Choosing the best models, lessons from diverse complex diseases: Breast Cancer

Montserrat García-Closas, M.D. Dr.P.H.

Deputy Director

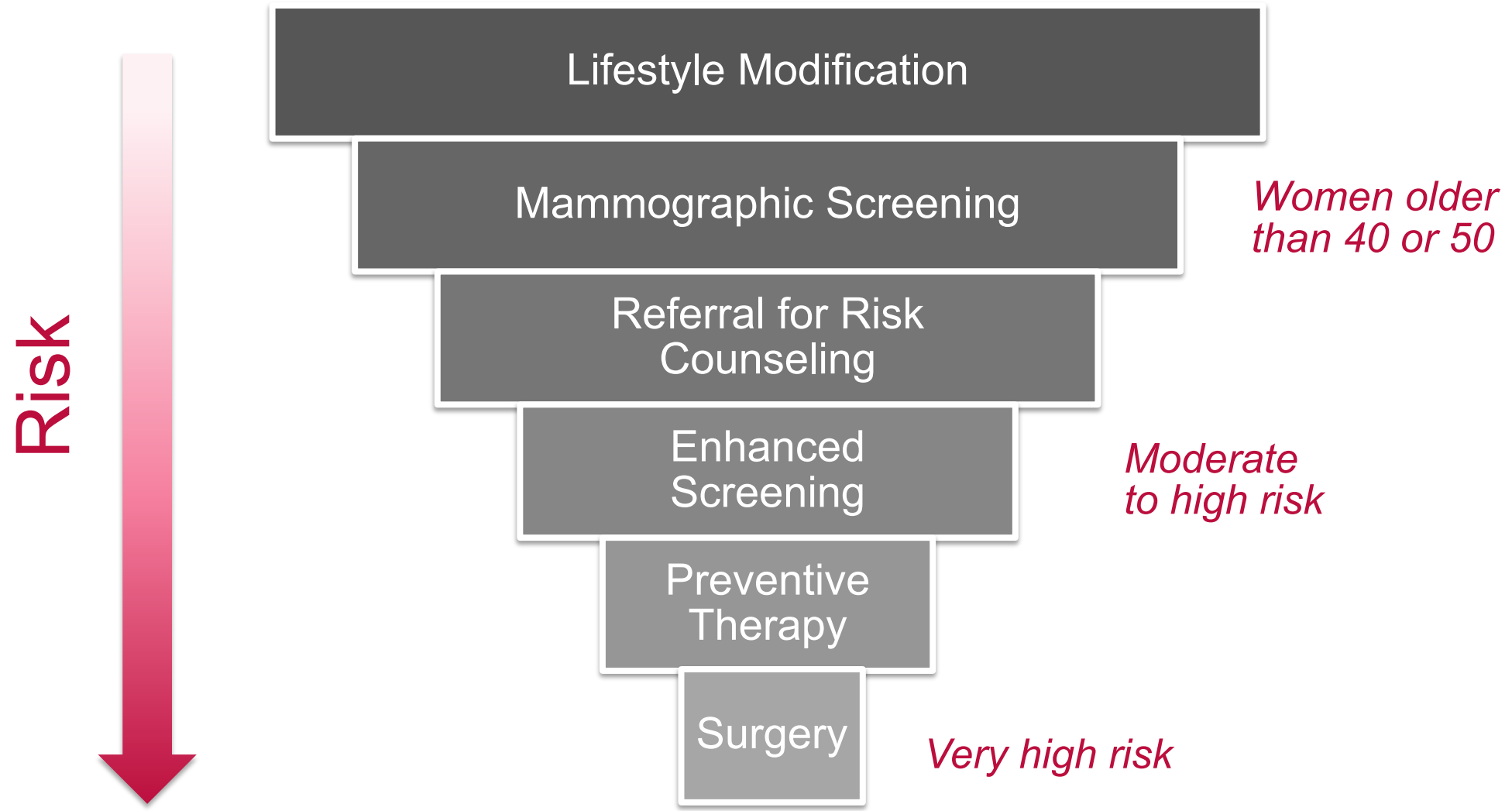
Division of Cancer Epidemiology and Genetics

NIH NATIONAL CANCER INSTITUTE

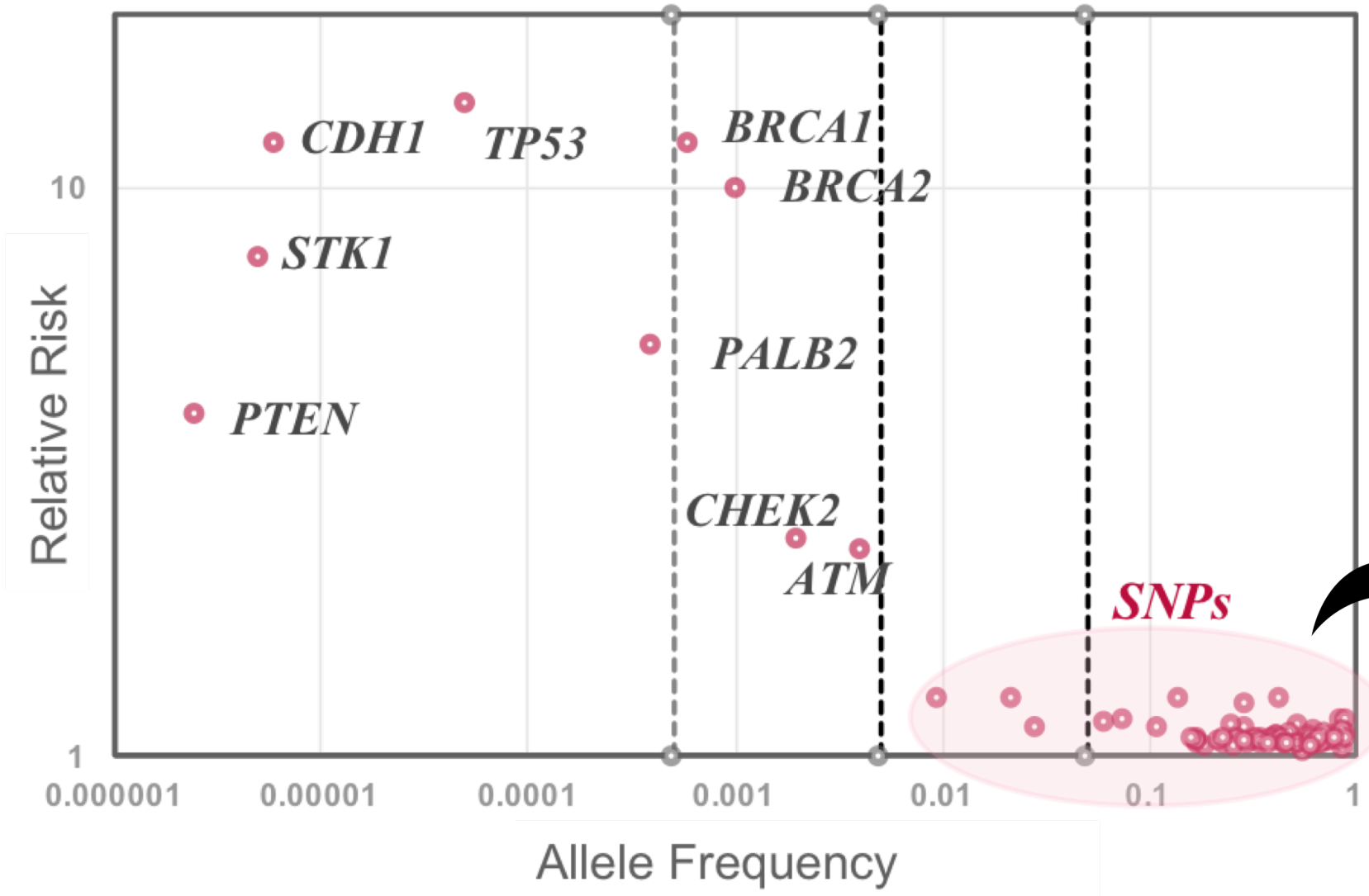
Outline

- Polygenic risk scores (PRS) for breast cancer:
  - How good are they now ?
  - How much better can they get ?
- Integrated breast cancer risk models incorporating PRS
- Future directions

Breast cancer risk reducing strategies tailored to risk



Genetic Architecture of Breast Cancer



Polygenic
Risk
Scores

Easton et al. NEJM 2015

Development of polygenic risk score (PRS)

Breast Cancer Association Consortium (BCAC), European ancestry

PRS	Studies	Cases	Controls
Development	69	94,075	75,017
Validation	10	11,428	18,323

Genome-wide arrays plus imputation (~7 million SNPs)

Mavaddat et al. AJHG 2019

PRS and breast cancer risk

PRS	Relative Risk per SD	95% CI	AUC (%)
77-SNP*	1.46	(1.42-1.49)	60.3
313-SNP	1.61	(1.57-1.65)	63.0
3,820-SNP	1.66	(1.61-1.70)	63.6

