UNIVERSITY OF CAMBRIDGE
Department of Public Health and Primary Care

CANCER RESEARCH UK | CAMBRIDGE CENTRE EARLY DETECTION

Assessing cancer risks for women and men with *BRCA1* and *BRCA2* mutations

The EMBRACE study

Antonis C. Antoniou

St George's Information Day for *BRCA* carriers

Outline

- Key clinical and research questions
- The EMBRACE study
- Key scientific findings
- Ongoing and future studies

BRCA1 and *BRCA2* mutation carriers: considerations

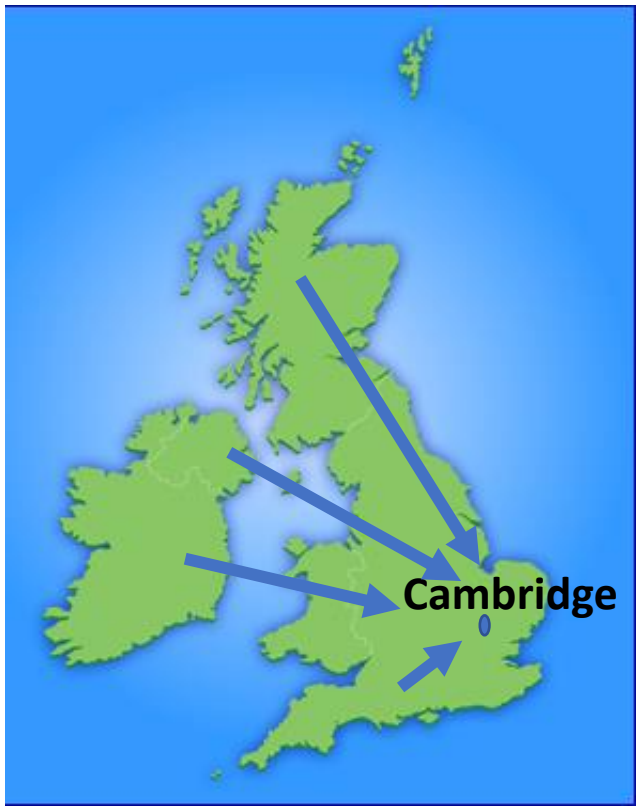
- What my risks of developing cancer over time?
- Risks of cancer recurrence, second cancers?
- What other factors influence risk?

©Cancer Research-UK

- Optimal timing for risk-reducing surgery, chemoprevention, screening? Changes in lifestyle? How do they affect future risk?
- What are the implications for my close relatives?
- Are there alternative methods for monitoring disease development?

The EMBRACE study

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



- **E**pide**m**iological Study of Familial **Br**east C**a**n**ce**r
- UK and Eire
- Begun: July 1998
- *BRCA1/2* mutation carriers and family members
- Men and women
- Collects data on affected and unaffected

