Tailoring Early Detection Strategies for Breast and Ovarian Cancer to Genomic Risk

MARY B. DALY M.D., PHD

JUNE 30, 2020

Purpose of the talk:

To propose novel approaches using genomic risk to improve risk prediction and early detection strategies for breast and ovarian cancer

The talk will cover:

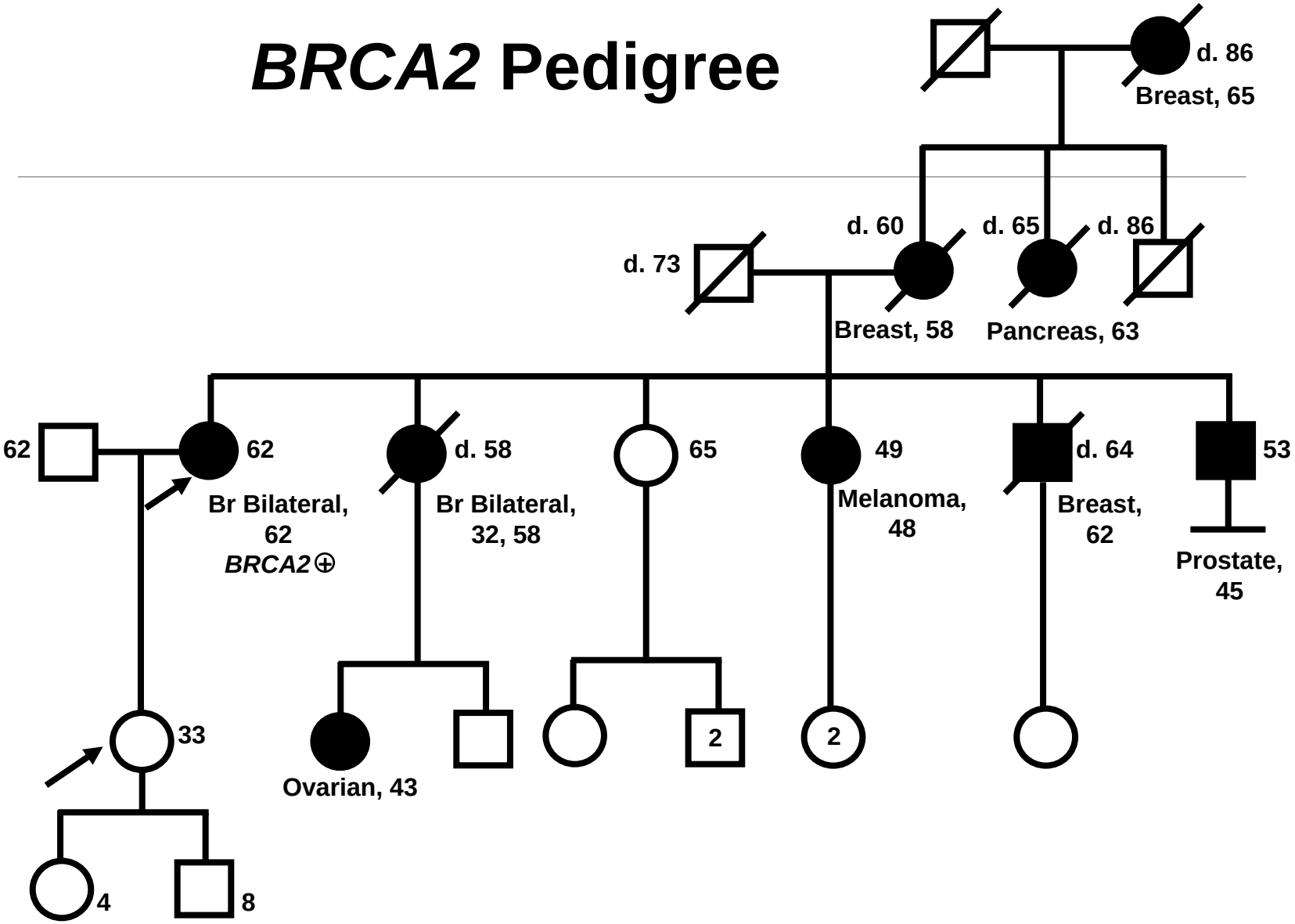
- What we know about germline pathogenic variants that increase risk of developing breast and/or ovarian cancer
- How we are currently using germline pathogenic variants to manage risk of developing cancer
- What we know about single nucleotide polymorphisms (SNPs) and Polygenic Risk Scores (PRS)
- How we can incorporate genomic risk into early detection strategies in novel ways

I. What do we know about germline pathogenic variants (PVs) that increase risk of developing breast and/or ovarian cancer?