*Mavaddat et al. JNCI 2015

Mavaddat et al. AJHG 2019

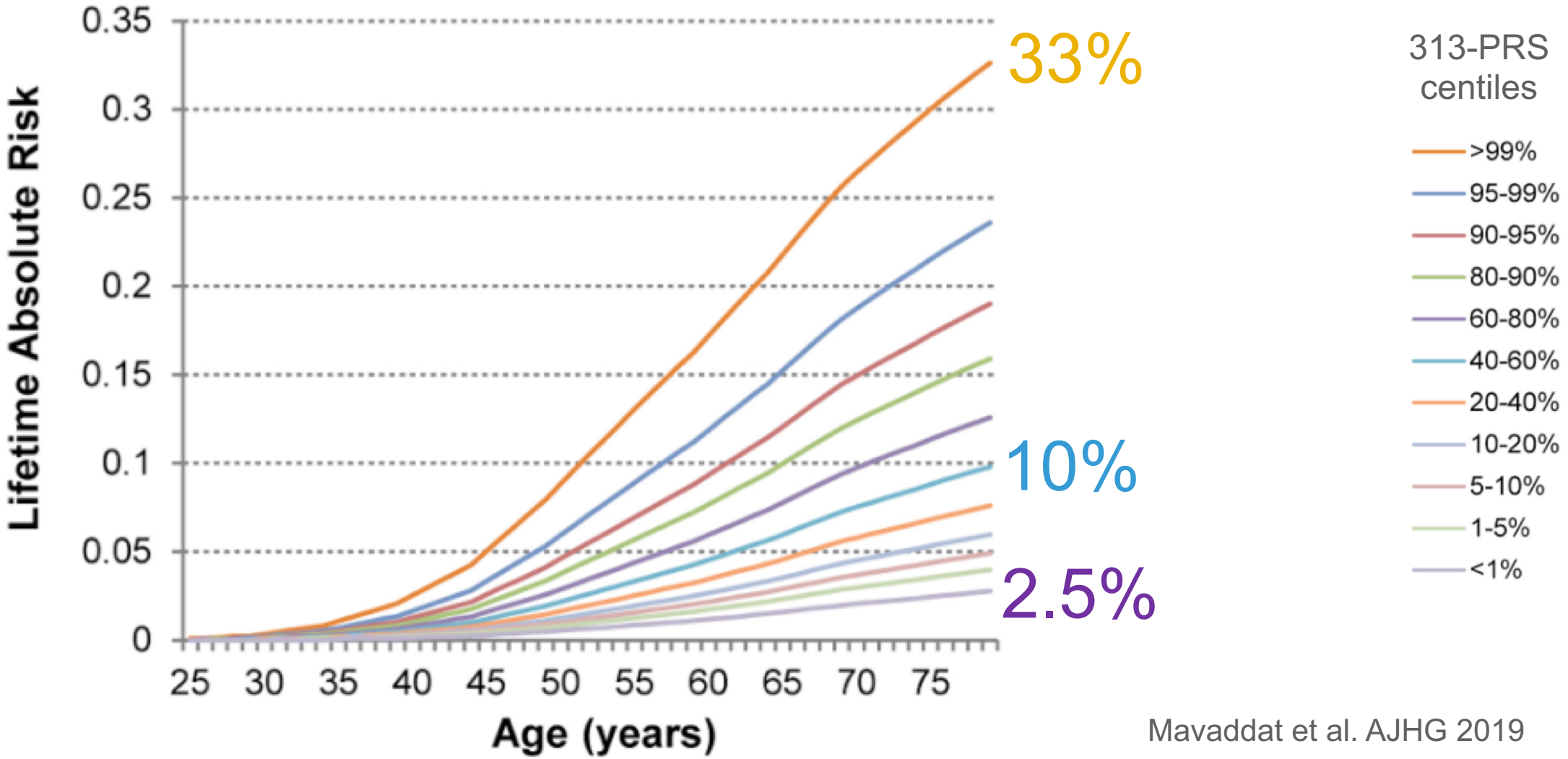
313-PRS by ER status of breast tumors

	Overall		ER-Positive		ER-negative	
PRS	OR	95% CI	OR	95% CI	OR	95% CI
BCAC (European)	1.61	1.57 – 1.65	1.68	1.63 – 1.73	1.45	1.37 - 1.53

Ahearn et al. In Preparation

Mavaddat et al. AJHG 2019

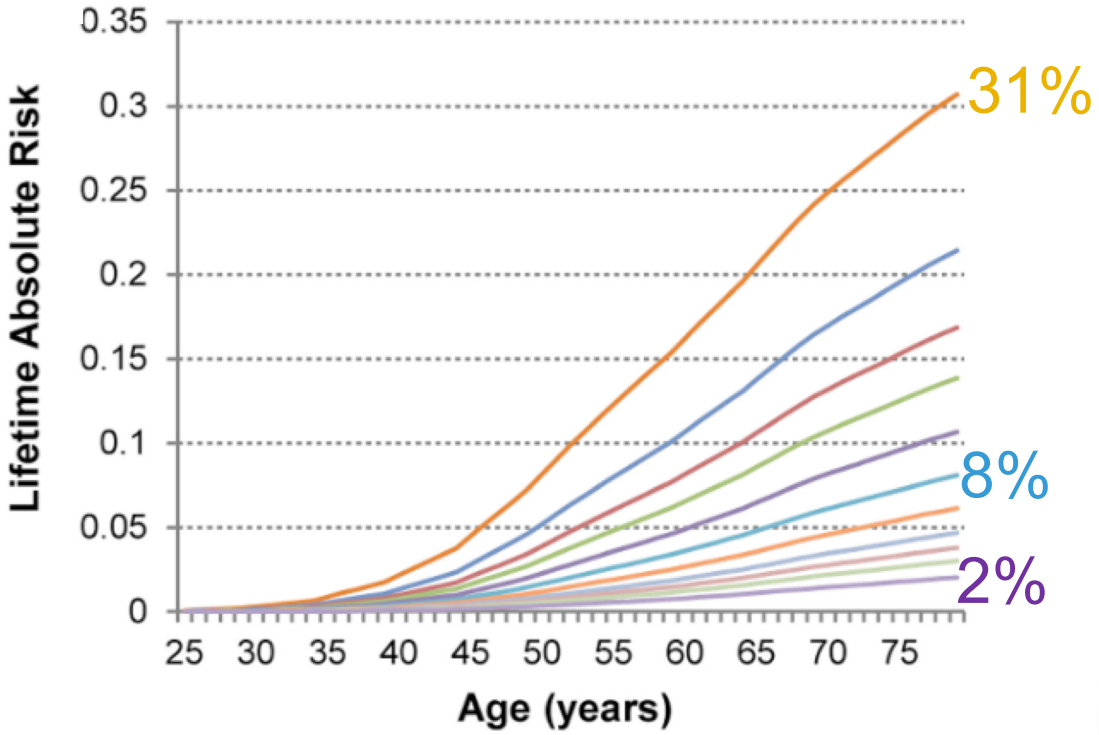
Absolute risk stratification of 313-SNP PRS – UK Women



