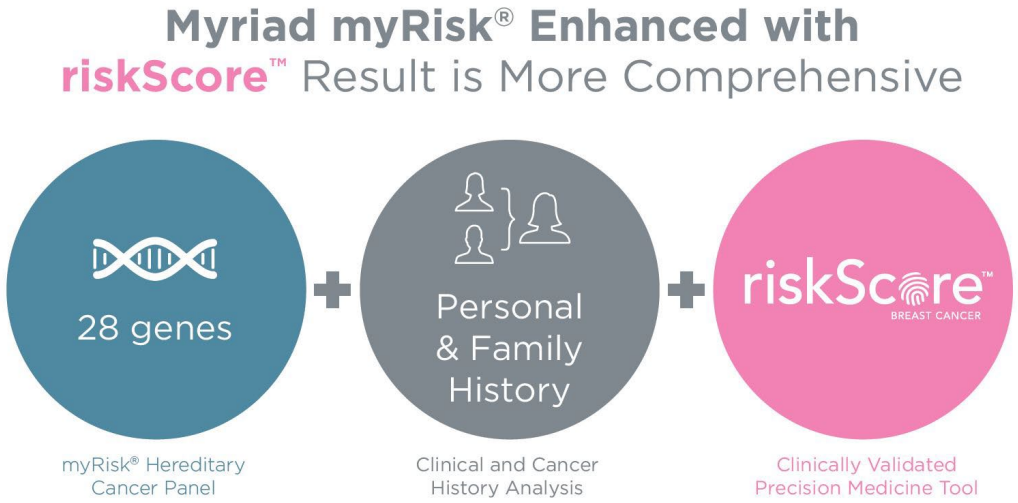
Thomas et al. Am J Hum Genet 2020, Nature Communication 2022; Archambault et al. Gastroenterol 2020

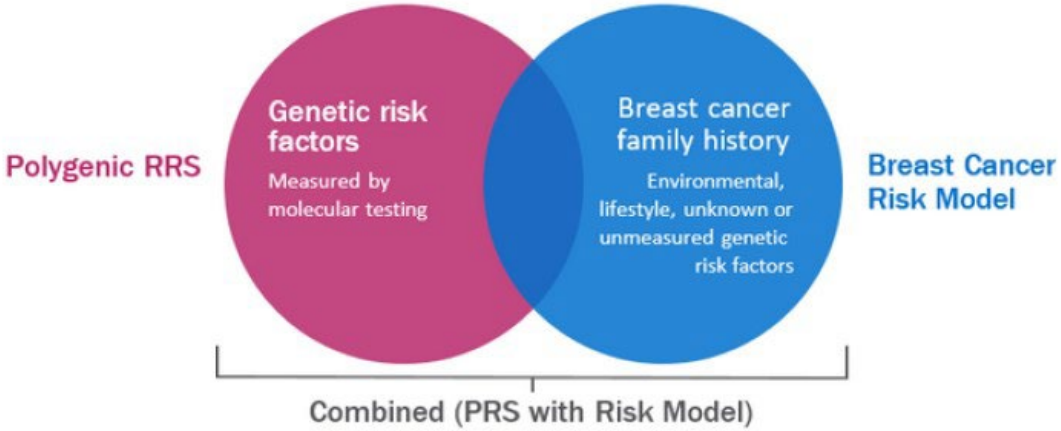
Several Studies Ongoing to Assess the Impact of Polygenic Risk Score in Other Cancers

- WISDOM Trial
  - Testing the effectiveness of *breast* cancer risk-stratified screening based on PRS and other factors
  - Results from WISDOM expected next year
- UK 100,000 Genomes Project
  - Accelerating Detection of Disease Program to test the impact of PRS and AI on early detection in 5 million volunteers
- eMERGE (emerge electronic medical records and genomics)
  - Assess the use of genetic-guided interventions in complex diseases across 25,000 participants, including breast and prostate cancer

Commercialization of polygenic risk scores

- Myriad has included polygenic risk score in genetic testing since 2017
- Other companies are following, such as Ambry Genetics, Color Genetics,…
- Polygenic risk scores as one of the top 10 Breakthrough Technologies in 2018 by MIT Technology Review