PI: Douglas Easton

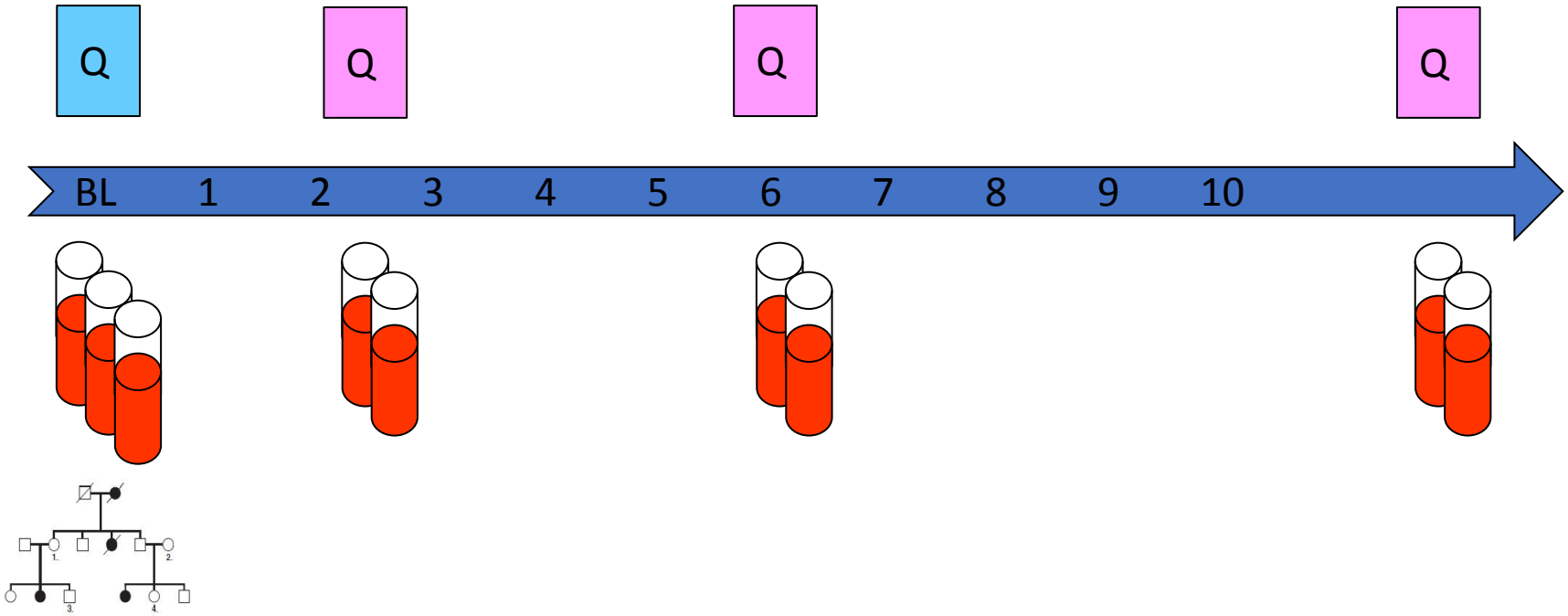
EMBRACE: Core components - baseline

- Baseline epidemiological questionnaire
- Blood sample
- Mutation details
- Family history as a pedigree drawing
- Clinical details of pre-baseline diagnoses and treatments