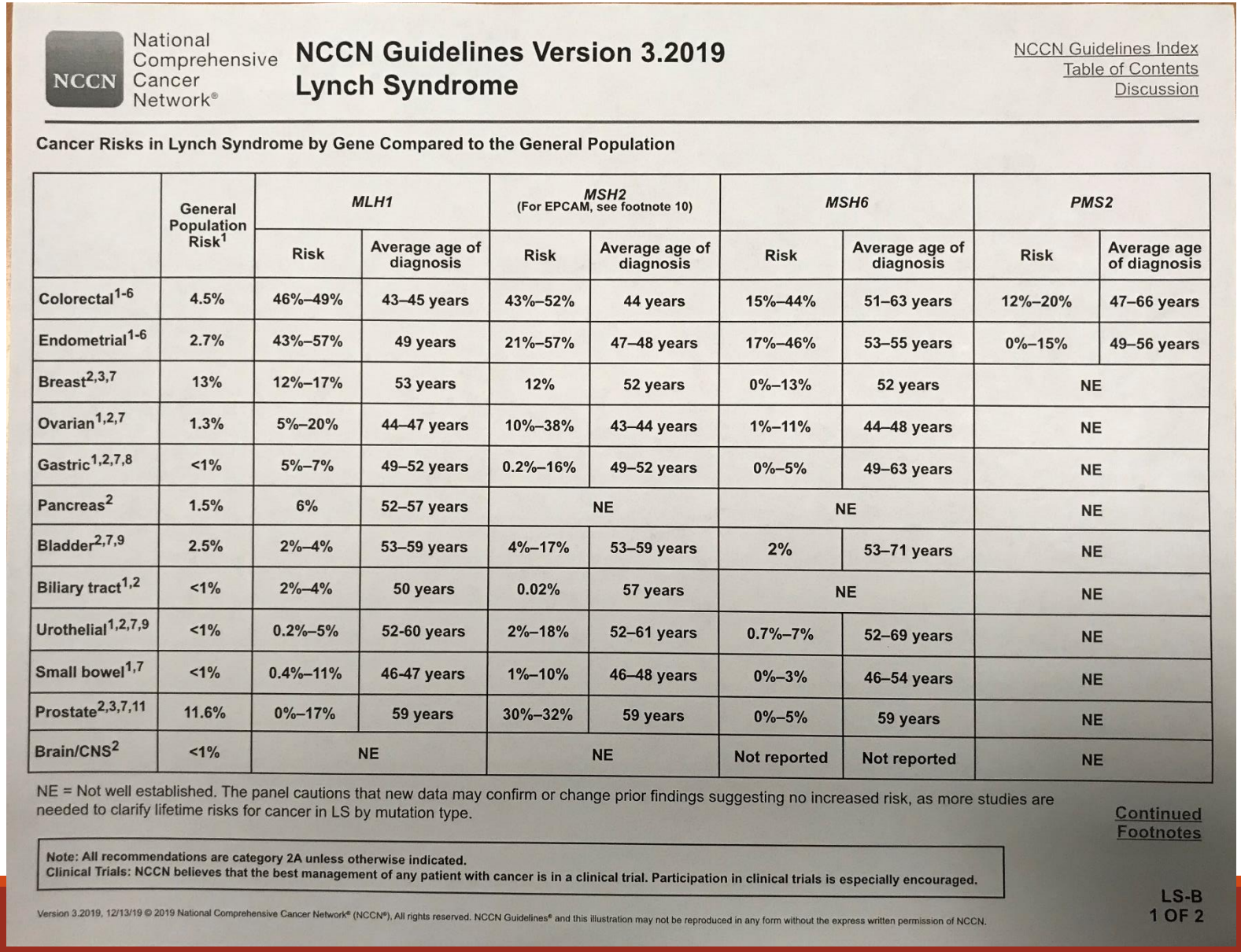
- Prevalence- how frequent the PV is in the population
  - AJ Founder mutations – 1/40
  - BRCA 1/2 – 1/400-1/800
  - PTEN 1/250,000

