Assessment of Breast Cancer Risk with Genetic Polymorphisms

Antonis C. Antoniou

Centre for Cancer Genetic Epidemiology
Department of Public Health and Primary Care
University of Cambridge

Cancer risk prediction in the era of NGS

- Next Generation sequencing technologies
- Multi-gene and SNP panels

- Clinical utility depends

  - Reliable cancer risk estimates?
  - Comprehensive cancer risk prediction models?

Outline

- Joint effects of common genetic variants?
- Joint effects of common and rare genetic variants?
- How do genetic and lifestyle/hormonal factors interact?
- Implications for breast cancer risk stratification?
- Available breast cancer risk prediction tools?
- BOADICEA updates: rare and common variants

Individual SNP associations

- Each SNP: 0, 1, 2 risk alleles
- Odds Ratio estimates per risk allele: 1.02-1.30
- Minor allele frequencies: >0.01

- Individual SNP predictive ability poor
- SNPs combine multiplicatively on risk scale

Michailidou et al, Nat Genet 2015

Combined SNP associations

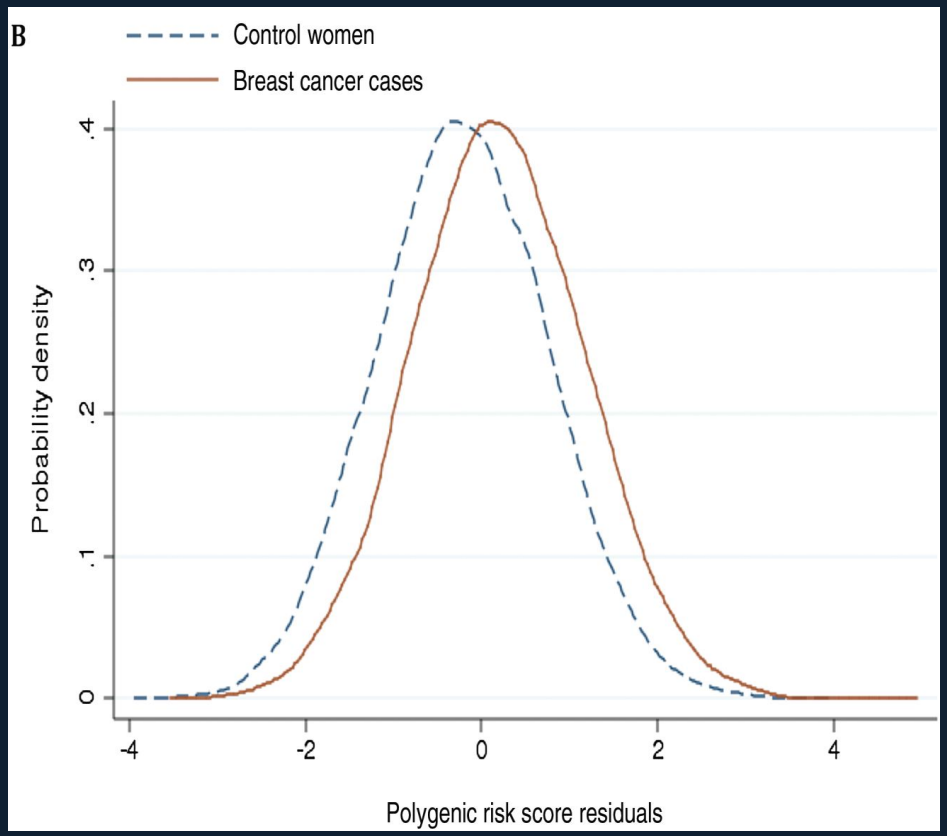
- Polygenic Risk Scores (PRS)

$$PRS = \beta_1 X_1 + \beta_2 X_2 \ldots + \beta_n X_n$$

Log(Odds Ratio) estimate

Number of risk alleles at each SNP

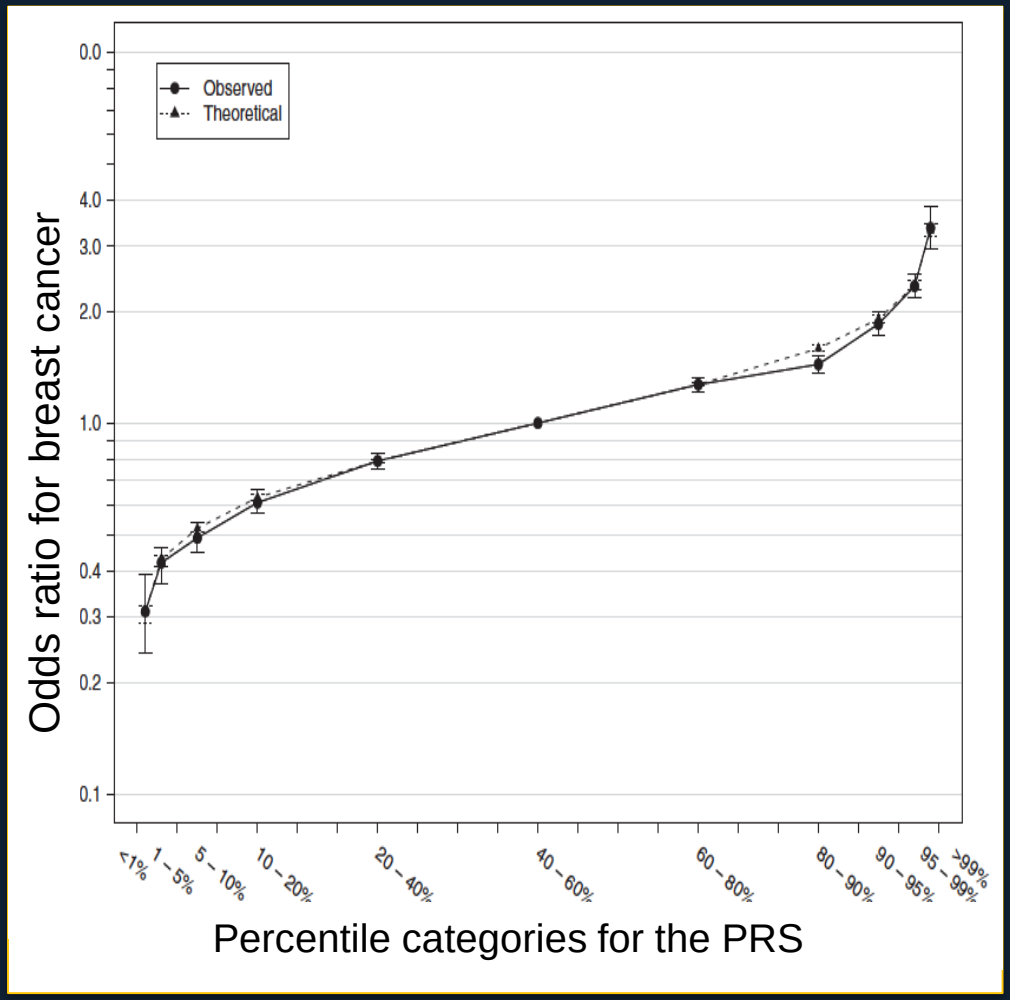
77- SNP Polygenic Risk Score



- Breast Cancer Association Consortium (BCAC)
- 33, 673 breast cancer cases and 33,381 control women
- PRS normally distributed in both cases and controls
- Mean PRS (cases)=0.69
  Mean PRS (controls)=0.49