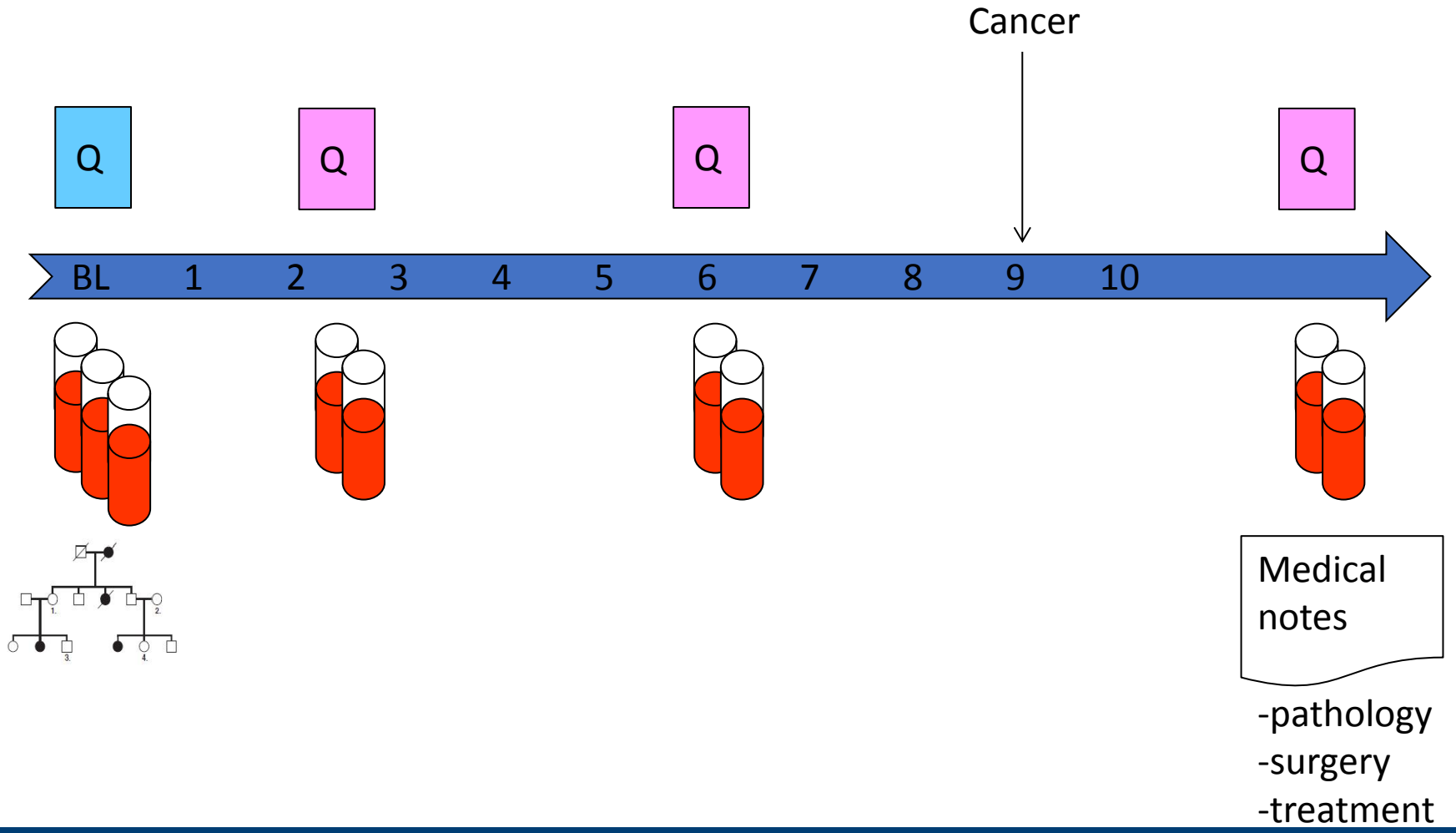
EMBRACE: Core components - follow up

- Follow up occurs at approximately 2, 5 and 10 years after recruitment
- Smaller epidemiological questionnaire
- Blood sample
- Clinical details of recent diagnoses / surgery / treatment