- Phenotype- which cancers are associated with a PV

BRCA2 Pedigree



Penetrance- What is the chance of getting a particular cancer for PV carriers?



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Lynch Syndrome

NCCN Guidelines Index
Table of Contents
Discussion

Cancer Risks in Lynch Syndrome by Gene Compared to the General Population

	General Population Risk[1]	*MLH1*		*MSH2* (For EPCAM, see footnote 10)		*MSH6*		*PMS2*	
		Risk	Average age of diagnosis	Risk	Average age of diagnosis	Risk	Average age of diagnosis	Risk	Average age of diagnosis
Colorectal[1-6]	4.5%	46%–49%	43–45 years	43%–52%	44 years	15%–44%	51–63 years	12%–20%	47–66 years
Endometrial[1-6]	2.7%	43%–57%	49 years	21%–57%	47–48 years	17%–46%	53–55 years	0%–15%	49–56 years
Breast[2,3,7]	13%	12%–17%	53 years	12%	52 years	0%–13%	52 years	NE	
Ovarian[1,2,7]	1.3%	5%–20%	44–47 years	10%–38%	43–44 years	1%–11%	44–48 years	NE	
Gastric[1,2,7,8]	<1%	5%–7%	49–52 years	0.2%–16%	49–52 years	0%–5%	49–63 years	NE	
Pancreas[2]	1.5%	6%	52–57 years	NE		NE		NE	
Bladder[2,7,9]	2.5%	2%–4%	53–59 years	4%–17%	53–59 years	2%	53–71 years	NE	
Biliary tract[1,2]	<1%	2%–4%	50 years	0.02%	57 years	NE		NE	
Urothelial[1,2,7,9]	<1%	0.2%–5%	52-60 years	2%–18%	52–61 years	0.7%–7%	52–69 years	NE	
Small bowel[1,7]	<1%	0.4%–11%	46-47 years	1%–10%	46–48 years	0%–3%	46–54 years	NE	
Prostate[2,3,7,11]	11.6%	0%–17%	59 years	30%–32%	59 years	0%–5%	59 years	NE	
Brain/CNS[2]	<1%	NE		NE		Not reported	Not reported	NE	

NE = Not well established. The panel cautions that new data may confirm or change prior findings suggesting no increased risk, as more studies are needed to clarify lifetime risks for cancer in LS by mutation type.

Continued
Footnotes

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

II. How are we currently using knowledge of pathogenic variants to manage risk of developing breast/ovarian cancer?

- Understanding familial clustering
- Defining potential individual risk of developing breast/ovarian cancer
- Adapting screening and risk reducing recommendations based on genomic risk
- Identifying candidates for targeted therapies (eg. PARP inhibitors)
- Cascade testing

Unfortunately, in most cases, one size fits all

III. How will the incorporation of genomic risk improve risk stratification and early detection strategies?

Or, What questions can genomic risk help us to answer?

- Who to screen (and who not to screen)
- At what age to start screening
- At what interval to screen
- What screening tool(s) to use
- Do biomarkers perform differently in individuals with germline mutations
- Do biomarkers perform differently by the function of a gene
- Who will develop aggressive disease
- Who will respond to different treatments

IV. Some examples of where we might be going

1. Polygenic Risk Scores (PRSs)
   - Common cancer susceptibility variants (single nucleotide polymorphisms-SNPs) discovered through genome-wide association studies (GWAS)
   - Confer small risk individually
   - When combined into a PRS can have a significant effect on risk
   - Can be combined with germline pathogenic variants, family history, non-genetic risk factors **and biomarker levels** and incorporated into risk models