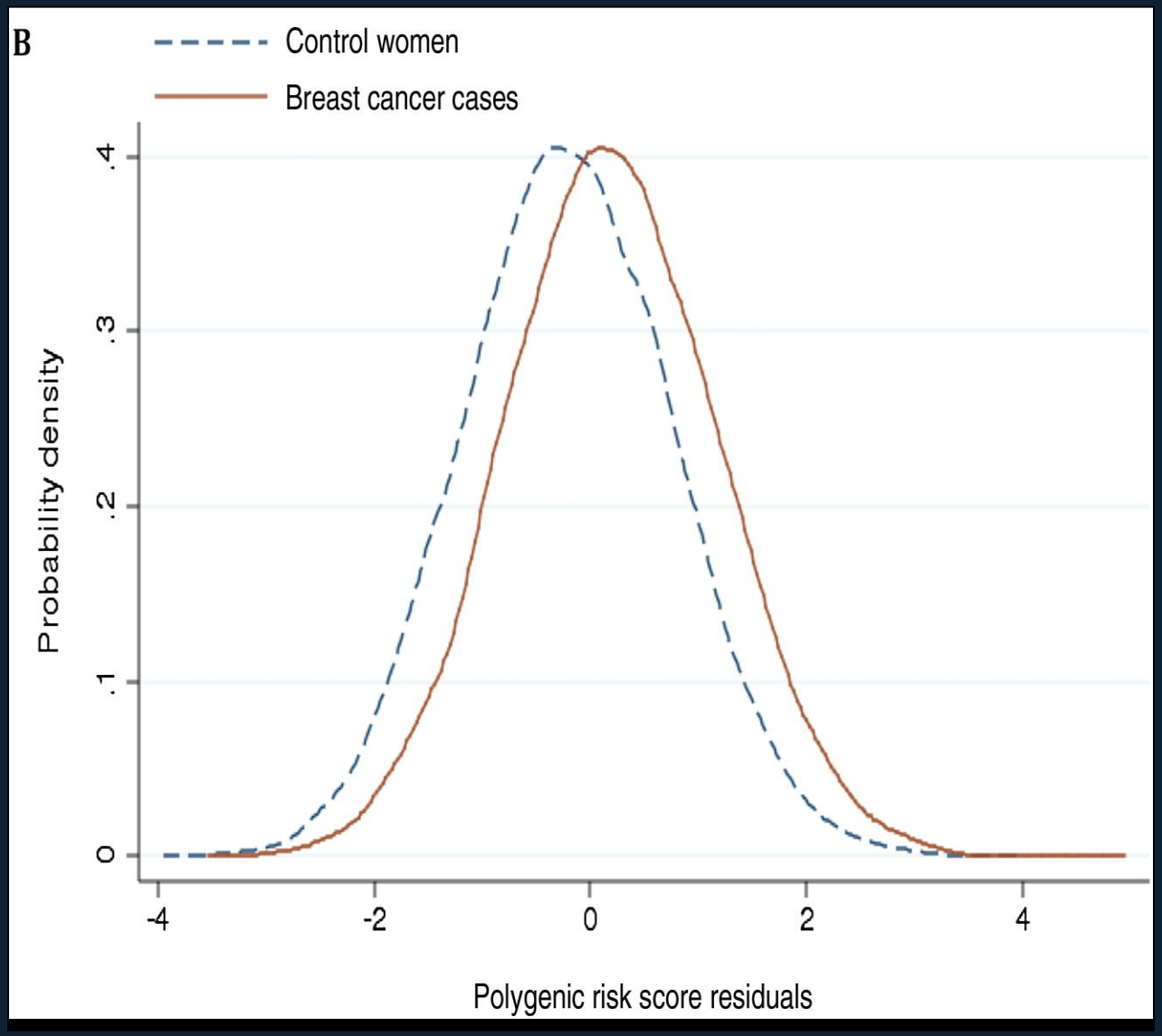
Mavaddat et al JNCI 2015

Empirical PRS Odds Ratios VS predicted under multiplicative model



Mavaddat et al JNCI 2015

77-SNP PRS and risk stratification



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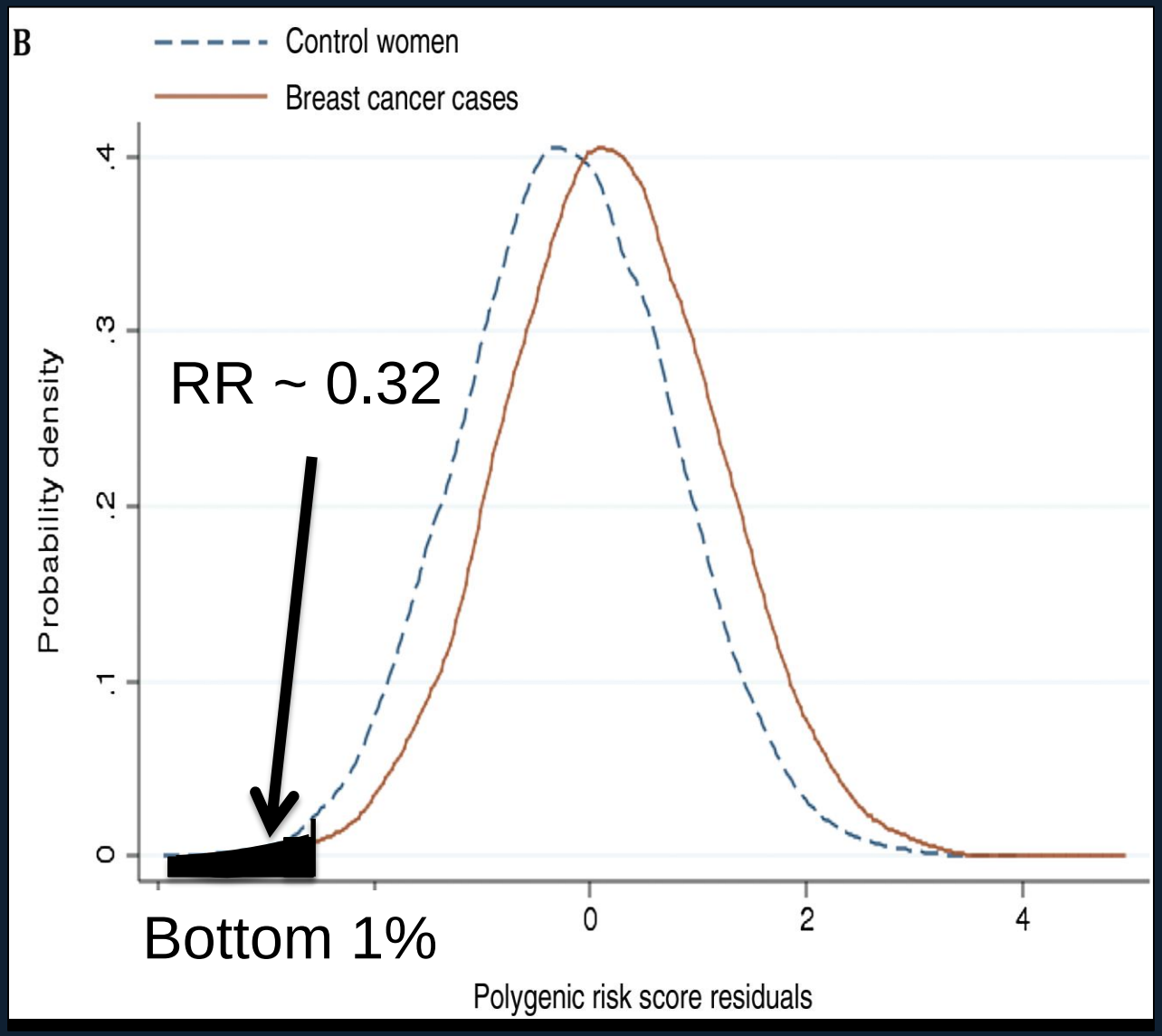

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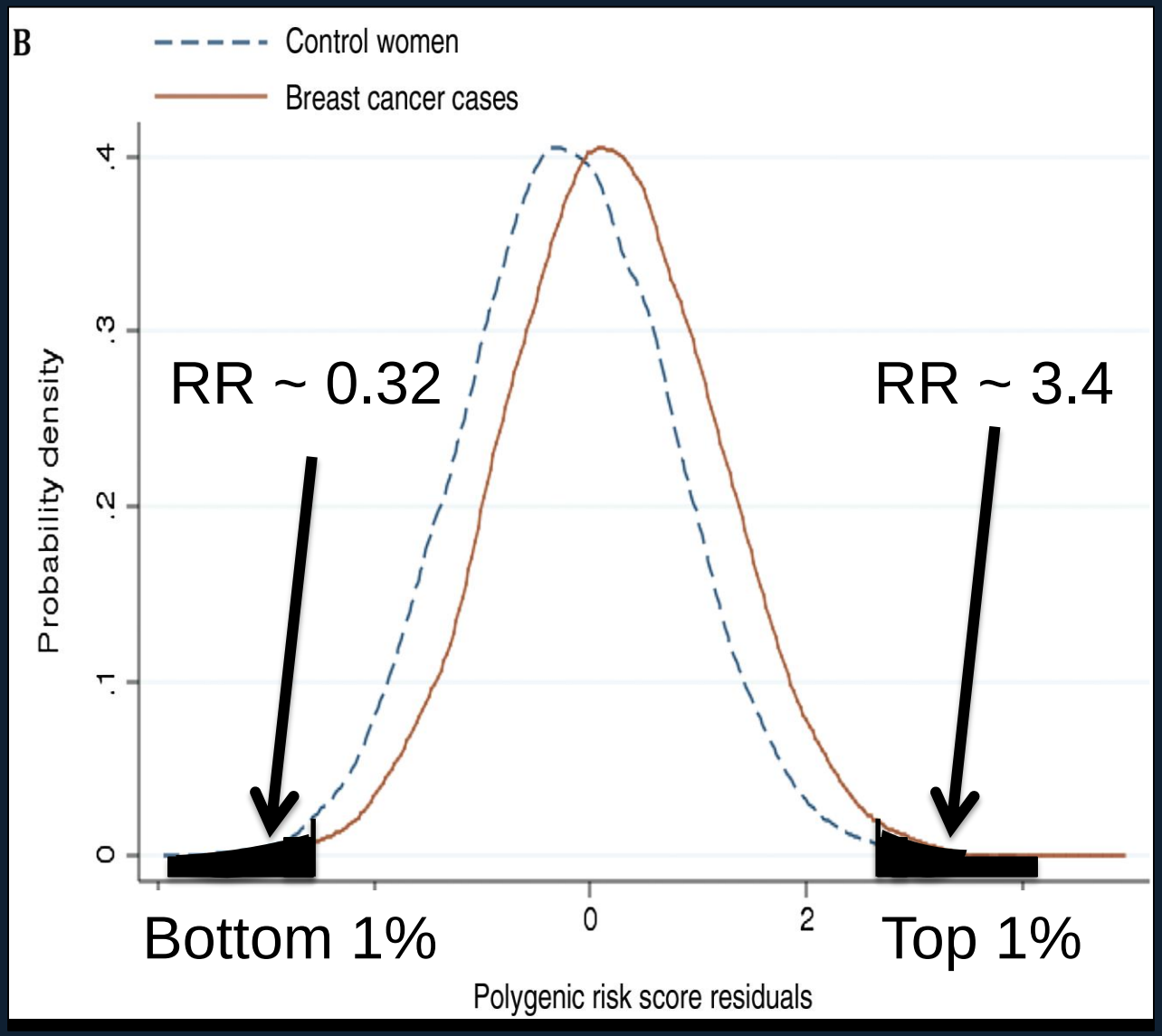
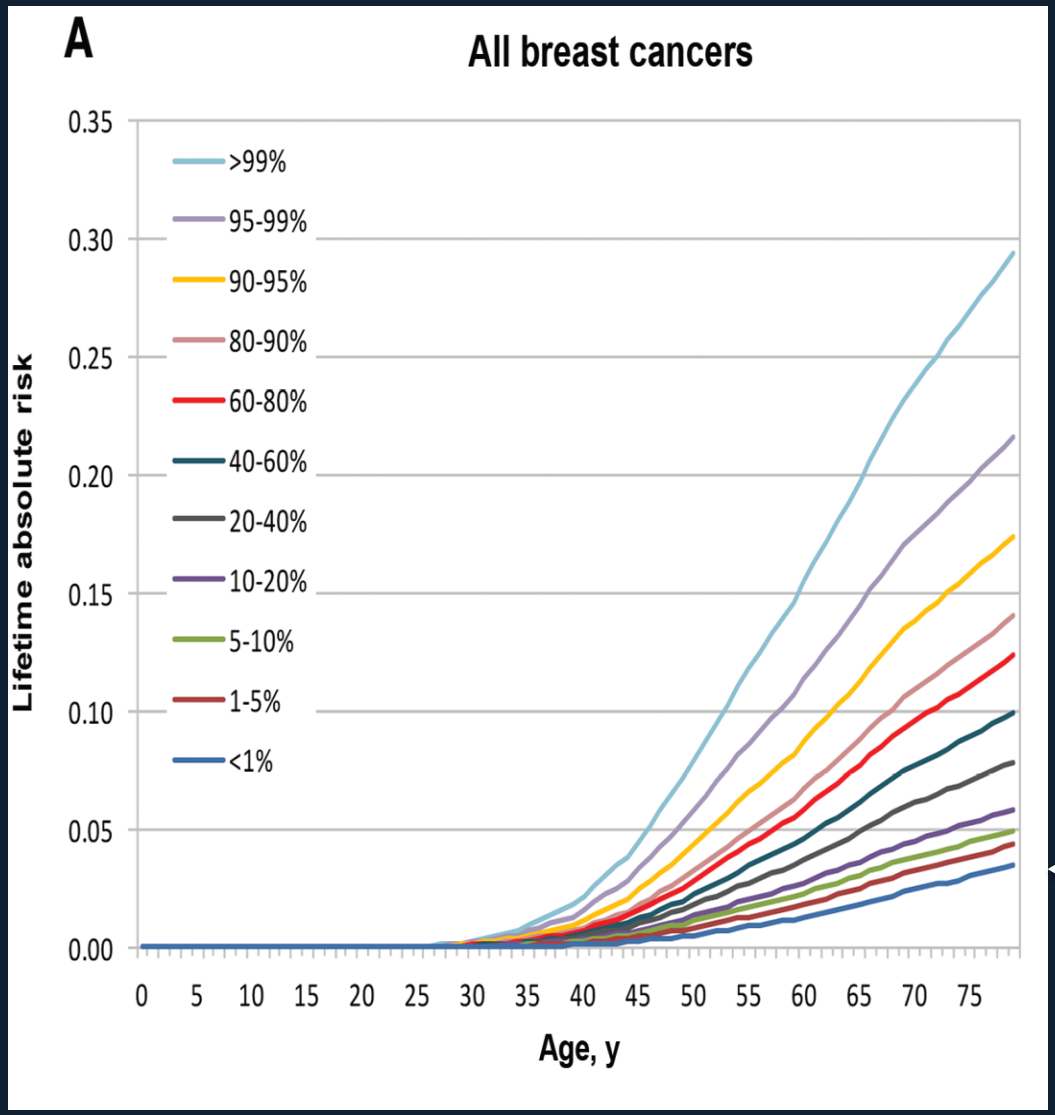