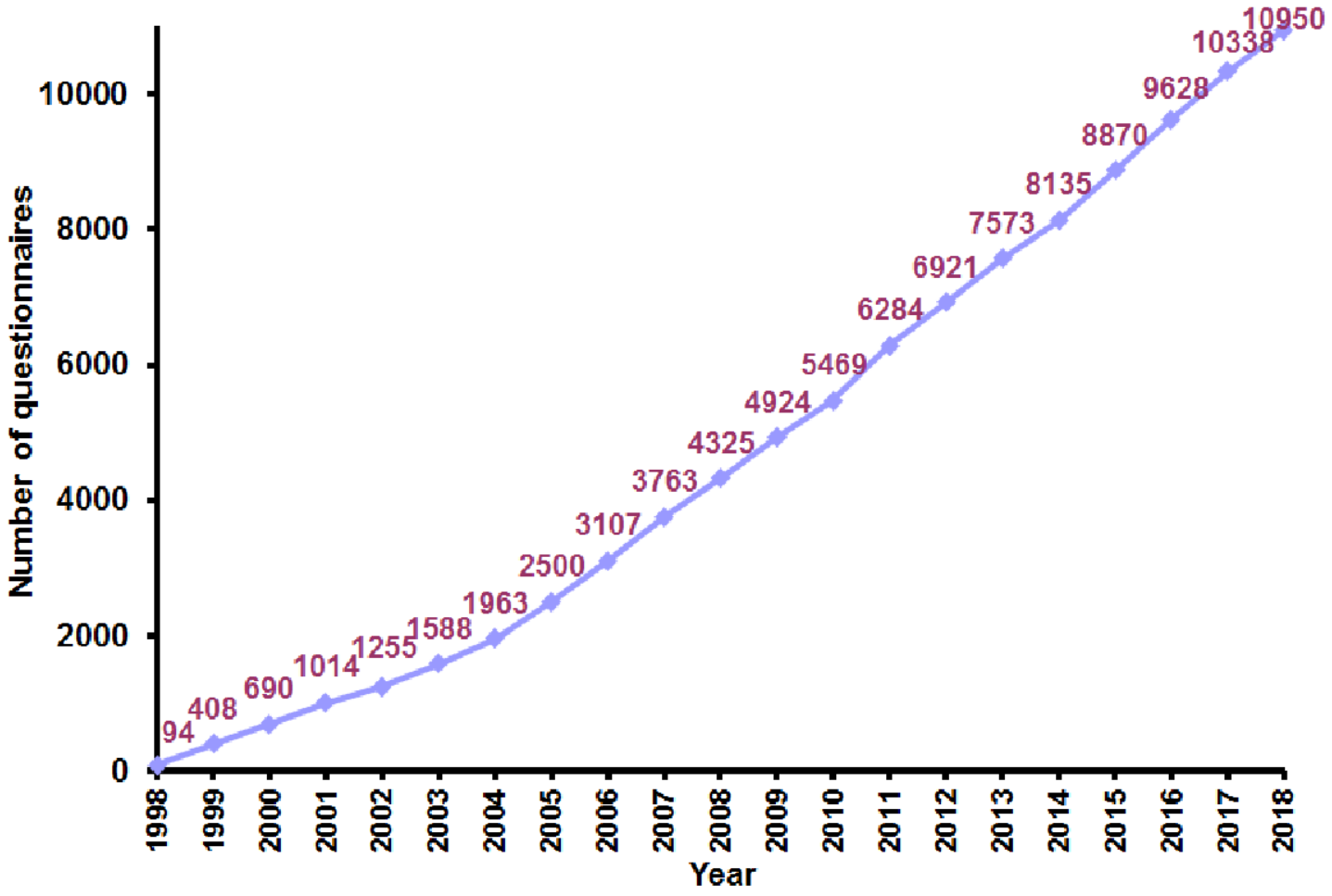
Follow up – mutation carriers



Follow up – mutation carriers



EMBRACE: study recruitment over time



International collaborations

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

EMBRACE