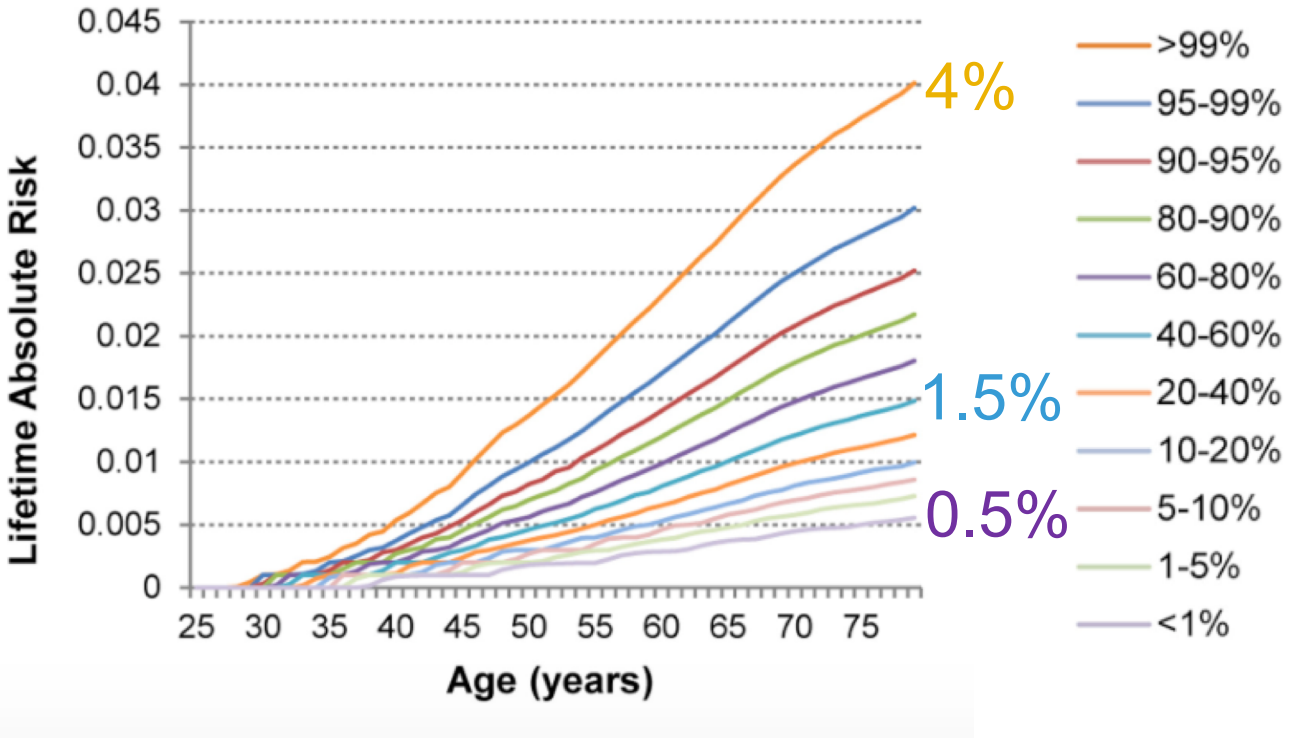
Mavaddat et al. AJHG 2019

Absolute risk stratification of 313-SNP PRS – UK Women

ER-Positive

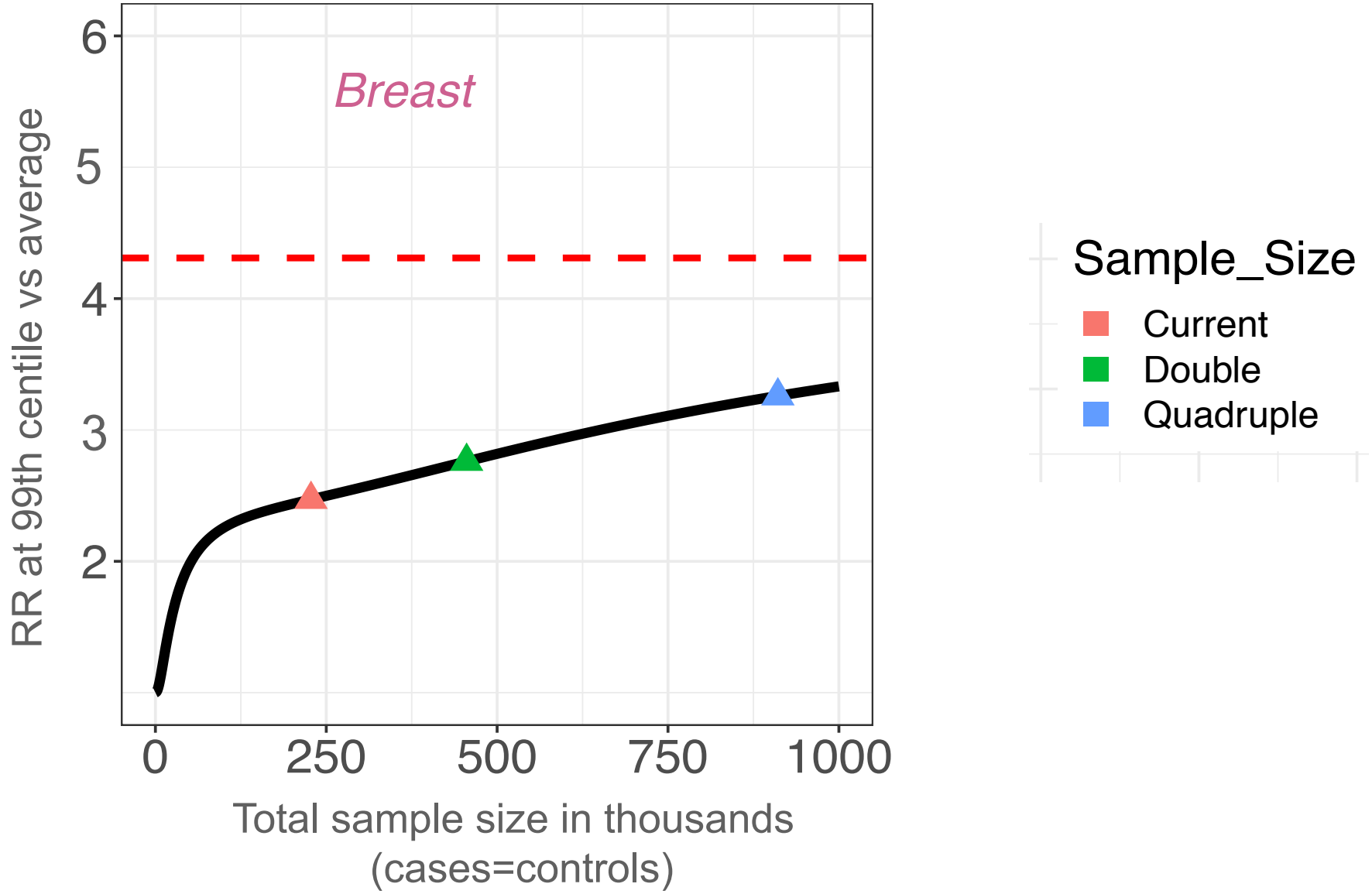


ER-Negative