Mavaddat et al JNCI 2015

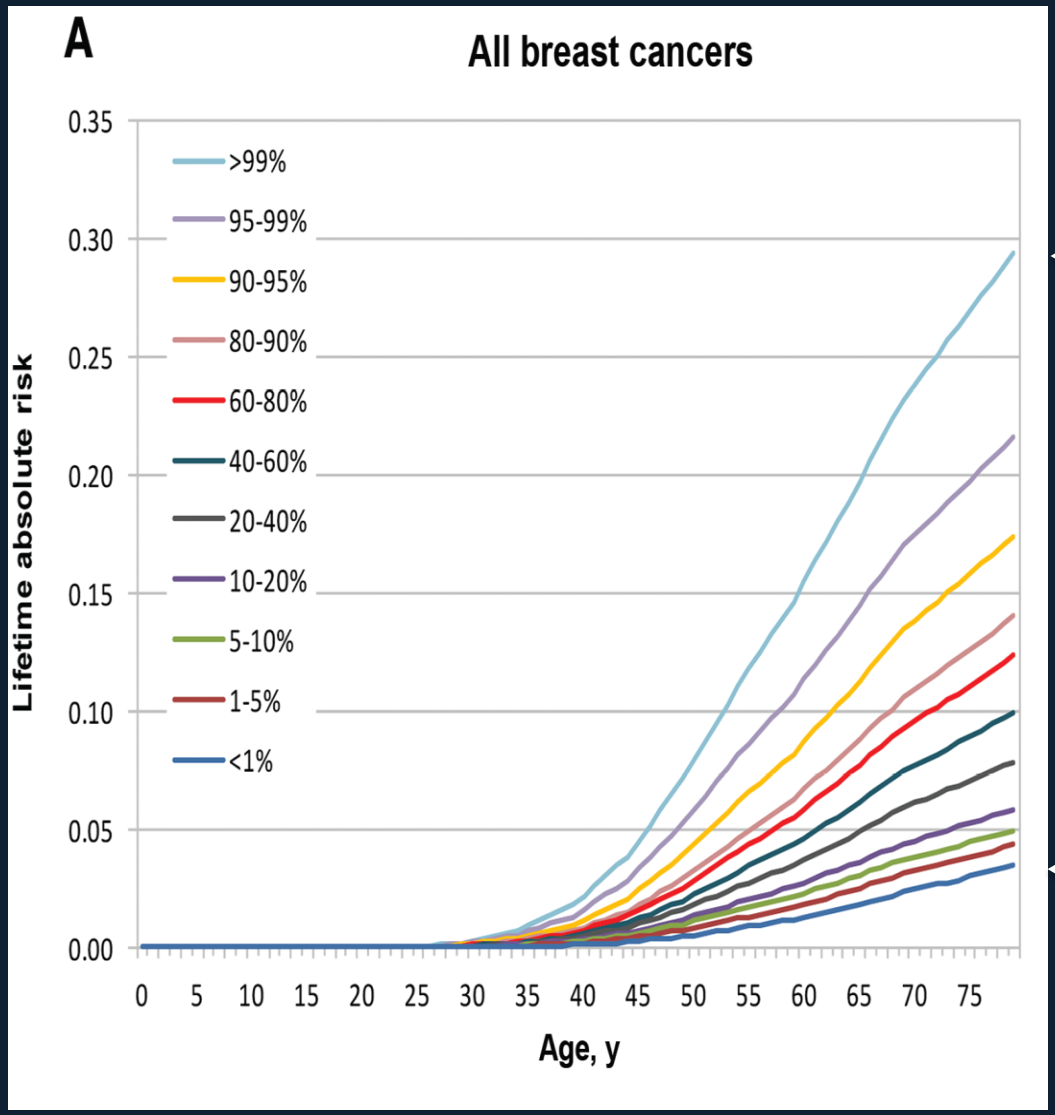
PRS and lifetime breast cancer risk



3.5%

Mavaddat et al JNCI 2015

PRS and lifetime breast cancer risk

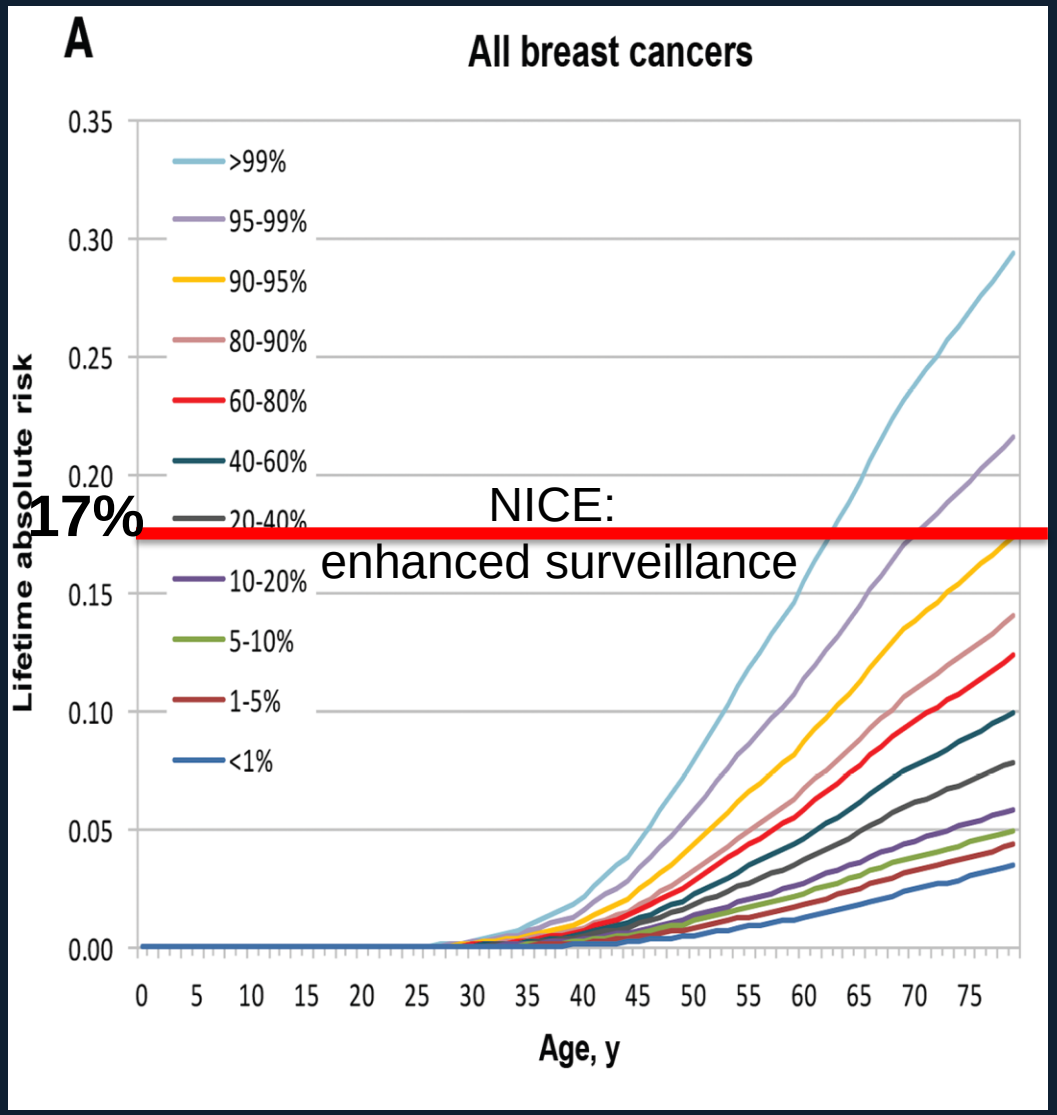


29%

3.5%

Mavaddat et al JNCI 2015

PRS: implications for clinical management



- 8% of all UK women
- 17% of all breast cancer cases

Mavaddat et al JNCI 2015

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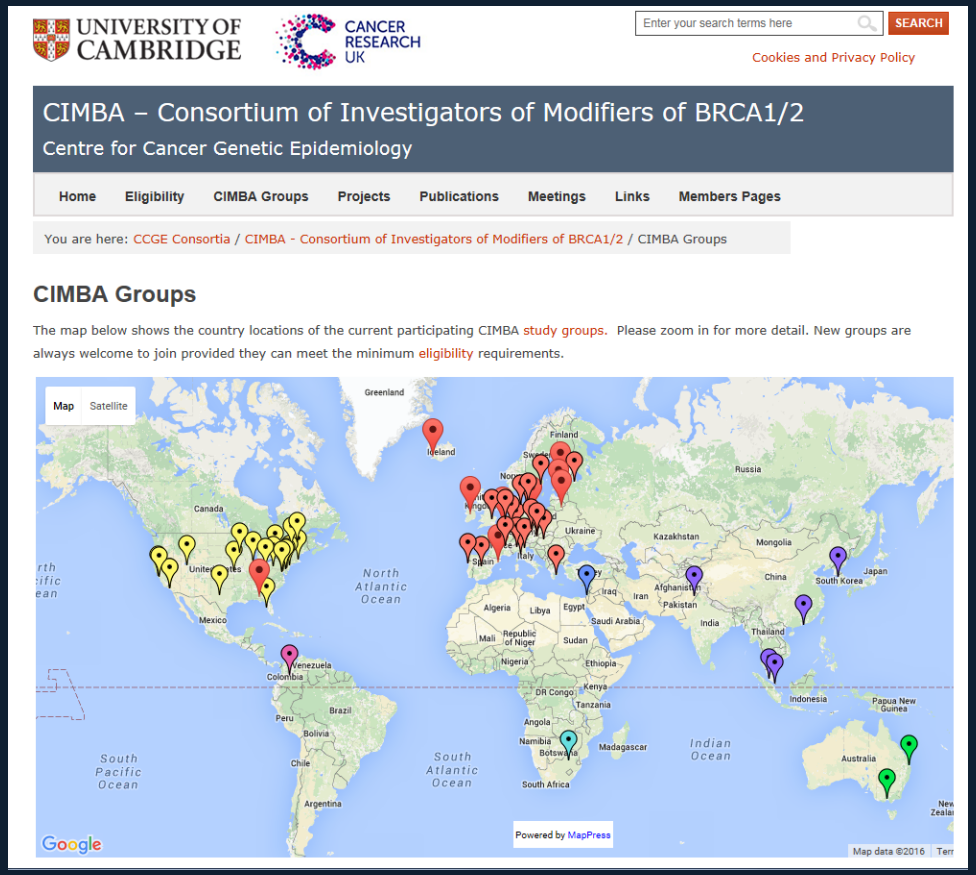
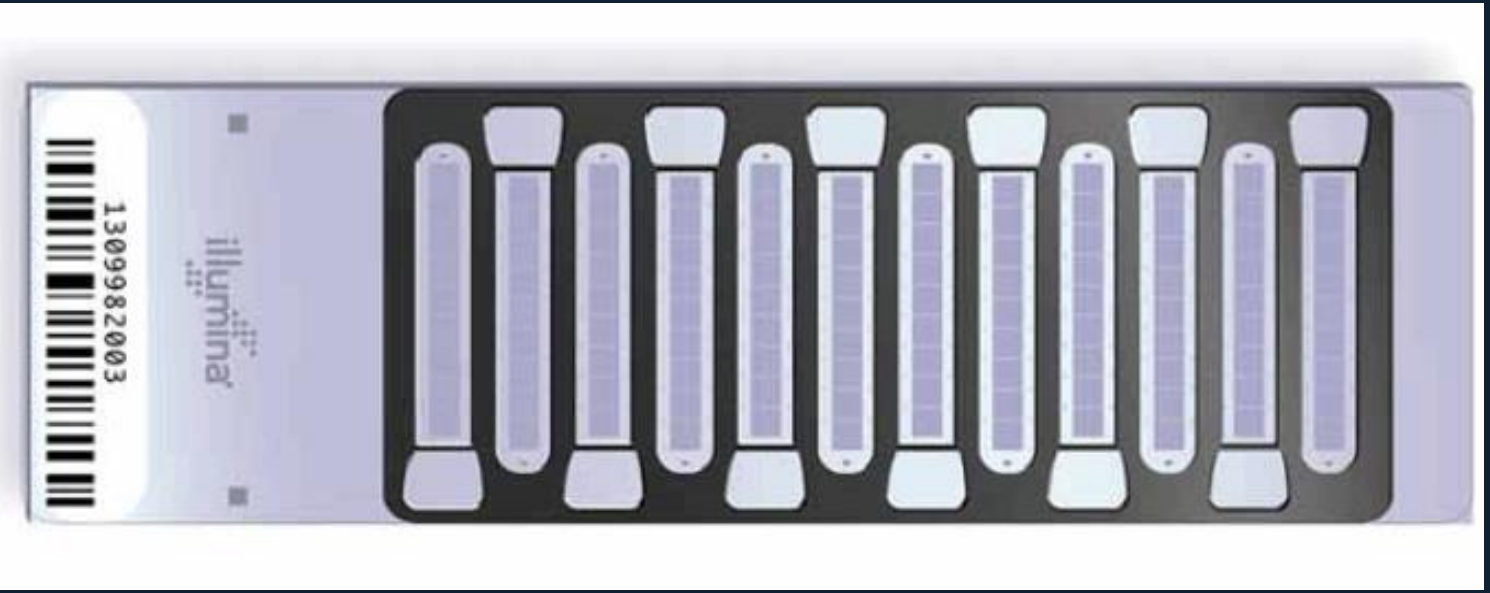
Consortium of Investigators of Modifiers of *BRCA1/2*



- >70 groups from Europe, North America, Australia, Asia, Africa and South America
- >55,000 *BRCA1, BRCA2* mutation carriers

iCOGS, OncoArray high-density custom arrays

Characterising cancer loci



>35,000 *BRCA1* and *BRCA2* samples genotyped

CIMBA: OncoArray results

- 10 new *BRCA1* breast cancer susceptibility loci (Milne et al, Nat Genet, In press)