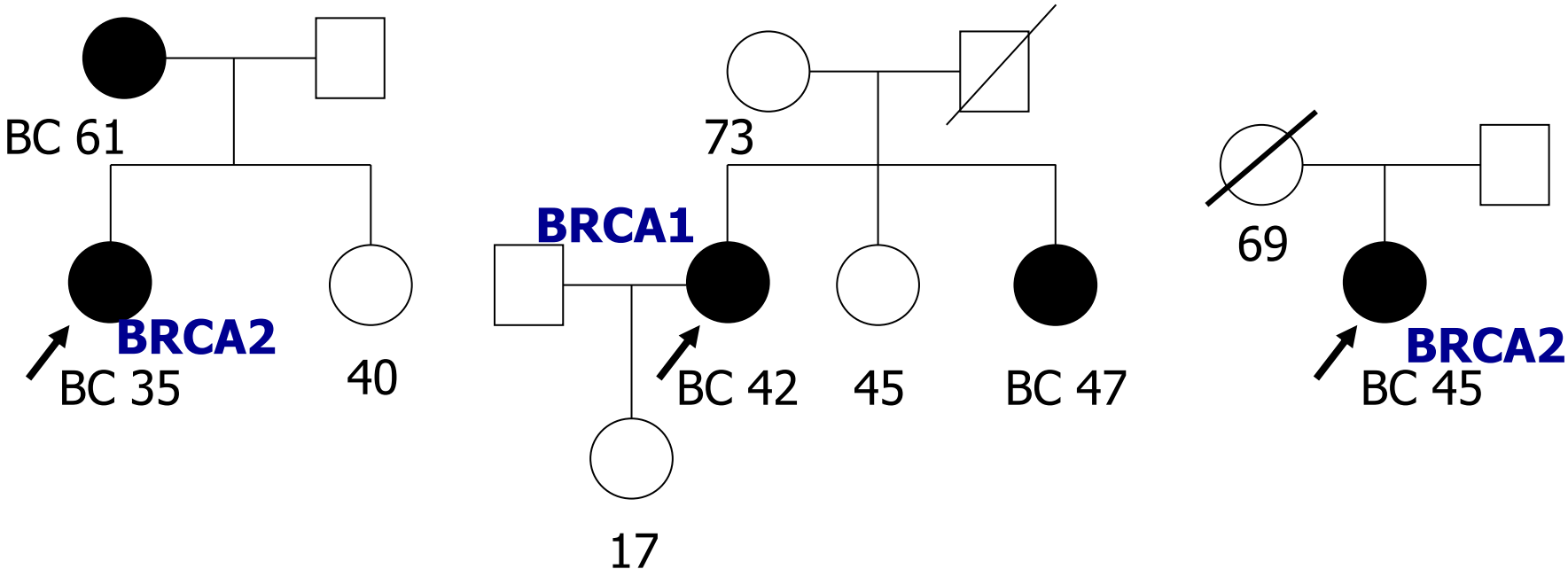
IBCCS — Lifestyle factors

CIMBA — Genetic modifiers

- ❑ 80 groups groups worldwide
- ❑ ~64,000 *BRCA1/2* mutation carriers
- ❑ >100 publications

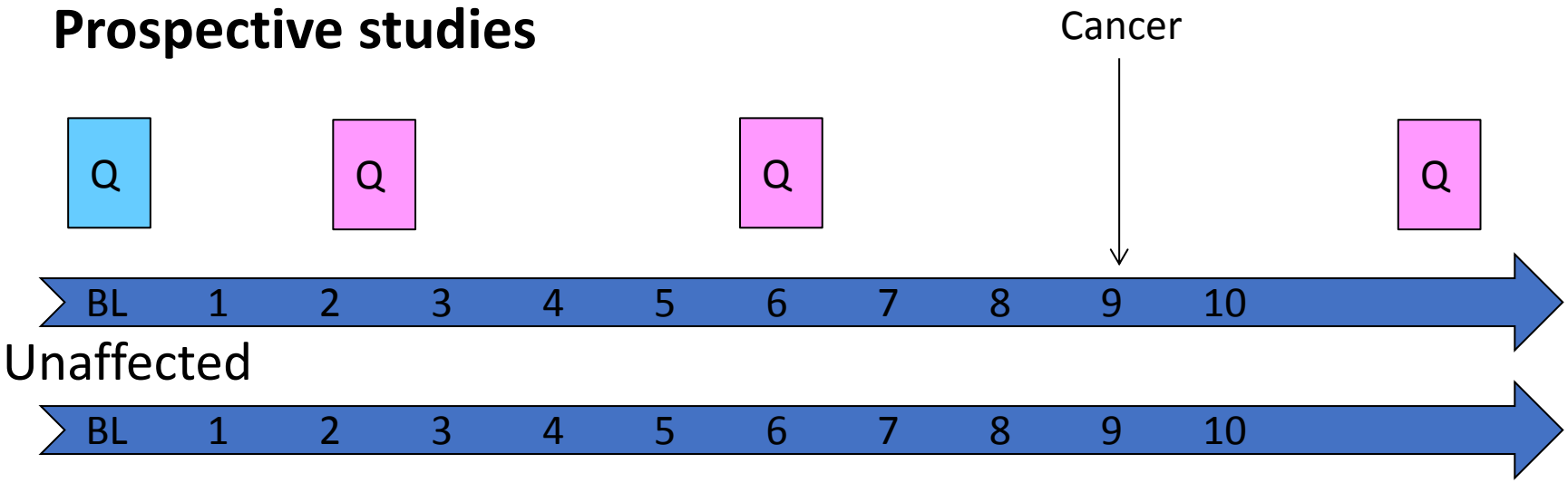
What are the future disease risks?