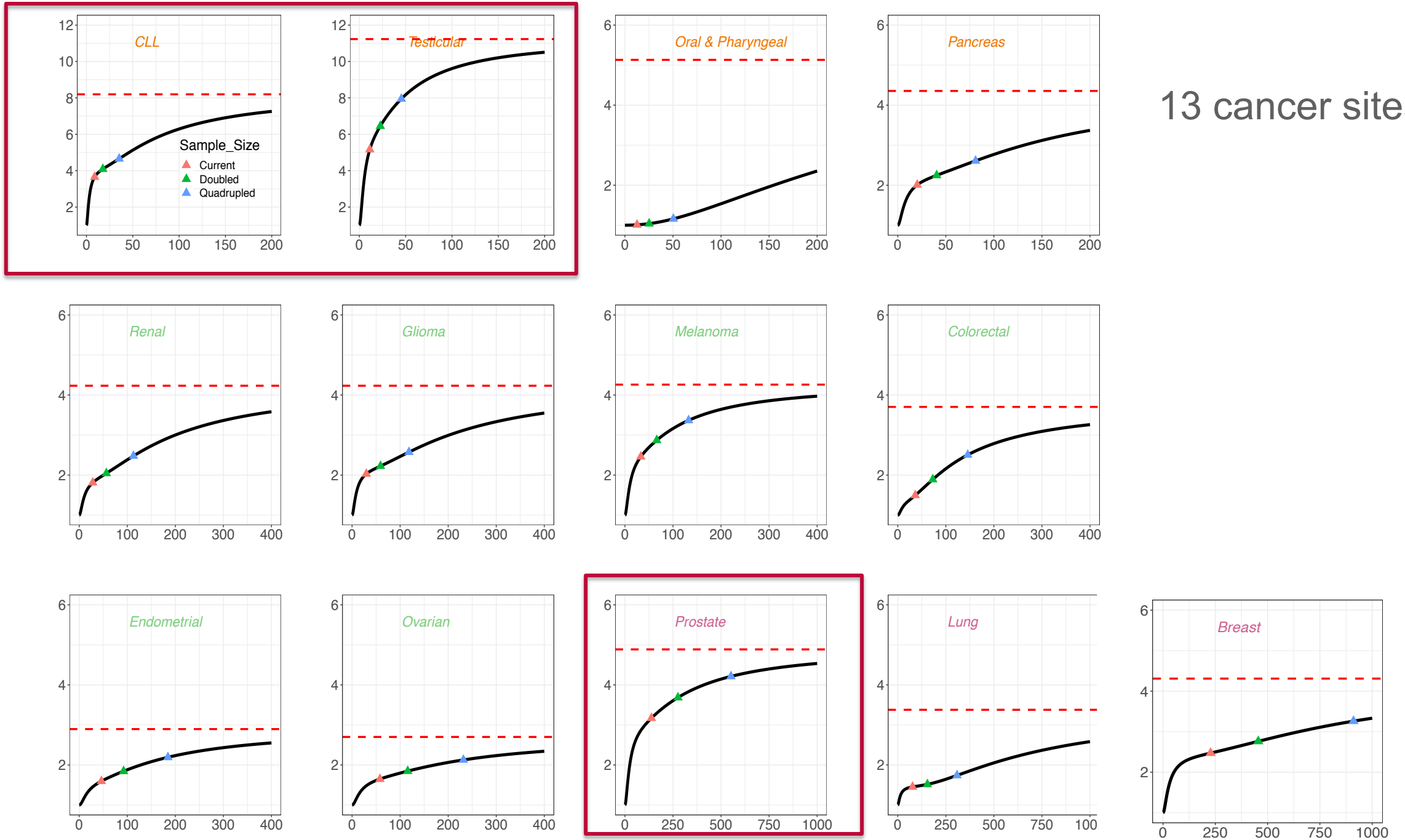


Mavaddat et al. AJHG 2019

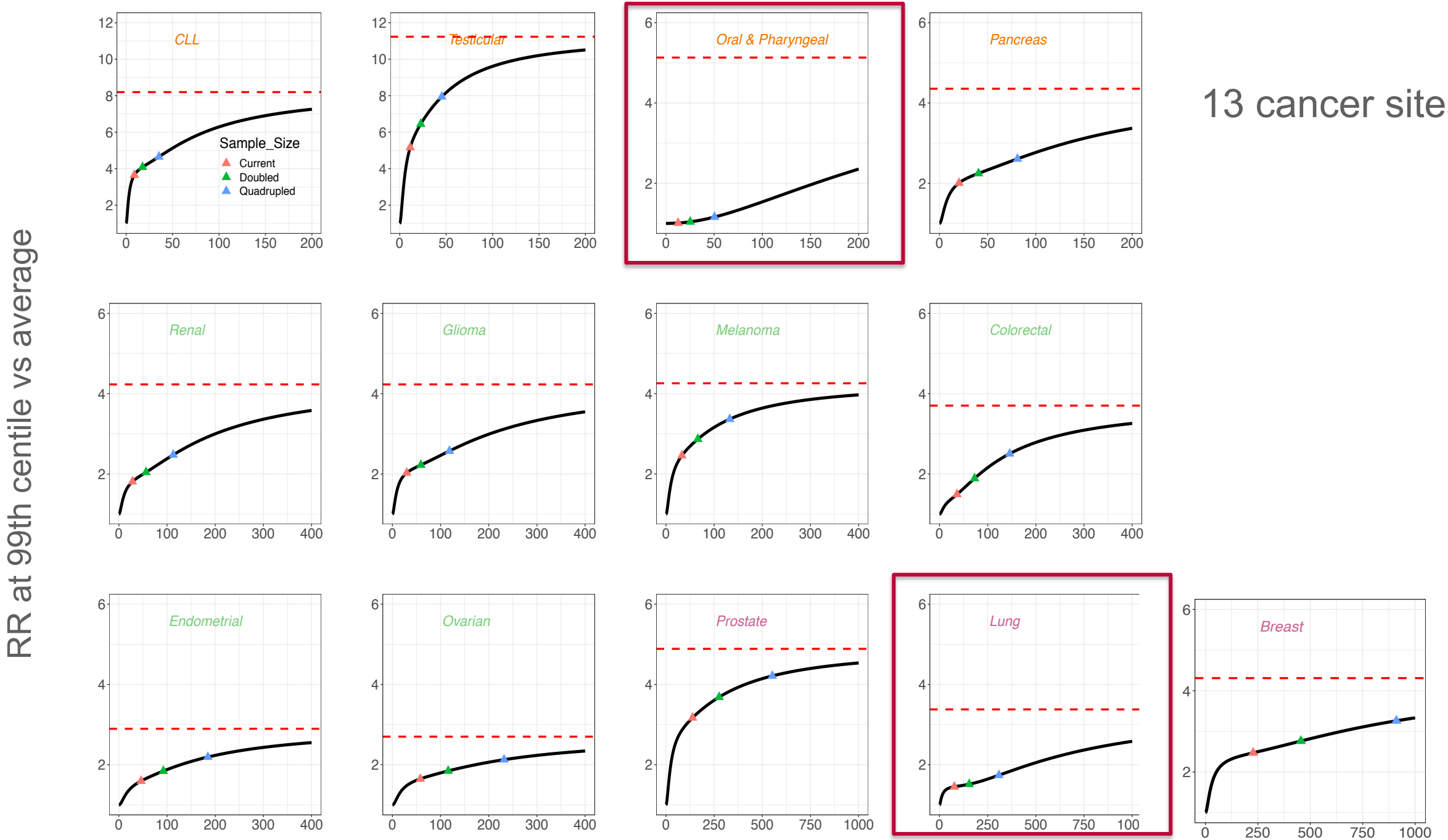
Projected gains in **risk stratification** with increasing GWAS size