  - 39 modifiers of BC risk for *BRCA1* carriers
  - 37 modifiers of BC risk for *BRCA2* carriers
- 3 new ovarian cancer susceptibility loci
  - 19 modifiers of OC risk for *BRCA1/2* carriers (Phelan et al, Nat Genet, 2017)

Risk modifying loci – patterns of association

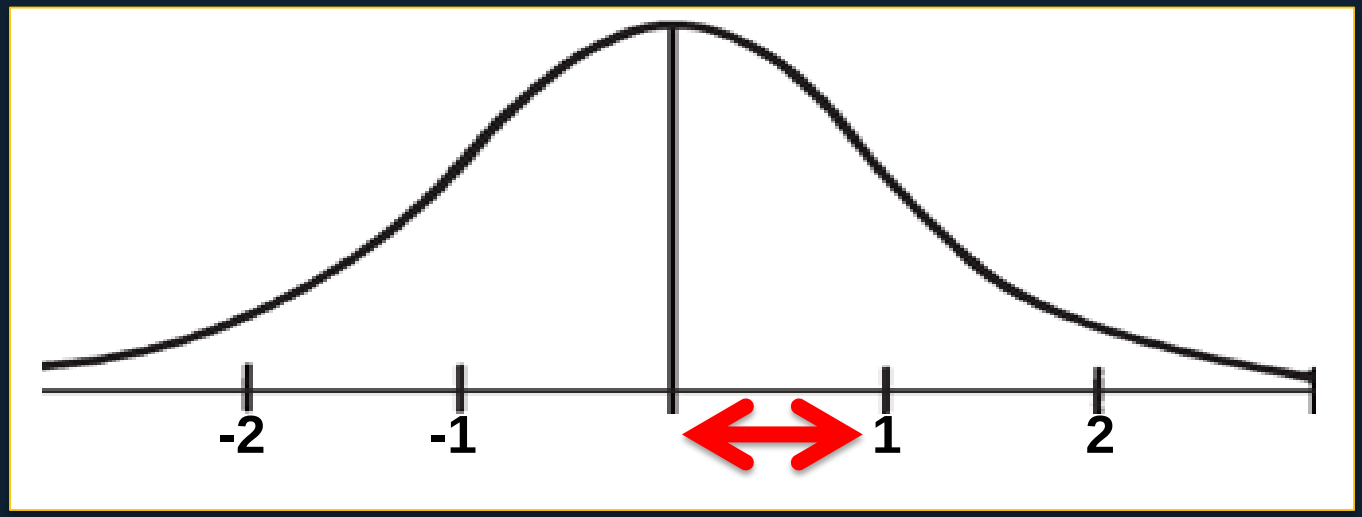
- Most SNPs associated with risk in the population also modify risk for carriers

- *BRCA1* BC modifiers: Primarily associated with ER-negative

Kuchenbaecker et al BCR (2014) & JNCI (2017); Milne et al Nat Genet (In press)

Polygenic Risk Scores: *BRCA1* – Breast Cancer

BRCA1 sample: 7,797 affected vs 7,455 unaffected



PRS type	HR	P-value
Overall breast cancer (88 SNPs)	1.14	$2x10^{-18}$
ER-positive (87 SNPs)	1.11	$3x10^{-13}$
ER-negative (53 SNPs)	1.27	$7x10^{-53}$

Kuchenbaecker et al, JNCI 2017

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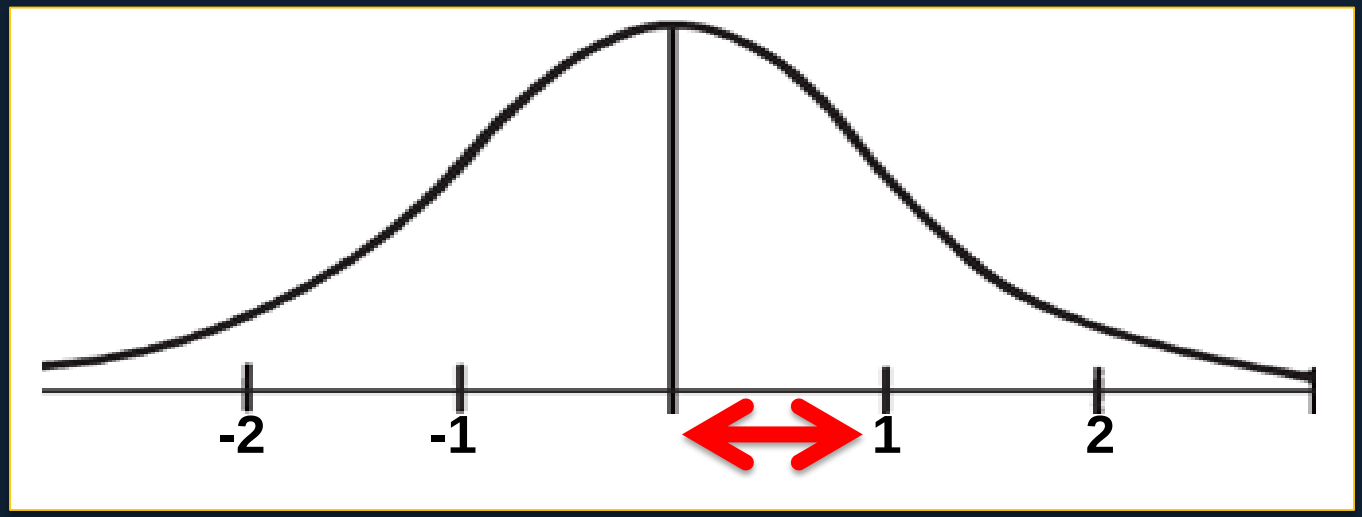