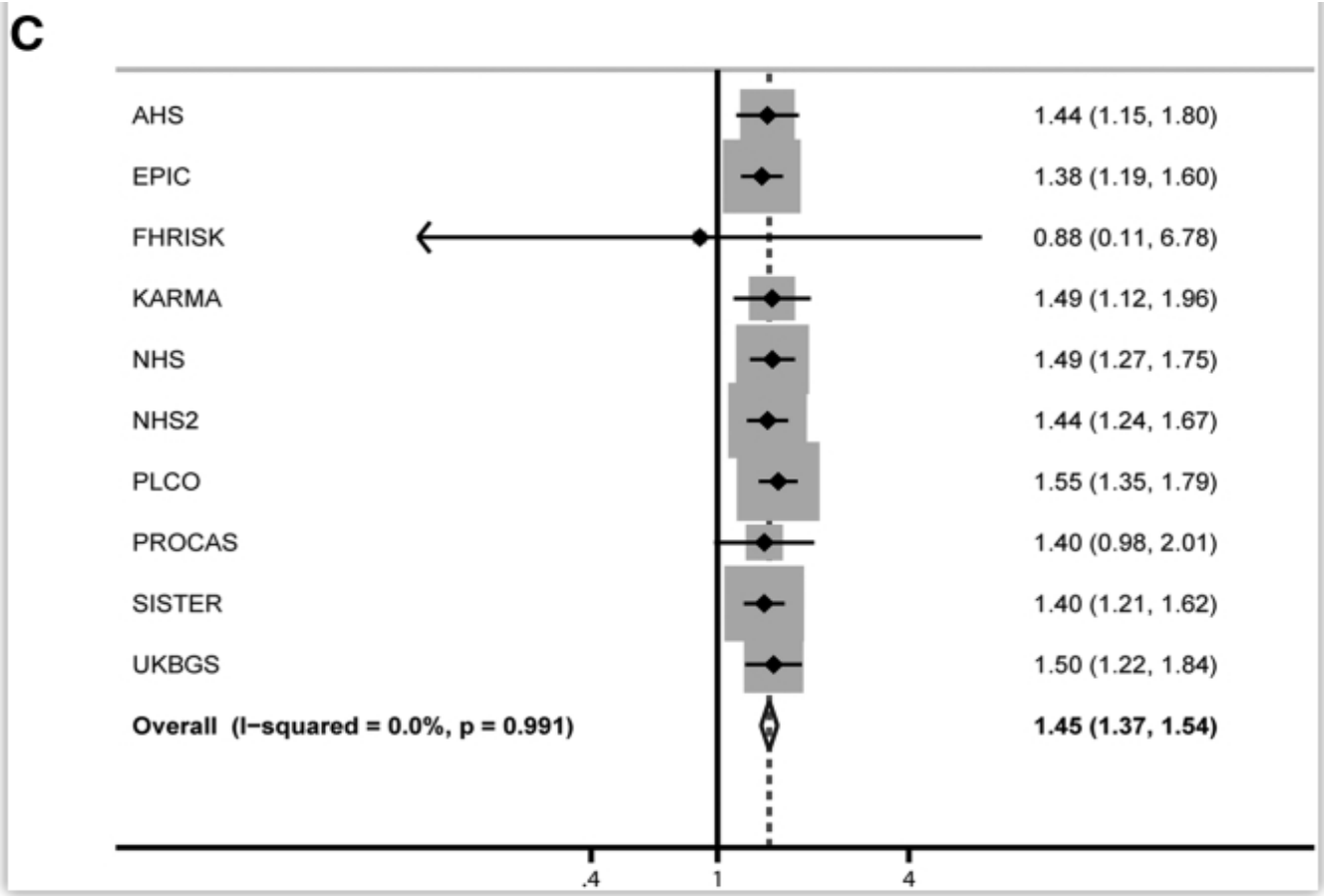
Tyrer Cusick model

- Age, weight, height
- Extensive reproductive history
- Ancestry
- Family history of cancer
- BRCA mutation (if known)
- Option to add PRS

BOADICEA model

- Age, weight, height
- Personal history of cancer
- Family history of cancer
- Genetic status
- Reproductive history (including hormone use)
- Alcohol use
- Option to add PRS

Example: Breast Cancer



Better for ER+ disease than ER- disease

Mavaddat N et al., AJHG, 2019

BREAST CANCER

Predicting-Risk-Of-Cancer-At Screening

PROCAS

Sample: Women presenting for screening mammogram unselected for family history.