Zhang et al. In Prep

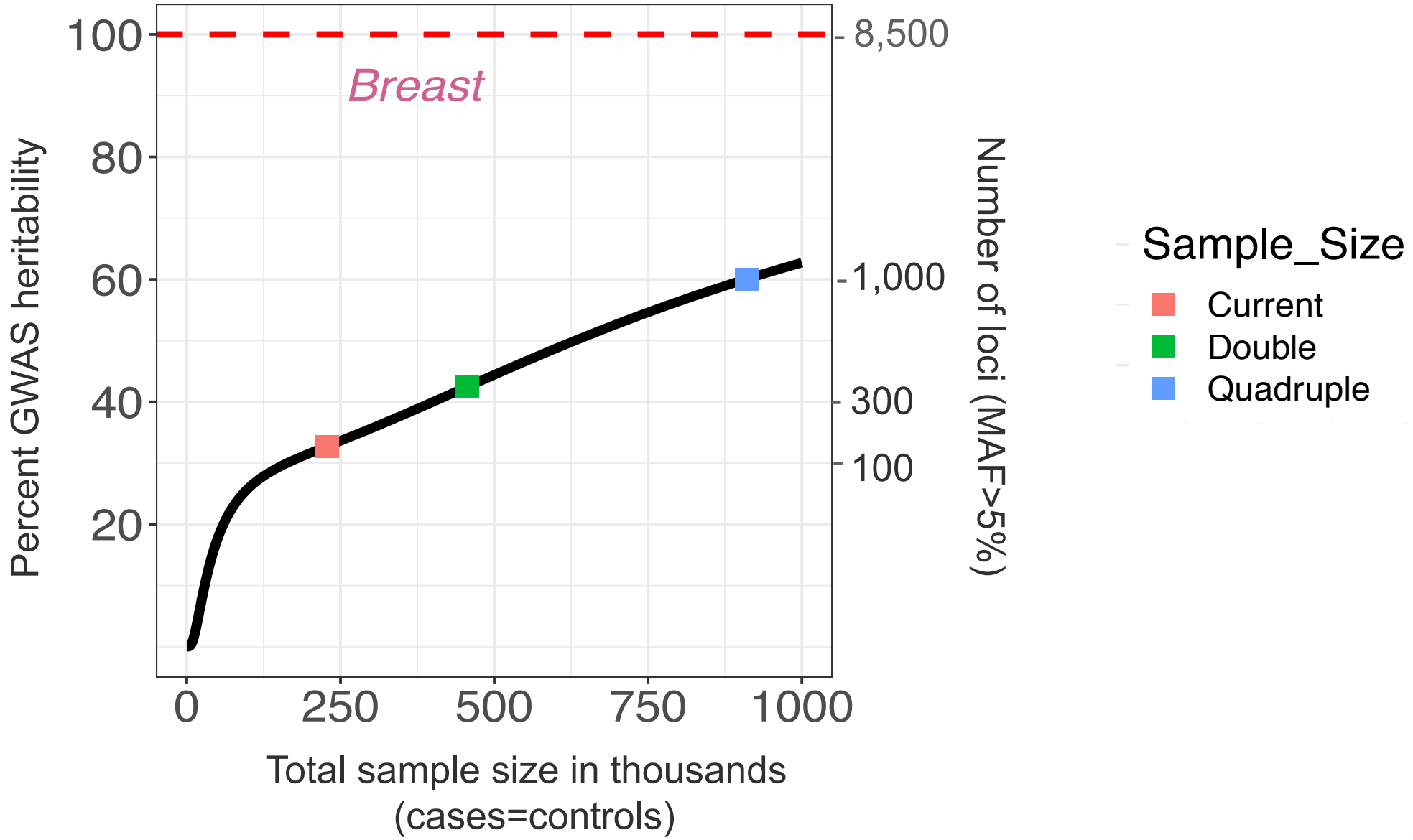


13 cancer sites



13 cancer sites

Projected gains in number of loci and percent GWAS heritability



Zhang et al. In Prep

Confluence

Uncovering breast cancer genetics

More than doubling the size of current breast cancer GWAS

>300,000
Breast Cancer Patients

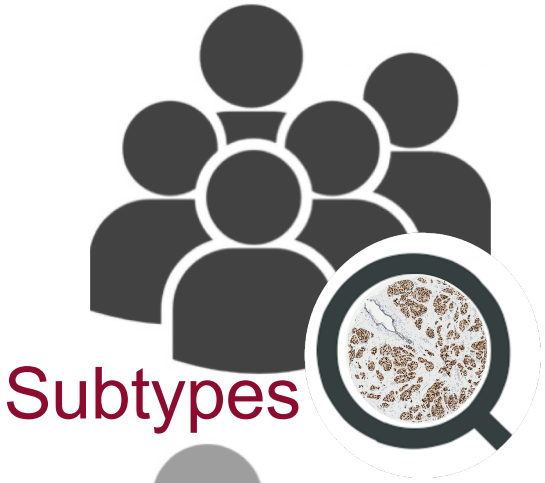
>300,000
Controls

International
Multi-Ancestry

Confluence

Uncovering breast cancer genetics

More than doubling the size of current breast cancer GWAS



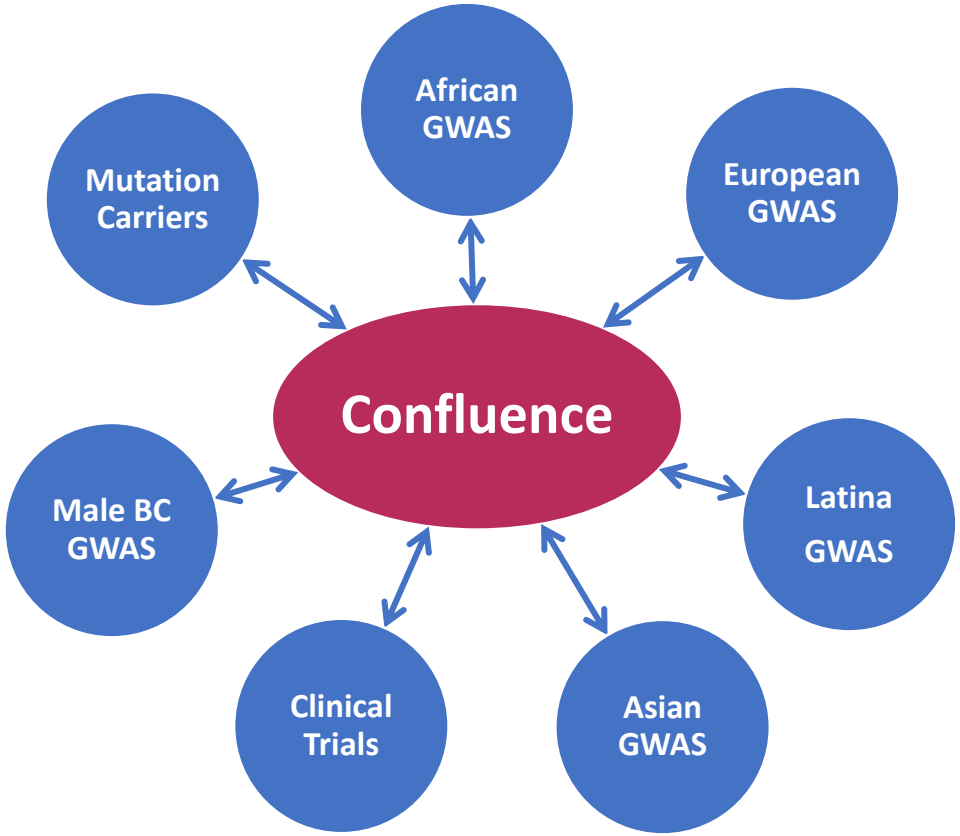
>300,000
Breast Cancer
Patients

>300,000
Controls

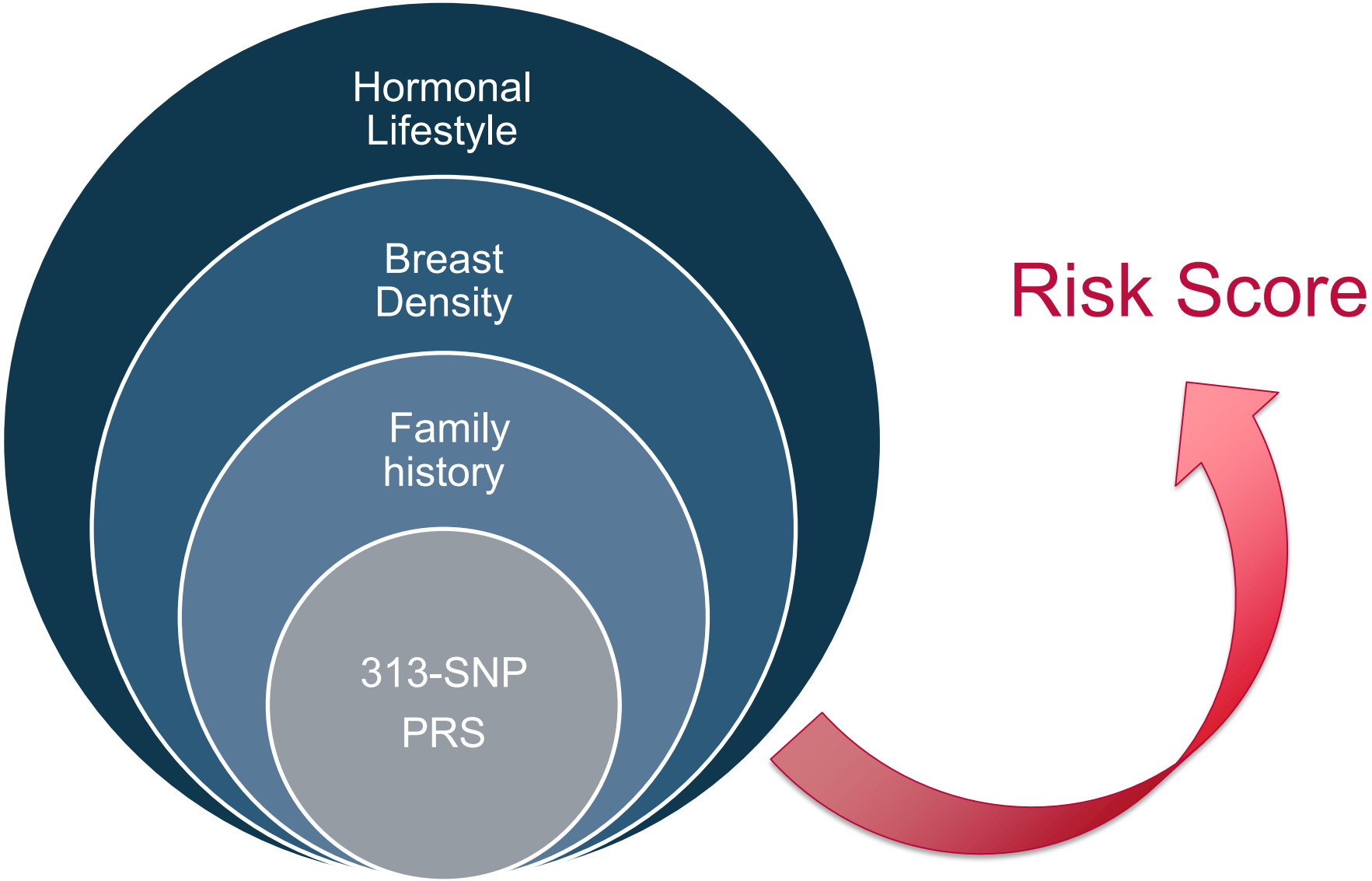
International
Multi-Ancestry

Consortium of consortia: confluence of research resources

- Breast Cancer Association Consortium (BCAC)
- Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)
- African-Ancestry Breast Cancer Genetic Study (AABCGS)
- Asia Breast Cancer Consortium (ABCC)
- Latin America Genomics Breast Cancer Consortium (LAGENO- BC)