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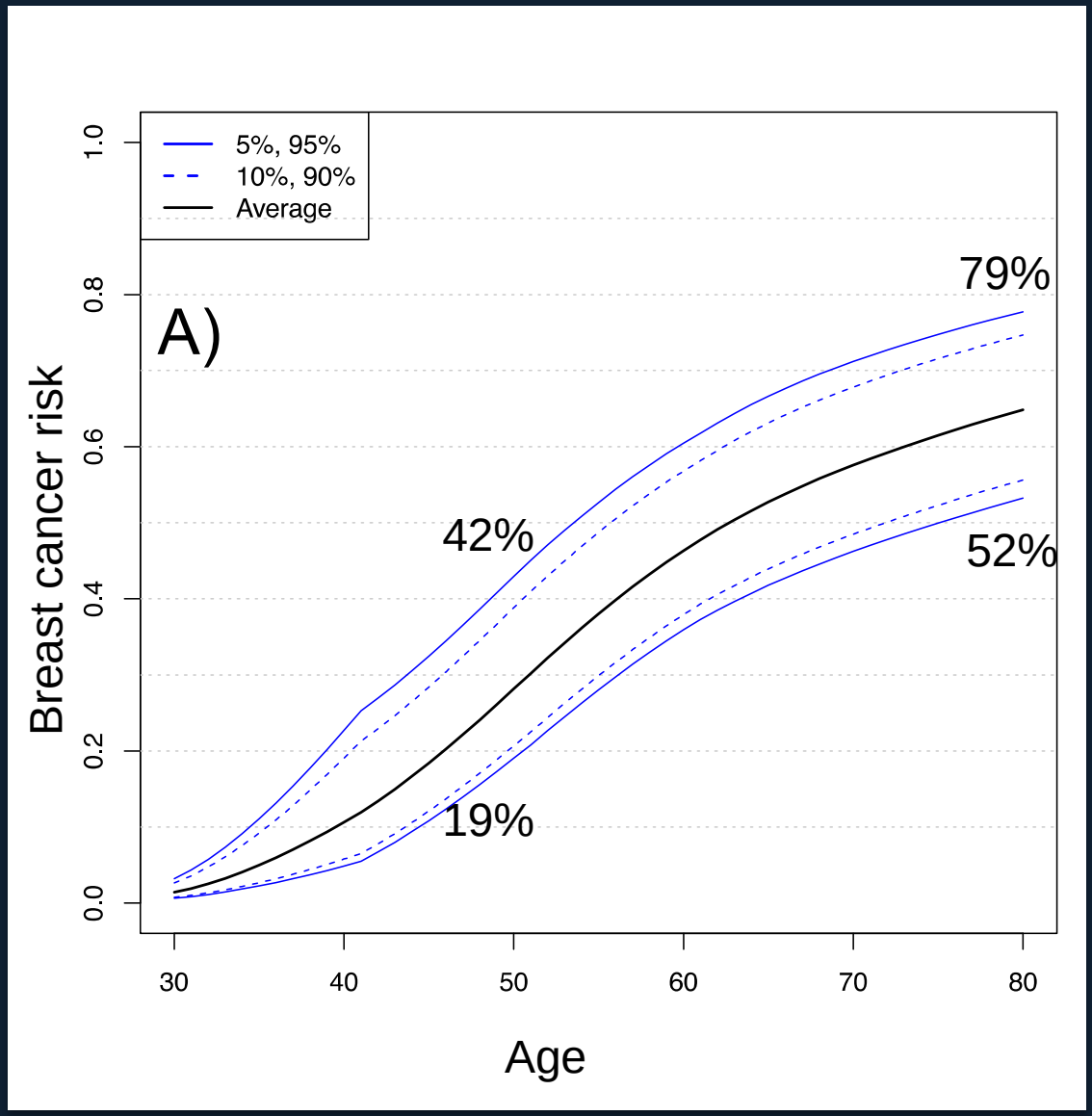
BRCA1 mutation carriers: Breast cancer risk by PRS



Kuchenbaecker et al, JNCI 2017

PRS and breast cancer risk associations in CHEK2*1100delC carriers

	Noncarriers		CHEK2*1100delC carriers	
	OR (95% CI)	*P*	OR (95% CI)	*P*
PRS[a]	1.58 (1.55–1.62)	<1.0E-10	1.59 (1.21–2.09)[b]	0.0008
Percentile of PRS, %				
<20	0.52 (0.48–0.56)	<1.0E-10	0.52 (0.16–1.74)	0.29
20–40	0.78 (0.72–0.84)	2E-11	0.72 (0.28–1.88)	0.51
40–60	Referent		Referent	
60–80	1.25 (1.16–1.34)	8E-10	0.93 (0.39–2.25)	0.88
>80	1.92 (1.80–2.06)	<1.0E-10	2.03 (0.86–4.78)	0.11

Muranen et al, Genet Med (2016)

Combined effects of genetic, lifestyle/hormonal factors

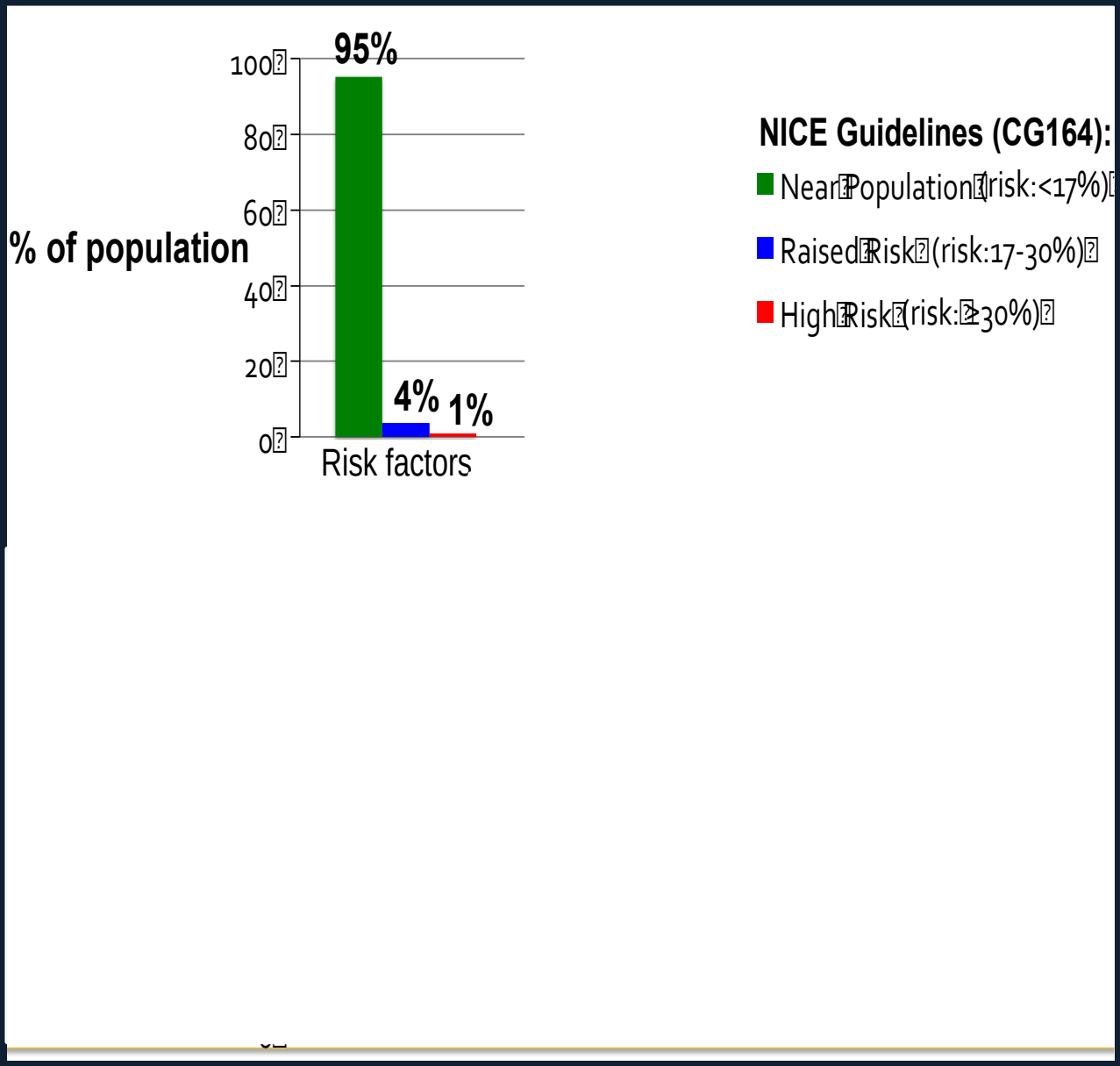
- Studies of PRS x Lifestyle/hormonal factors ongoing

- SNP x Lifestyle/hormonal factors

  - **Multiplicative model plausible**

Nickels et al Plos Genet (2013); Campa et al , JNCI 2011; Rudolph et al BCR 2015; Rudolph et al IJC (2015); Vachon et al JNCI (2015); Maas et al JAMA Oncol (2016)