Family based studies



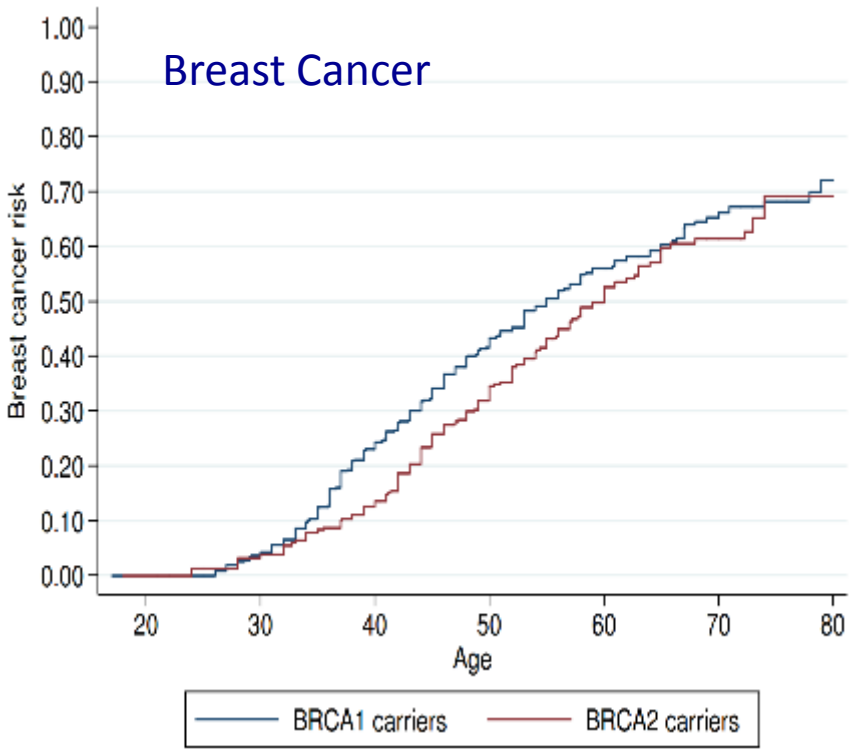
- Possible biases in family selection
- Imprecise information on relatives

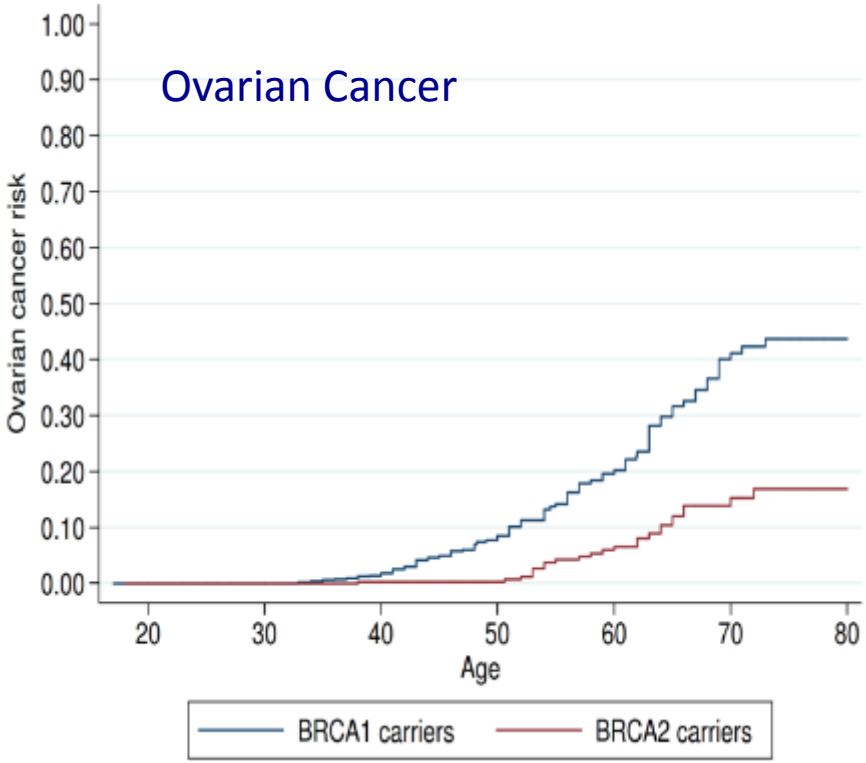
What are the future disease risks?



- Optimal epidemiological study design, but
  - Requires long periods of observation
  - Until recently no large studies available for *BRCA1/2*