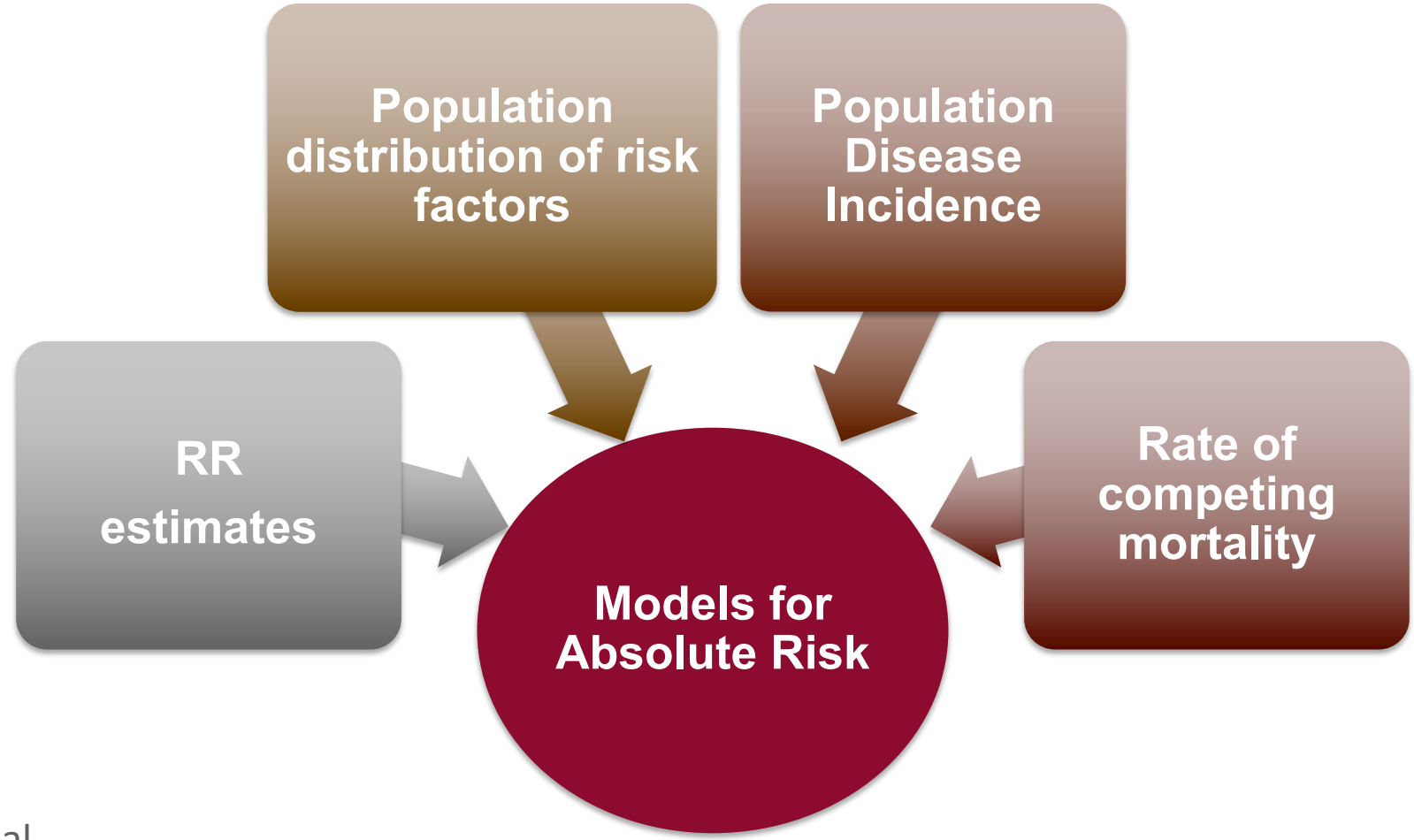


Building integrated breast cancer risk models



Flexible tool to develop and validate absolute risk models

Individualized Coherent Absolute Risk Estimator (iCARE)



Choudhury et al.

https://www.biorxiv.org/content/early/2018/08/23/079954

Performance of risk prediction models

- **Calibration**
  - How close is predicted to actual risk ?

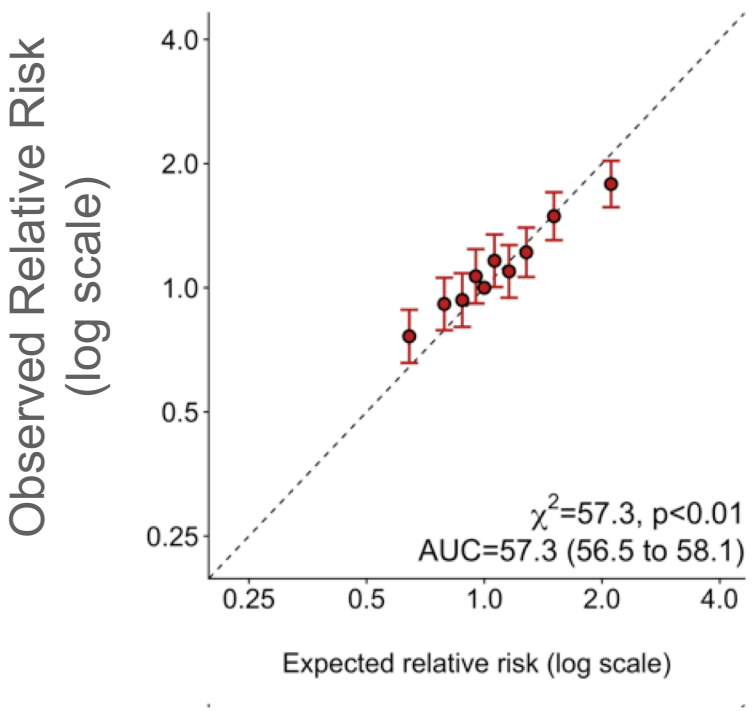
- **Discrimination**
  - How well can predicted risk stratify women?

- **Personal and clinical utility**
  - How useful is the prediction to make decisions ?

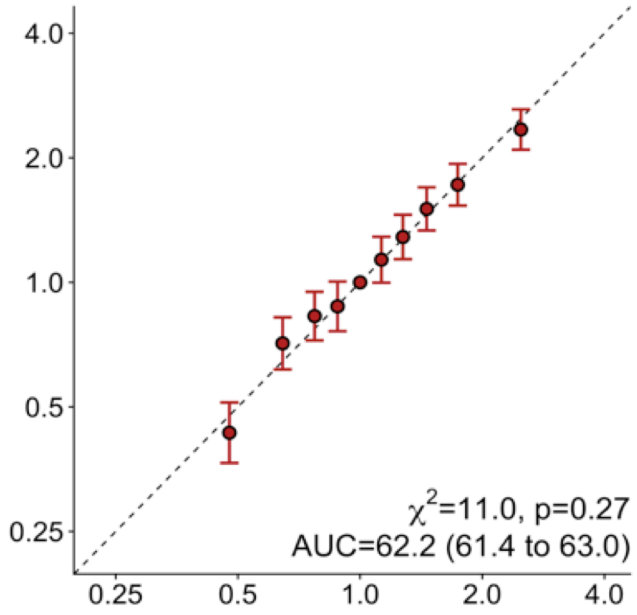
Relative Risk Calibration Risk Models

Meta-analysis for 11 cohorts with 232,743women, 5,920 breast cancers
Age ≥ 50 years