Potential for transformative risk stratification



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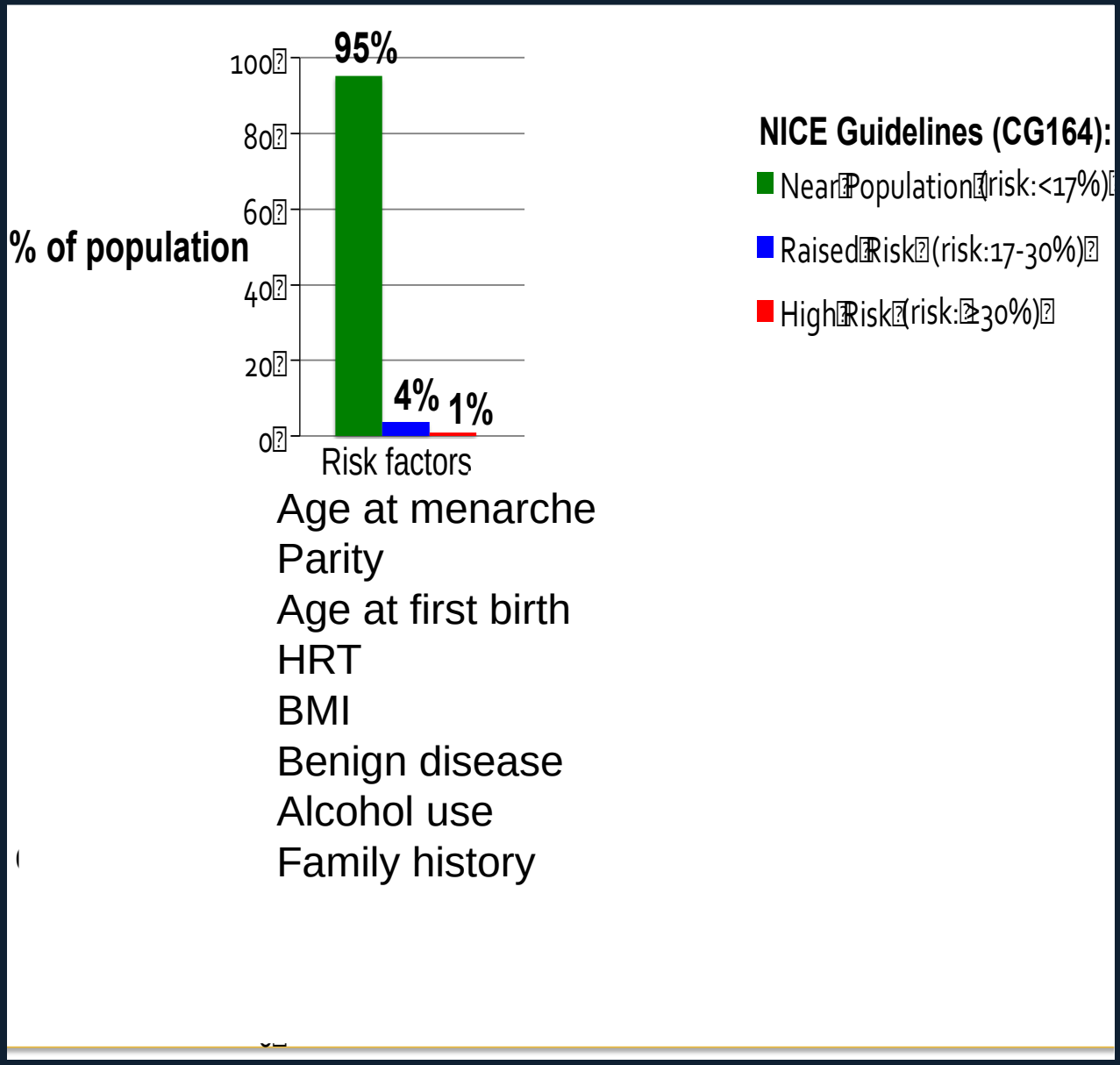
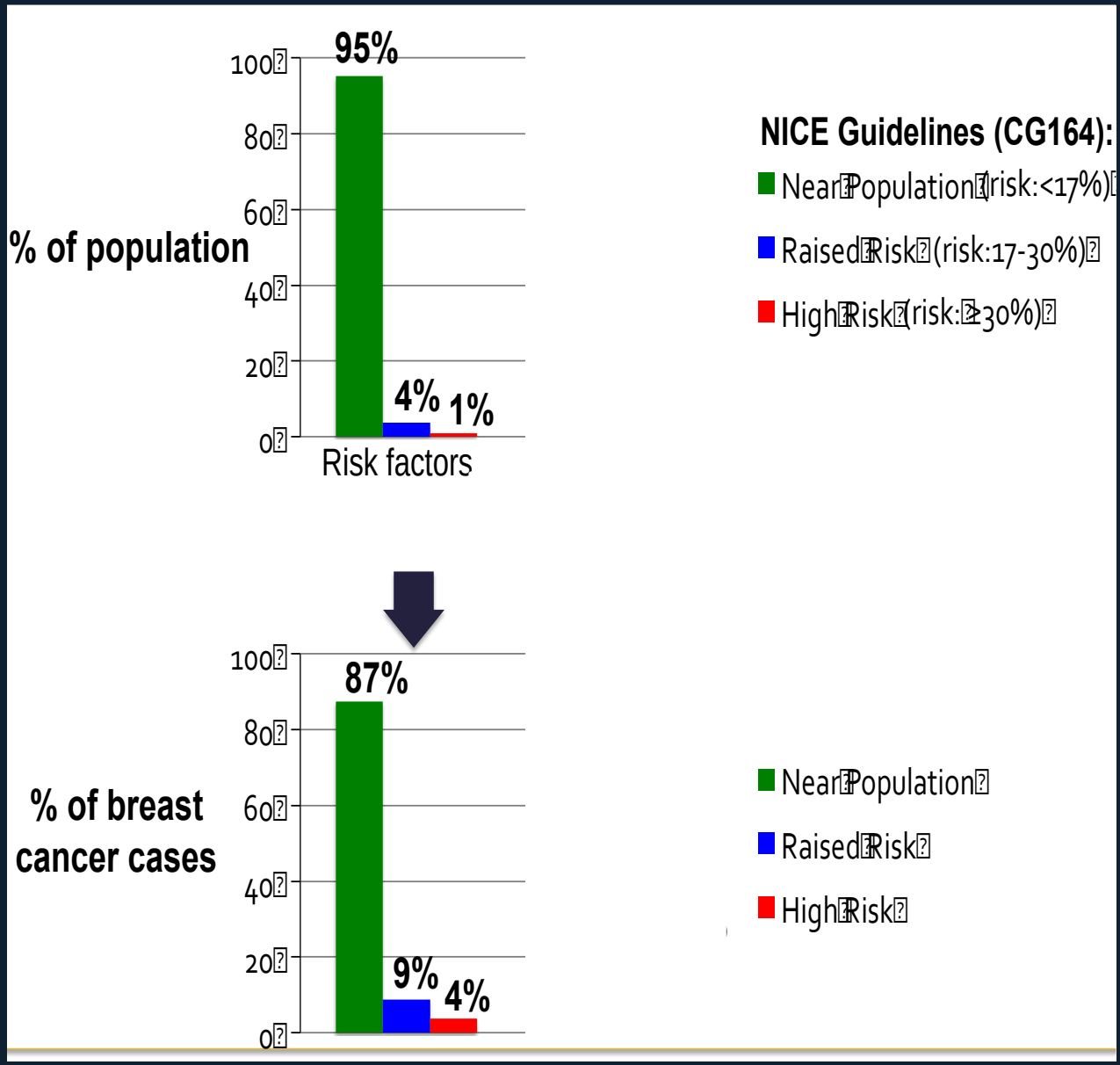


Age at menarche
Parity
Age at first birth
HRT
BMI
Benign disease
Alcohol use
Family history

Potential for transformative risk stratification



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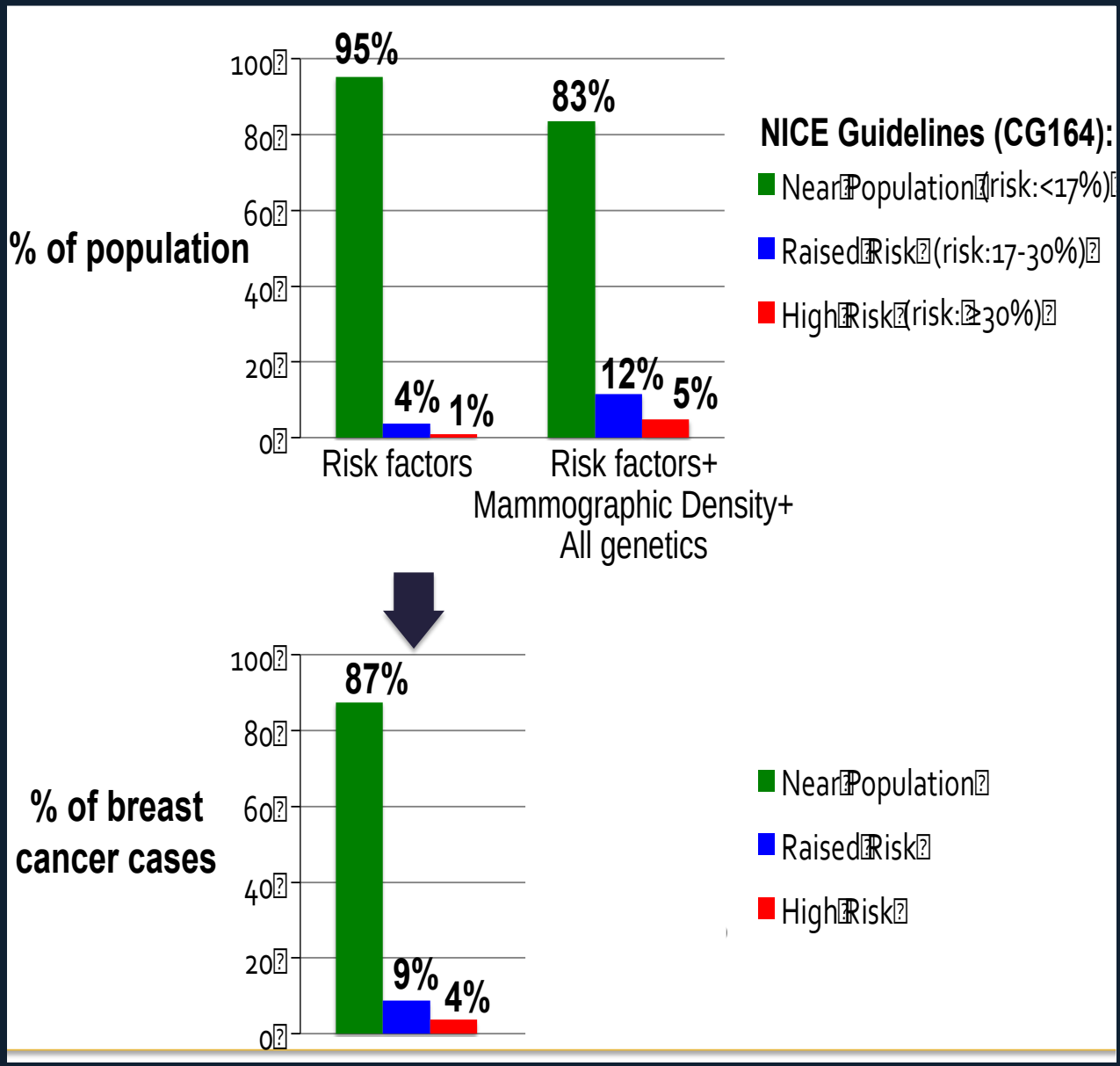