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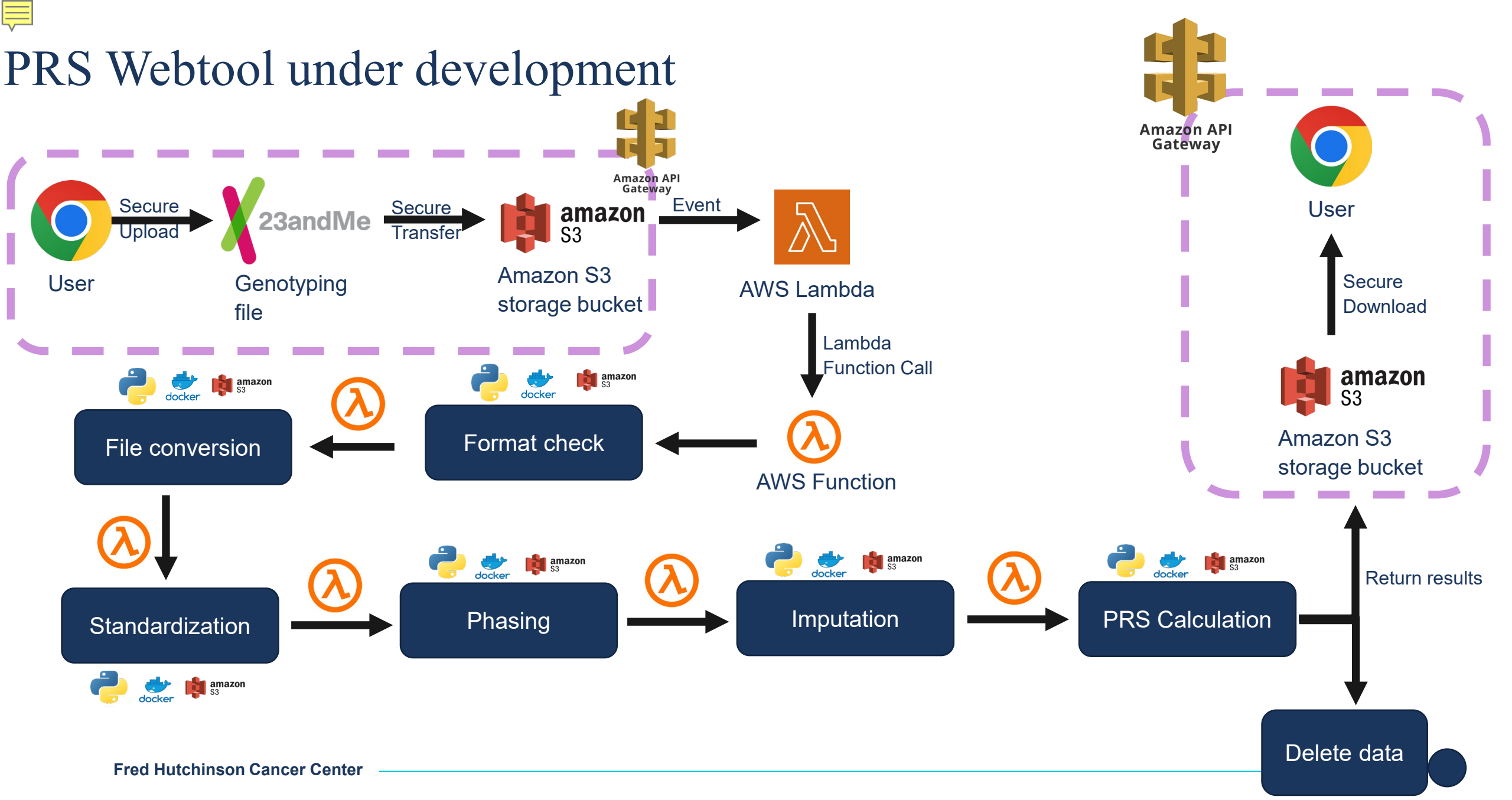
Ongoing Work and Future Directions

PRS Webtool under development



Ongoing Developments and Future Directions

- **Ongoing Developments**
  - Improve risk prediction in Hispanic and African American individuals
  - Assess if polygenic risk score PRS can inform surveillance after a positive colonoscopy (R01-CA276306, PI Jeff Lee)
  - Cost effectiveness analyses using MISCAN model (led by Iris Lansdorp-Vogelaar)
  - Develop pragmatic trial to investigate if genetic prediction improves screening uptake
    - With Larissa White at Kaiser Permanente CO
- **Future Directions**
  - Combined PRS (+ERS) with other non-invasive screening test to improve performance
    - Such as continuous value of FIT test or any blood-based biomarker

=> we are always interested in collaborating with new groups