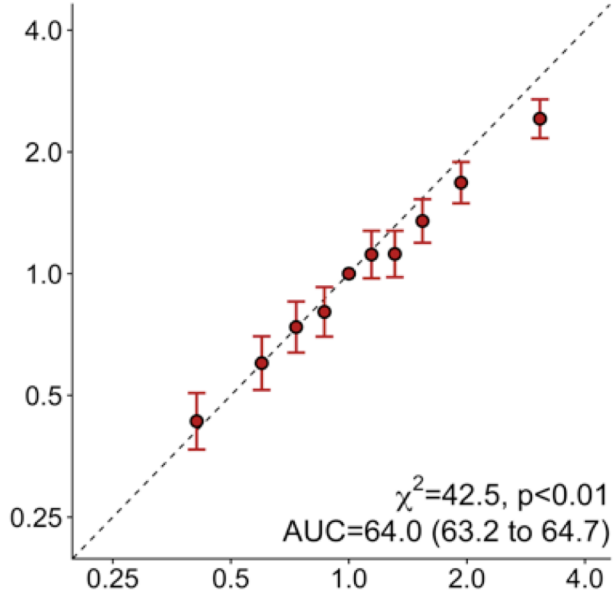
Classical Risk Factors



313-SNP PRS

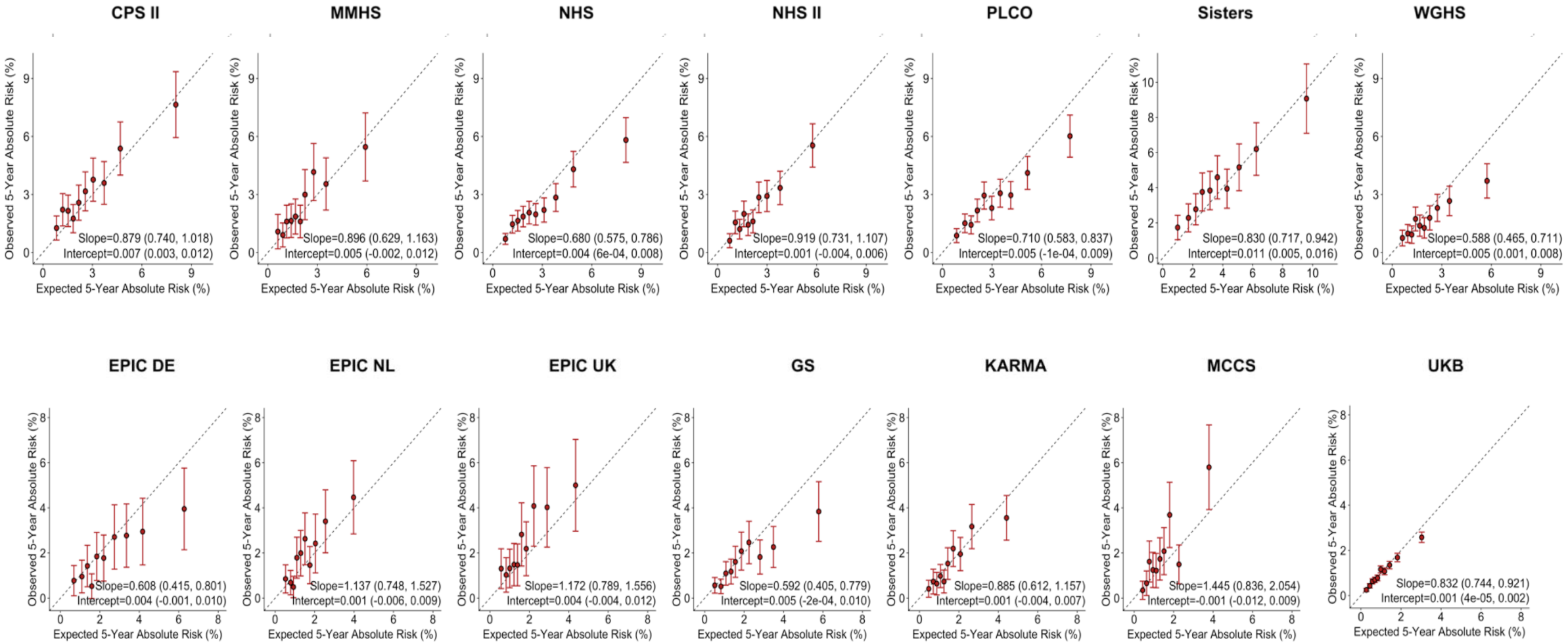


Classical + PRS



Wilcox et al. In Prep

Absolute risk calibration across multiple study populations



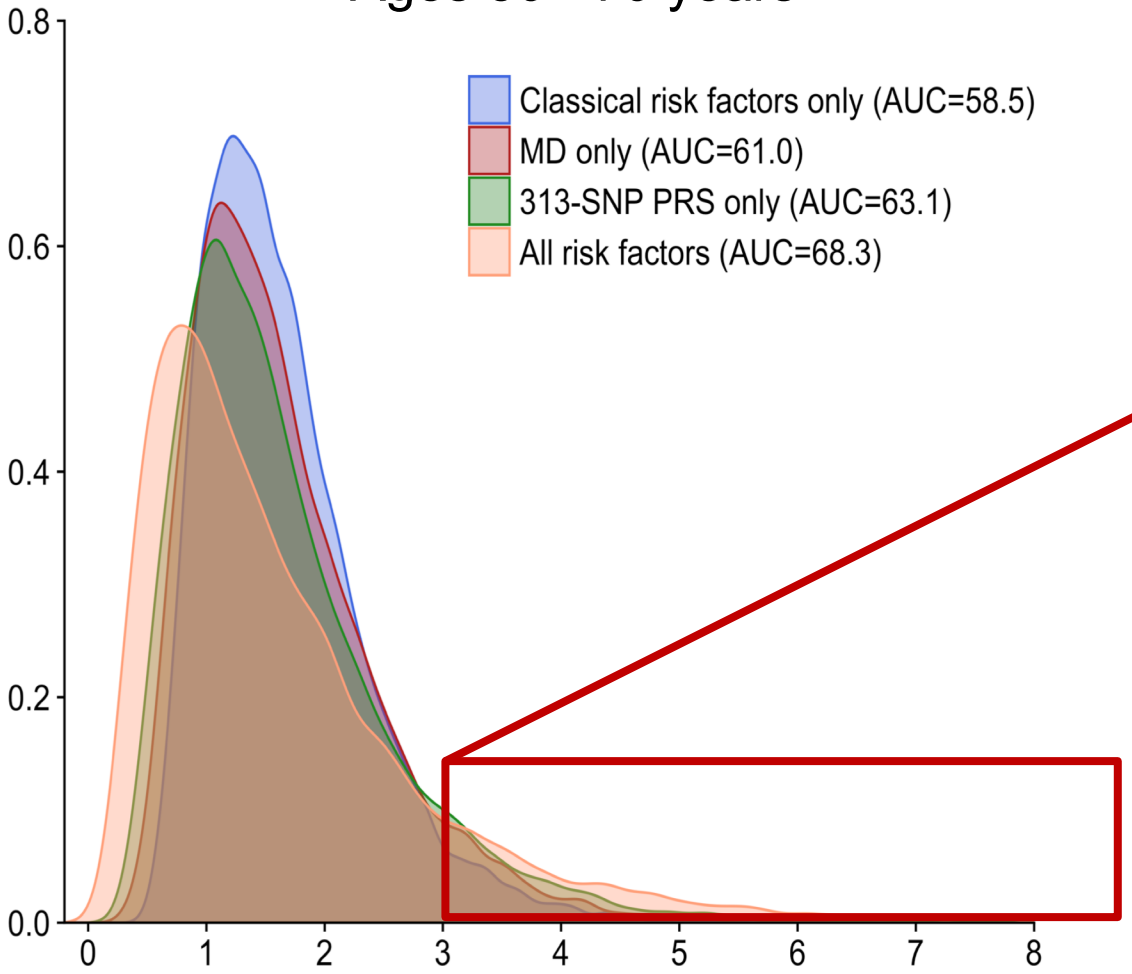
Wilcox et al. In Prep

connect for cancer prevention | ADVANCING CANCER RESEARCH TOGETHER

- 200,000 adults
- Long-term follow up
- Serial assessments
- Comprehensive
- Tissue collections
- Case ascertainment

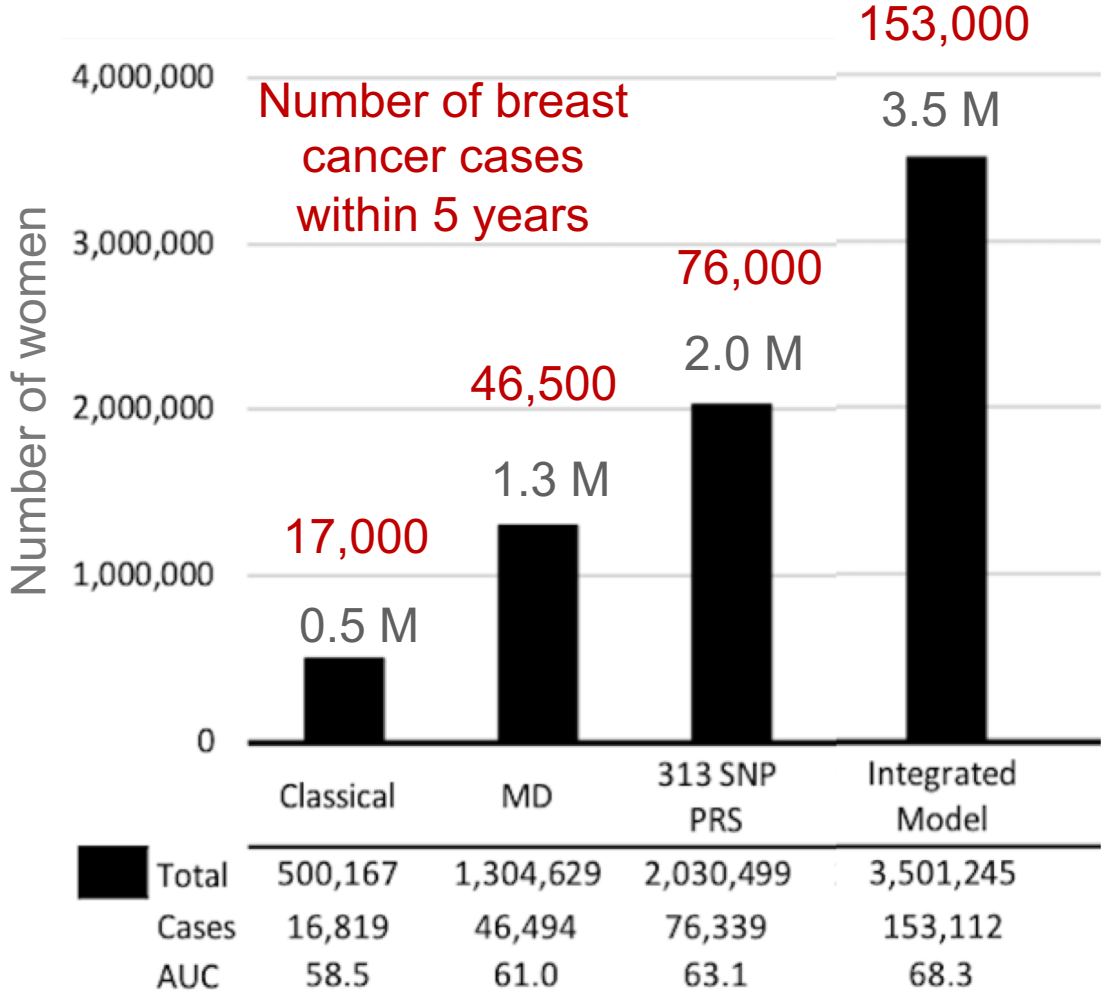
Breast cancer risk stratification by different risk factors