Risk Prediction Model: Tyrer Cuzick + Breast Density + 18-SNP PRS

Evans et al., Breast Cancer Res and Treatment, 2019

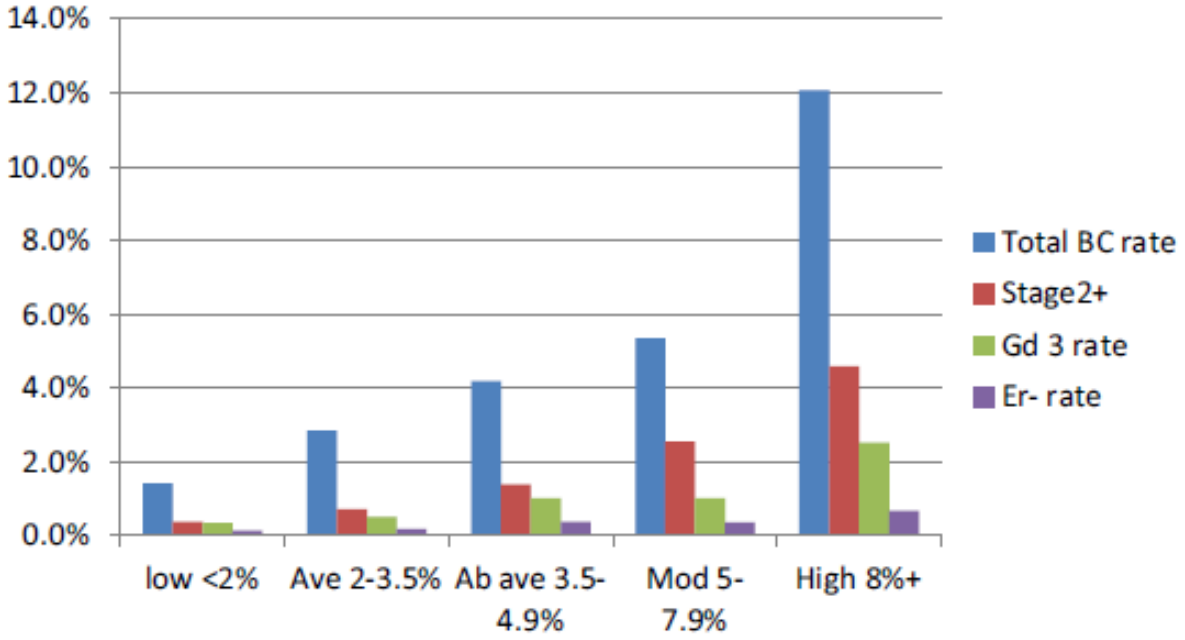


Fig. 1 10-year actual prospective breast cancer rates by combined TC-DR-SNP18 group excluding prevalent cancers at first screen