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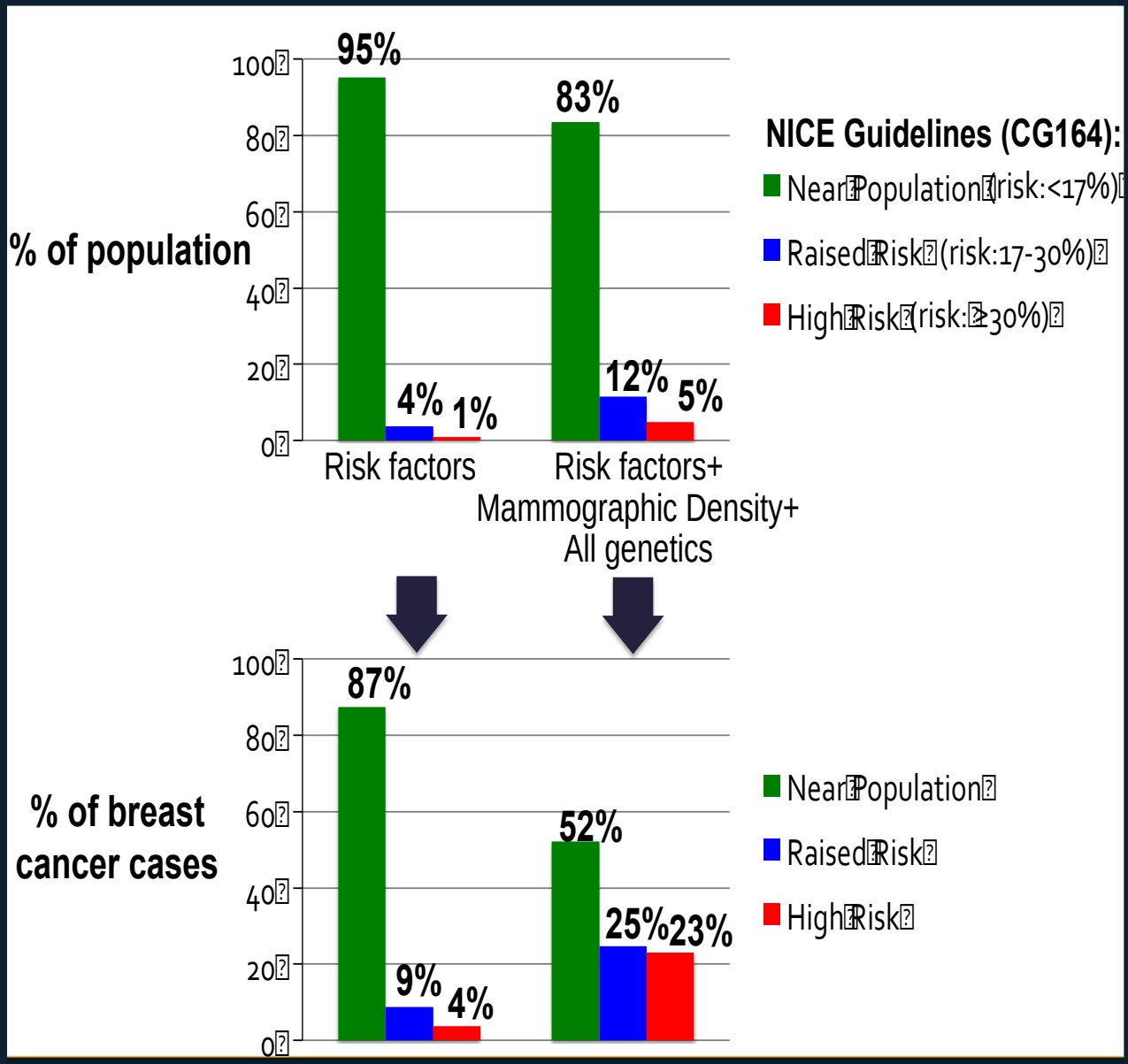


Breast cancer risk assessment tools

TABLE 2. Breast Cancer Risk Assessment Tools Used in Clinical Practice: Components and Assumptions

Factor*	Gail	Claus	BRCAPRO	IBIS	BOADICEA
Family history	YES (descriptive)	YES	YES	YES	YES
BRCA1, BRCA2 mutations	NO	NO	YES	YES	YES
Common low-risk alleles	NO	NO	NO	NO	NO
Intermediate-high risk mutations (***CHEK2, PALB2, ATM,*** etc.)	NO	NO	NO	NO	YES**
Residual non-***BRCA1/2*** familial aggregation	NO	NO	NO	YES; dominant 3rd gene	YES; polygenic
BRCA1/2 breast cancer pathology associations	NO	NO	YES†	NO	YES
BRCA1/2 risk modification by family history	NO	NO	NO	NO	YES
Variants of uncertain significance	NO	NO	NO	NO	NO
Predicting estrogen receptor (ER)-specific risks	NO	NO	NO	NO	NO
Mammographic density	NO	NO	NO	NO	NO
Hormonal, lifestyle, and reproductive risk factors	YES	NO	NO	YES; assumes same effect on *BRCA1/2*	NO
Other cancers (nonbreast or ovarian cancer)	NO	NO	YES	NO	YES
Predicting second cancer risks (contralateral breast, ovarian cancer)	NO	NO	NO	NO	YES

Kurian, Antoniou & Domchek, 2016 ASCO Educational handbook

Genetic variants in existing breast cancer risk tools

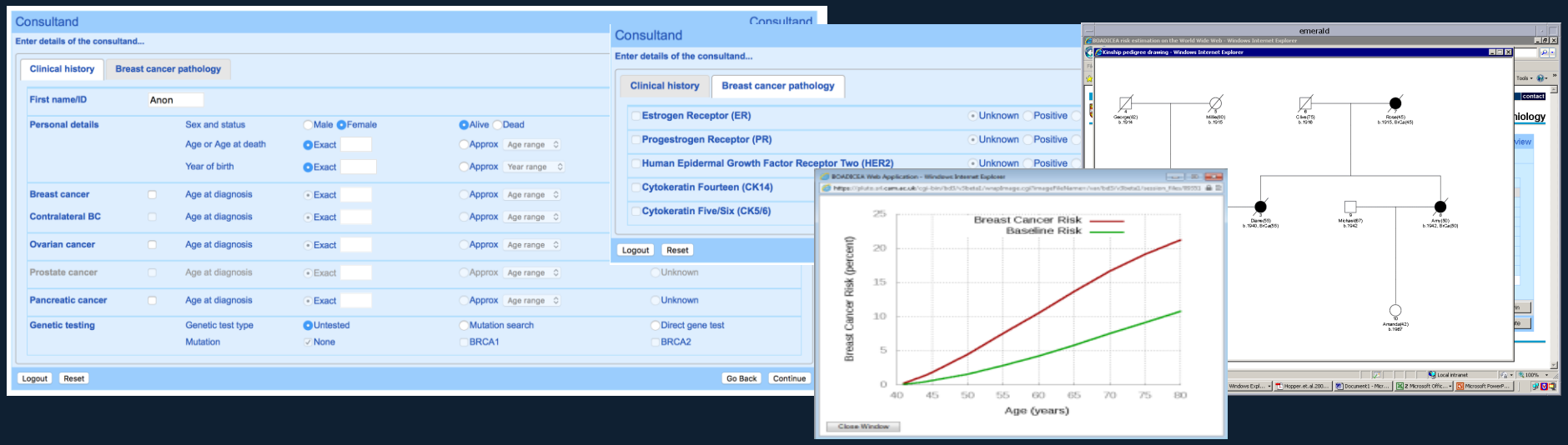
- *BRCA1, BRCA2* mutations
  - BRCAPRO, IBIS, BOADICEA

- Common genetic variants – SNPs
  - No tool incorporating SNPs & risk factors available for clinical use
  - Improved performance of existing algorithms (e.g. IBIS, BOADICEA, Gail) Dite et al (2015); Brentnall et al (2014); Darabi et al (2012)
  - Consistency in modeling joint genetic & lifestyle/hormonal factors required
  - **BPC3 model** (Maas et al 2016)

- Truncating variants in moderate/high risk genes (*PALB2, CHEK2, ATM)*
  - BOADICEA Lee et al Genet Med (2016)

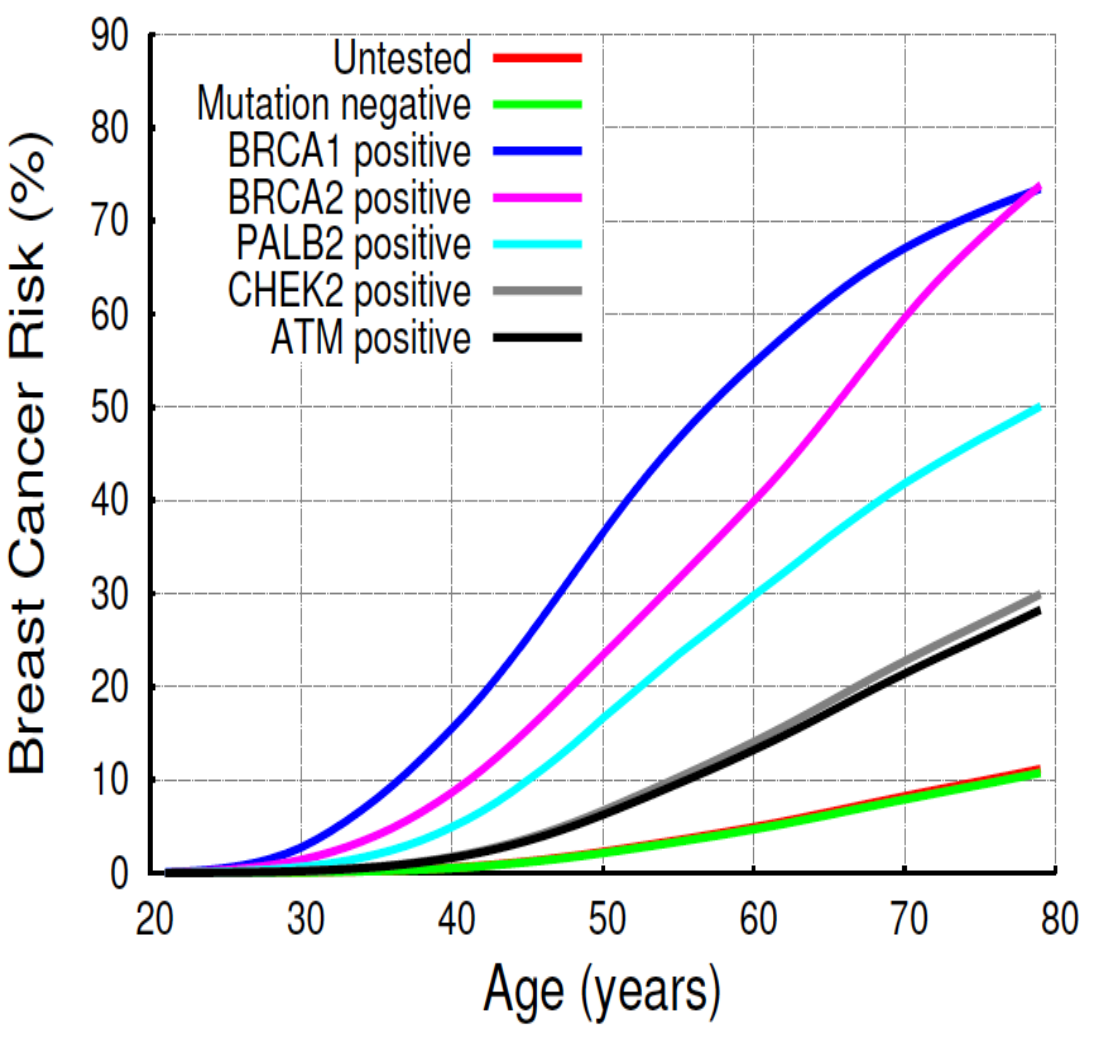
BOADICEA

http://ccge.medschl.cam.ac.uk/boadicea/



- *BRCA1, BRCA2*, polygenic (unobserved genetic effects)
- Family history breast, ovarian prostate, pancreatic cancer
- Tumour characteristics - ER/PR/HER2/Cytokeratin markers
- Population, ethnicity, year of birth