US Non-Hispanic Whites
Ages 50 - 70 years



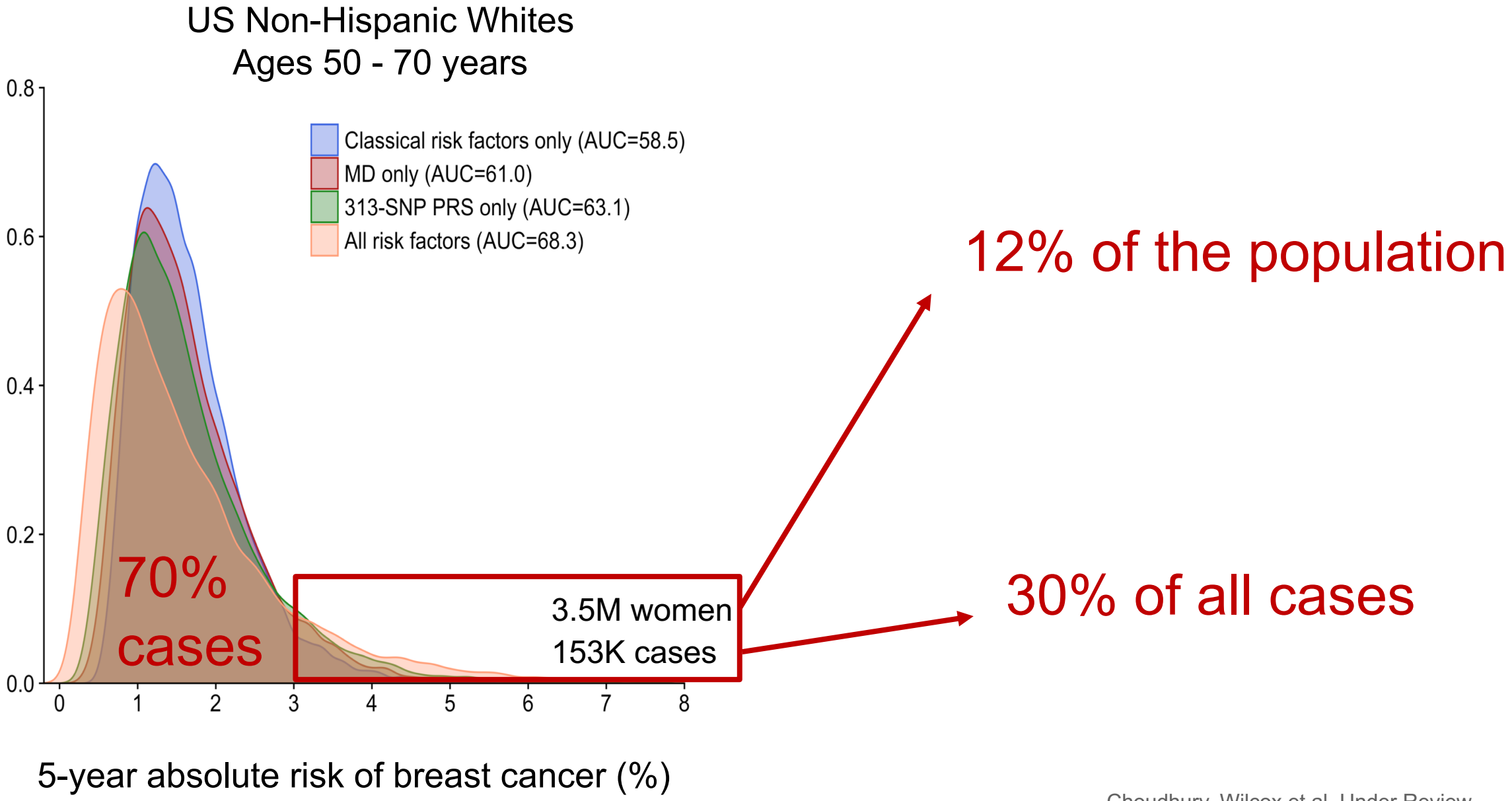
5-year absolute risk of breast cancer (%)

Number of women crossing a 3% risk threshold



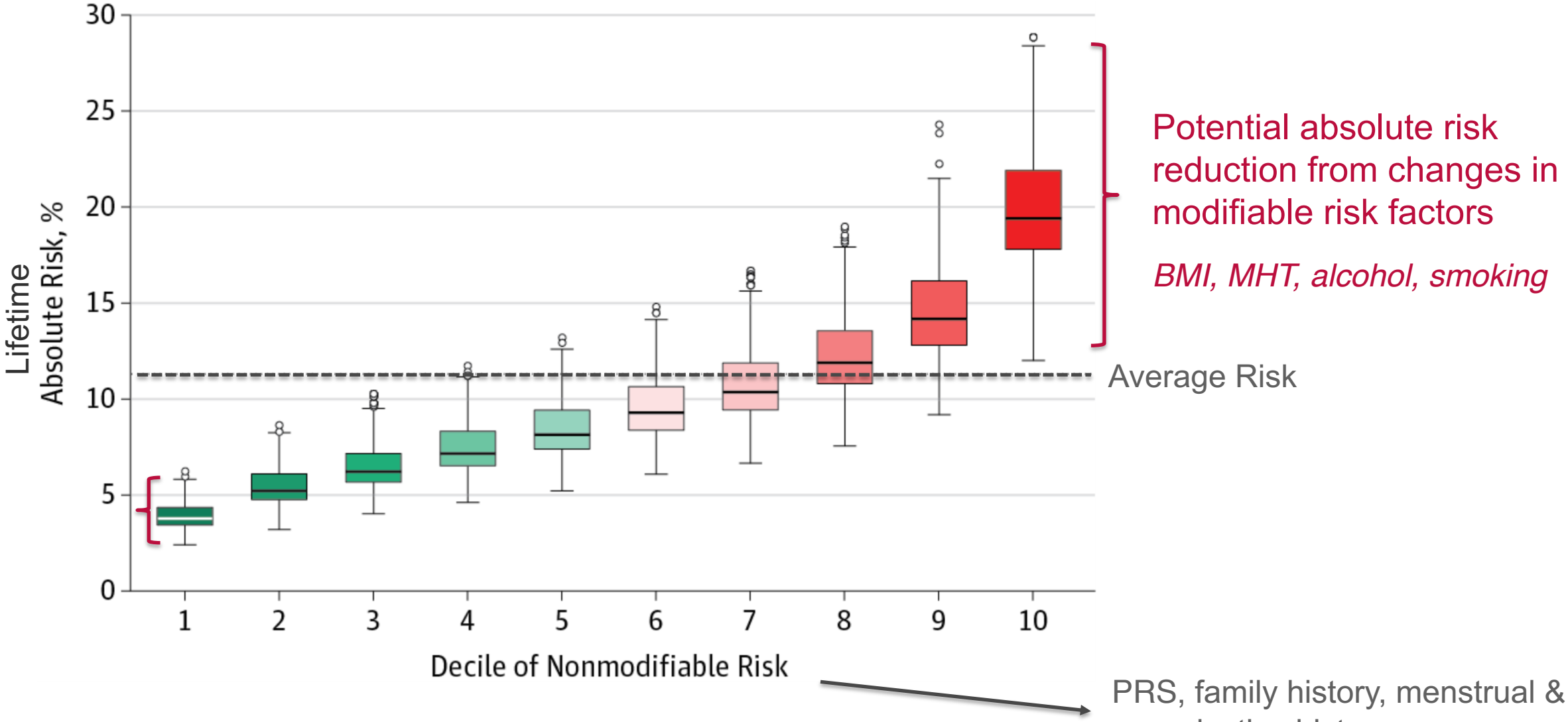
Choudhury, Wilcox et al. Under Review

Breast cancer risk stratification by different risk factors



Choudhury, Wilcox et al. Under Review

Distribution of modifiable risk by deciles of non-modifiable risk



Potential absolute risk reduction from changes in modifiable risk factors

BMI, MHT, alcohol, smoking

Average Risk

PRS, family history, menstrual & reproductive history, menopause

Maas et al, JAMA Oncology 2016

Conclusions

- PRS adds substantially to risk stratification, with good model calibration
- Integrated models can identify larger numbers of women at elevated risk risk -> targeted strategies
- Most cases will still occur outside “high-risk” groups -> population-wide strategies

Future directions

- Improve PRS, subtype, ancestry-specific
- New risk factors/biomarkers needed to further improve risk stratification
- Better preventive and early detection strategies needed to control the disease

Acknowledgements

DCEG, NCI
Amber Wilcox
Tom Ahearn
Mitch Gail
Stephen Chanock

Johns Hopkins University
Nilanjan Chatterjee
Parichoy Pal Choudhury
Haoyu Zhang

Institute of Cancer Research
Mark Brook
Tony Swerdlow

Cambridge University
Antonis Antoniou
Doug Easton
Kyriaki Michailidou
Nasim Mavaddat
Paul Pharoah

Netherlands Cancer Institute
Marjanka Schmidt
Sandra Broek

Harvard School of Public Health
Pete Kraft

German Cancer Center
Jenny Chang-Claude

University of Melbourne
Roger Milne

Karolinska Institute
Per Hall

Laval University
Jaques Simard

University of Queensland
Georgia Chenevix-Trench

Prospective Cohorts for Breast Cancer Risk Modelling

GS: Swerdlow, Brook

CPS II: Brian Carter, Mia Gaudet

EPIC: Anika Husing, Myrto Barrdahl

KARMA: Mikael Eriksson, Per Hall

MCCS: Kara Martin, Roger Milne

MMHS: Chris Scott, Celine Vachon

NHSI/NHSII, WGHS: Chi Gao, Pete Kraft

PLCO/UKBiobank: Garcia-Closas, Chatterjee

PROCAS: Elaine Harkness, Gareth Evans

SISTERS: Min Shi, Clarise Weinberg, Dale Sandler