Evans et al., Breast Cancer Res and Treatment, 2019

PROSTATE CANCER

>170 SNPs associated with prostate cancer

SNPs account for 1/3 of the genetic component of prostate cancer risk

PRS are associated with a 3-6-fold increase in prostate cancer

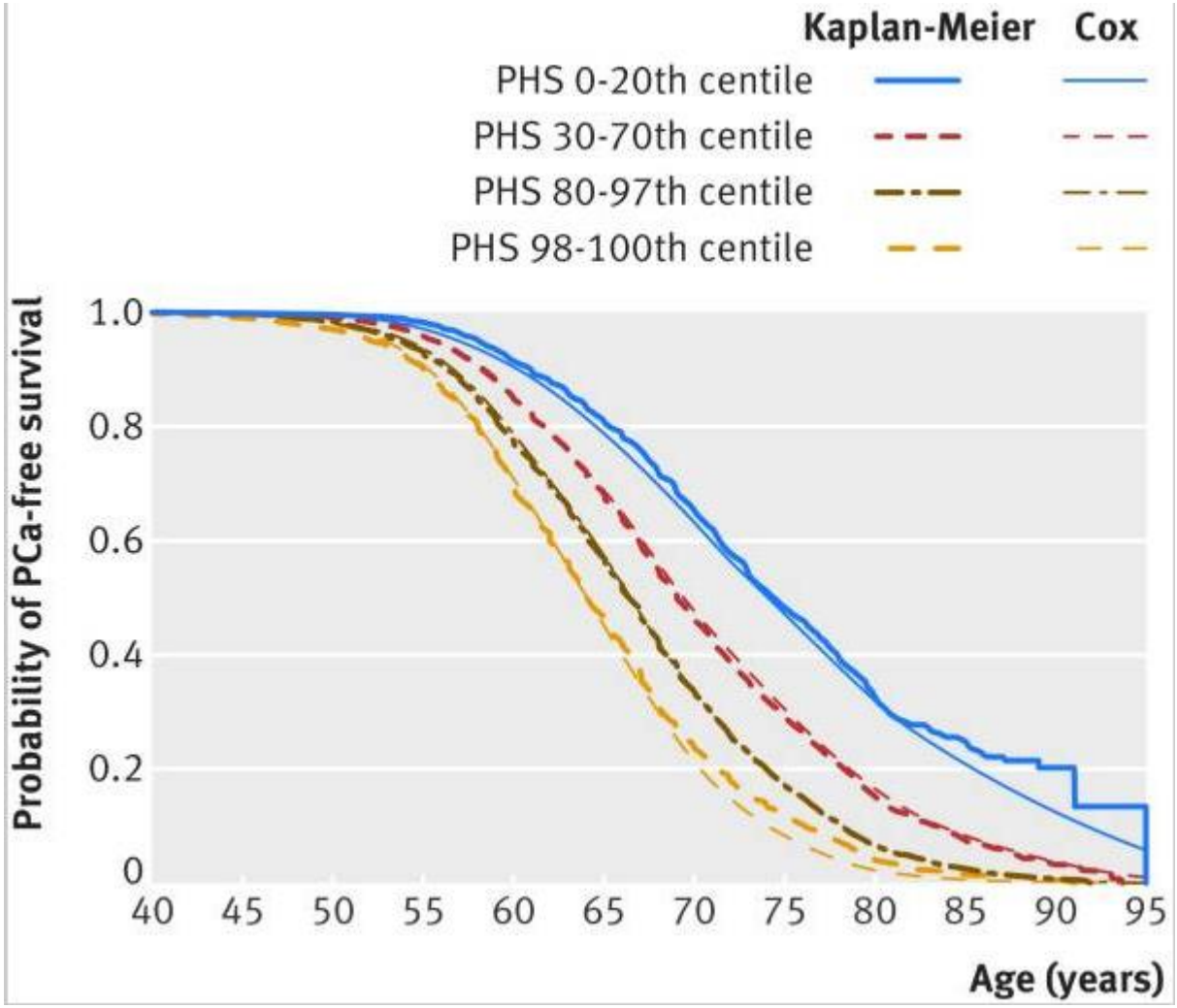
Fantus R, Clinical Chemistry, 2019

Prostate Cancer Associated Group to Investigate Cancer Associated Alterations in the Genome PRACTICAL

- 54 SNPs used to create a PRS
- Predicted any prostate cancer
- Predicted aggressive prostate cancer
- Correlated with positive predictive value of PSA for aggressive disease
- Genomic risk was independent of family history