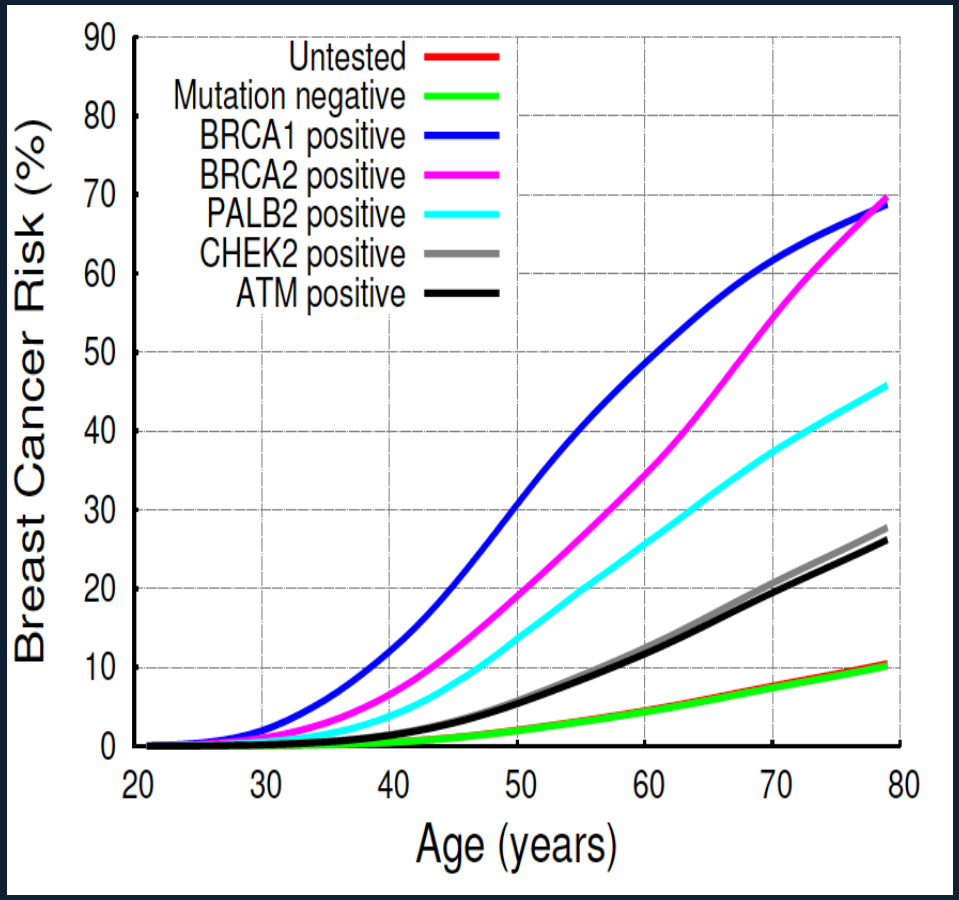
BRCA1, *BRCA2*, *PALB2*, *ATM* and *CHEK2* average breast cancer risks in BOADICEA



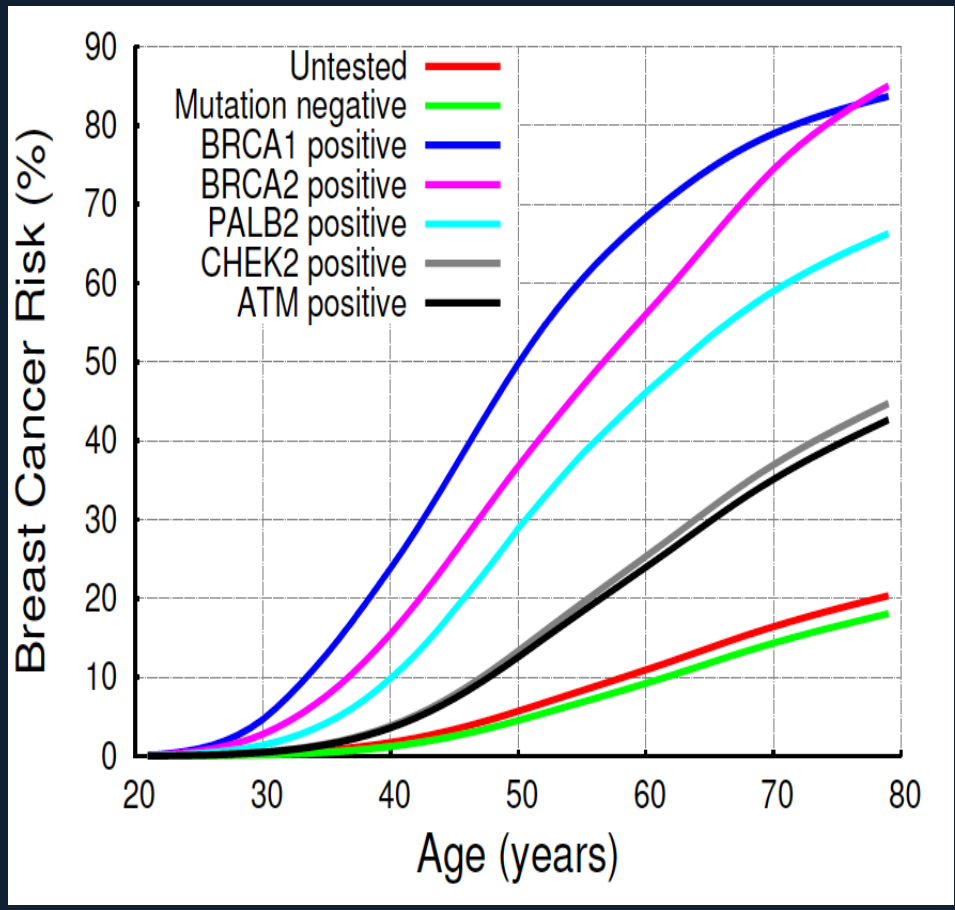
Lee et al, Genet Med (2016)

Risks are family history specific

No affected relatives



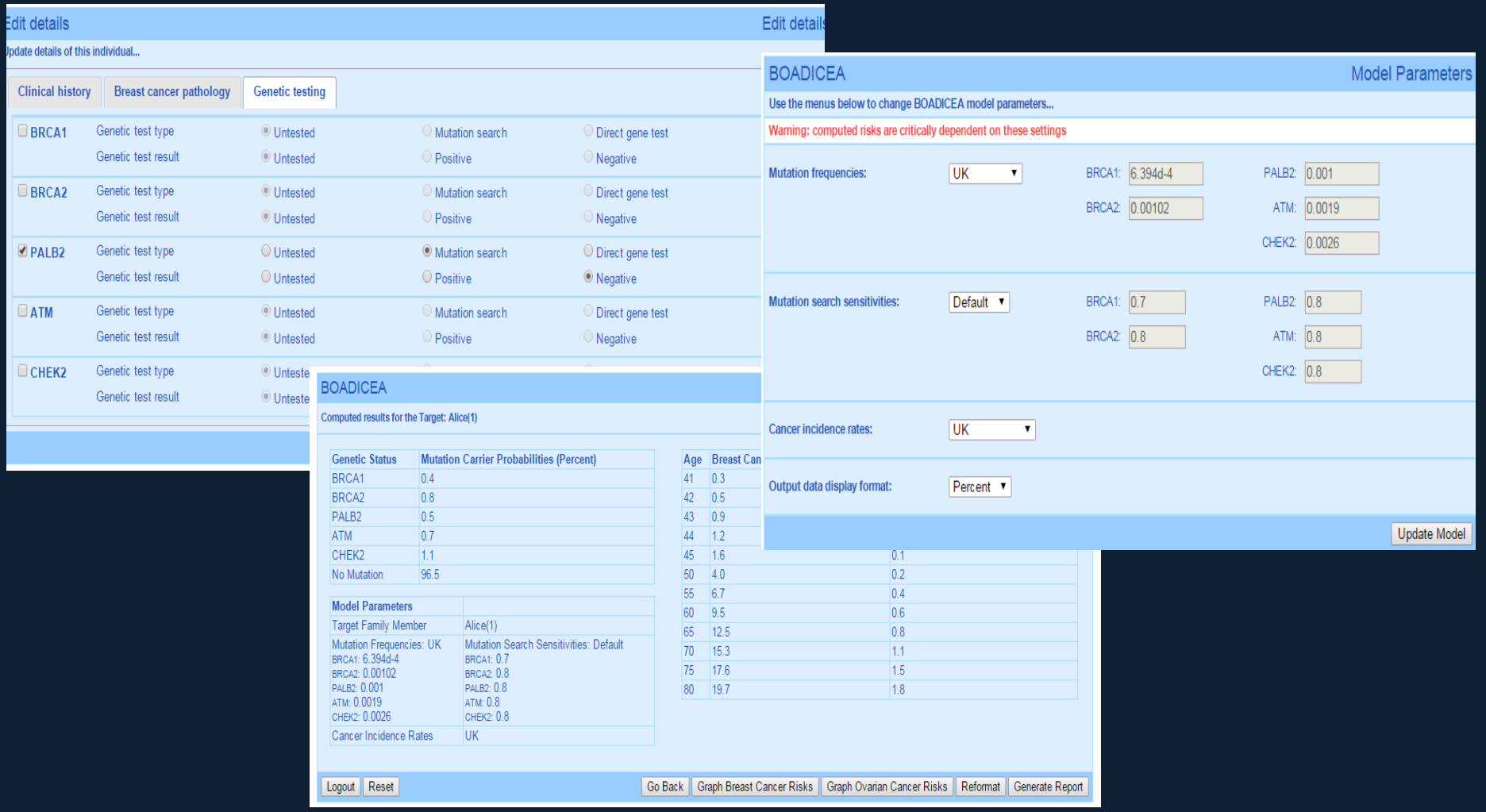
Mother with BC at age 40



Lee et al, Genet Med (2016)

BOADICEA: Beta v.4

https://pluto.srl.cam.ac.uk/cgi-bin/bd4/v4beta14/bd.cgi



Conclusions

- PRS stratifies breast cancer risk in women with and without a family history of breast cancer, *BRCA1/2* mutations
- High levels of stratification can be achieved by combining all genetic and lifestyle/environmental factors
- Levels of risk stratification informative for targeted screening and prevention strategies
- Novel models (e.g. BOADICEA) available that can be used to counsel women undergoing gene-panel testing
- Risk prediction models and tools required based on valid assumptions about the joint risk factor effects
- Risk model validation required in large prospective cohorts

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