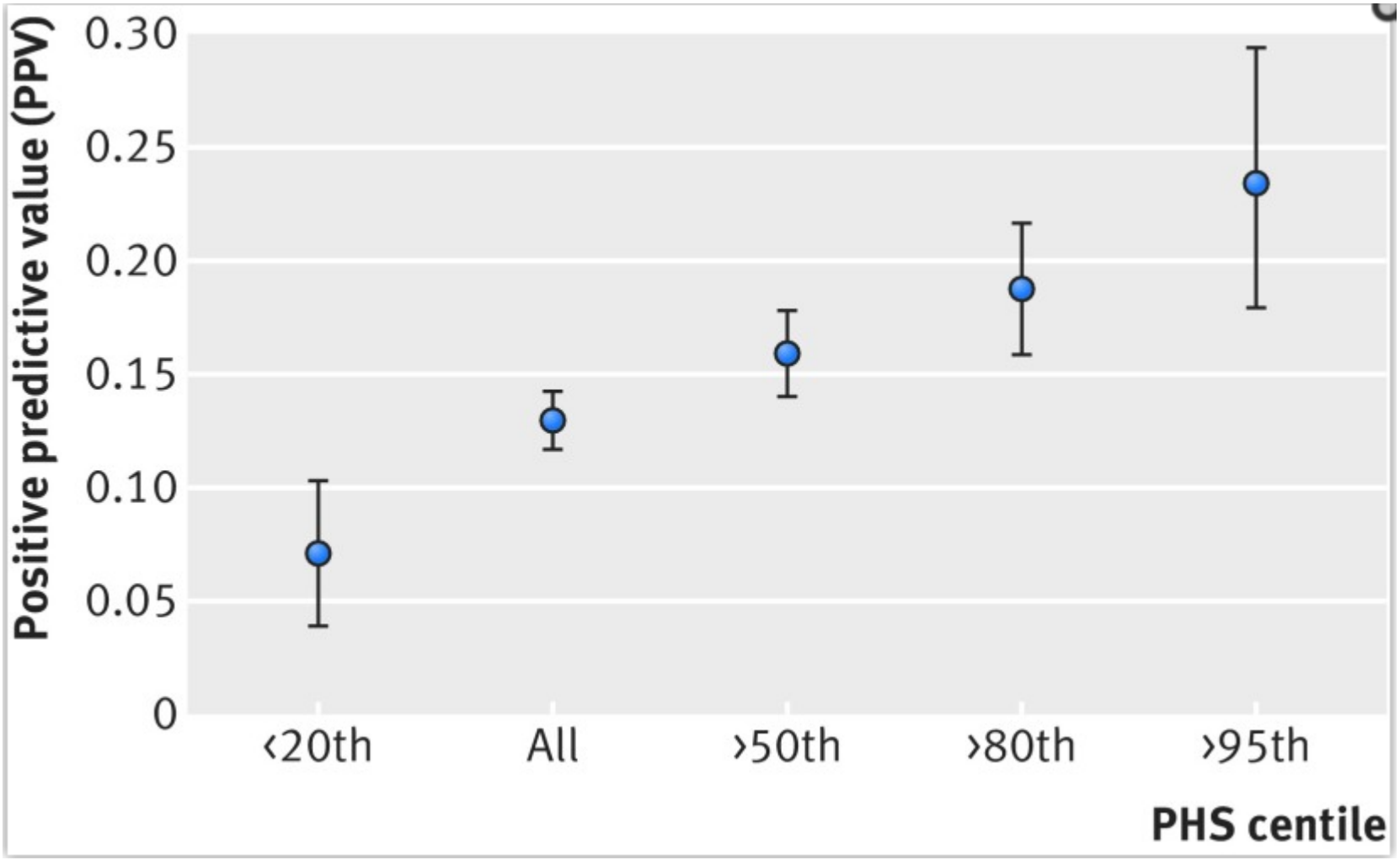
Seibert T et al., BMJ, 2018

Prostate Cancer



Seibert T et al., BMJ, 2018

Prostate Cancer



Seibert T et al., BMJ, 2018

Limitations

- What level of predictive values should be included in PRSs
- How will they perform in non-European populations
- How will they perform across the lifespan
- Is clinical application feasible

2. Another opportunity to explore the interaction of genomic data and screening biomarkers

-Solving the problem of variable penetrance. Can we link function to biomarker performance?

- Genetic modifiers
- Epigenetics
- Non-genetic modifers
- Functional studies (eg., mRNA transcript expression)

V. Cautionary Tales

- Patient preference
- Labeling
- Over and under diagnosis
- Lack of provider and consumer education