Female *BRCA1, BRCA2* prospective risk estimates:9,856 women





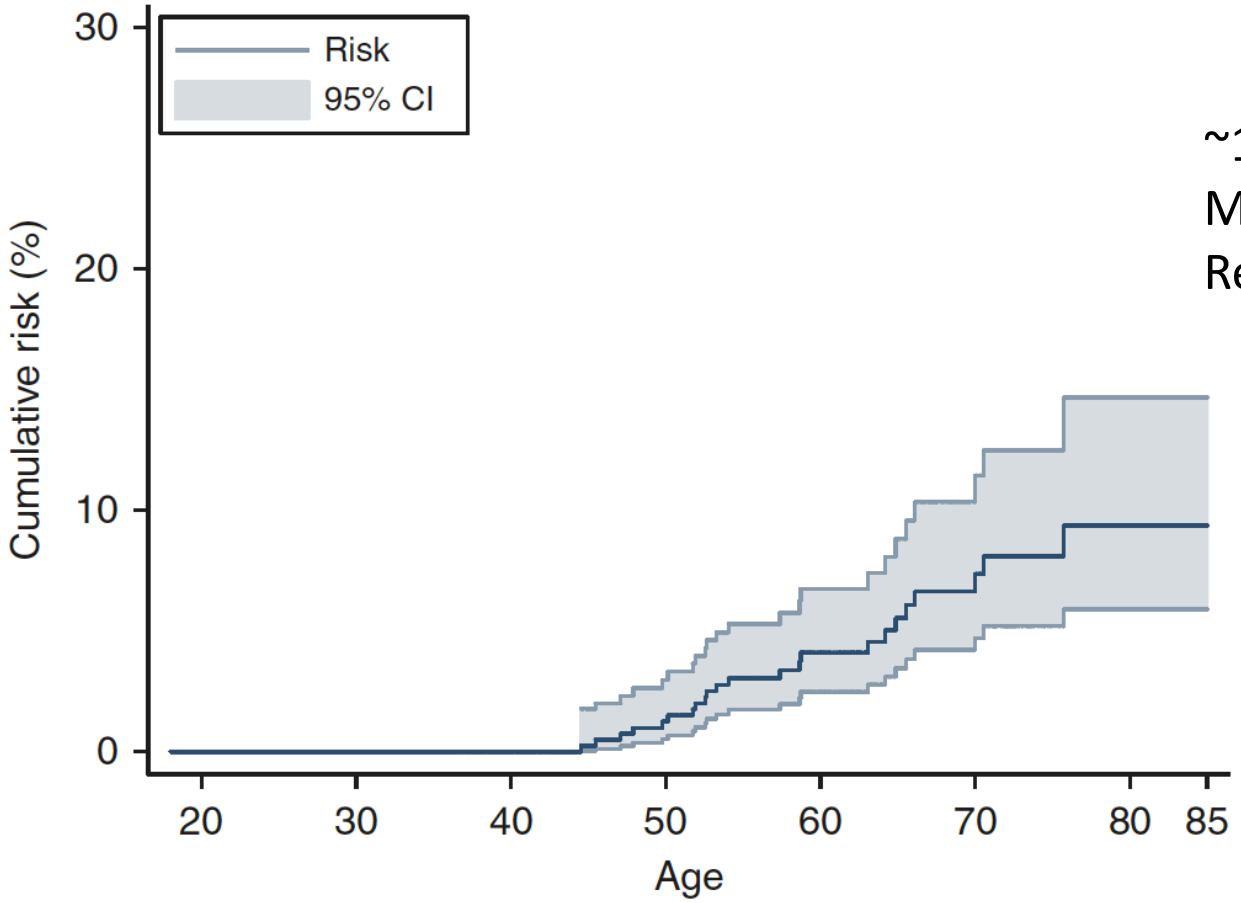
JAMA | Original Investigation

Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers 2017

Karoline B. Kuchenbaecker, PhD; John L. Hopper, PhD; Daniel R. Barnes, PhD; Kelly-Anne Phillips, MD; Thea M. Mooij, MSc; Marie-José Roos-Blom, MSc; Sarah Jervis, PhD; Flora E. van Leeuwen, PhD; Roger L. Milne, PhD; Nadine Andrieu, PhD; David E. Goldgar, PhD; Mary Beth Terry, PhD; Matti A. Rookus, PhD; Douglas F. Easton, PhD; Antonis C. Antoniou, PhD; and the *BRCA1* and *BRCA2* Cohort Consortium

Are my relatives at elevated risk?

EMBRACE data: breast cancer risk for *BRCA1/2* predictive test negatives



~1900 women relatives
Mean follow-up ~7yrs
Relative risk ~1.0

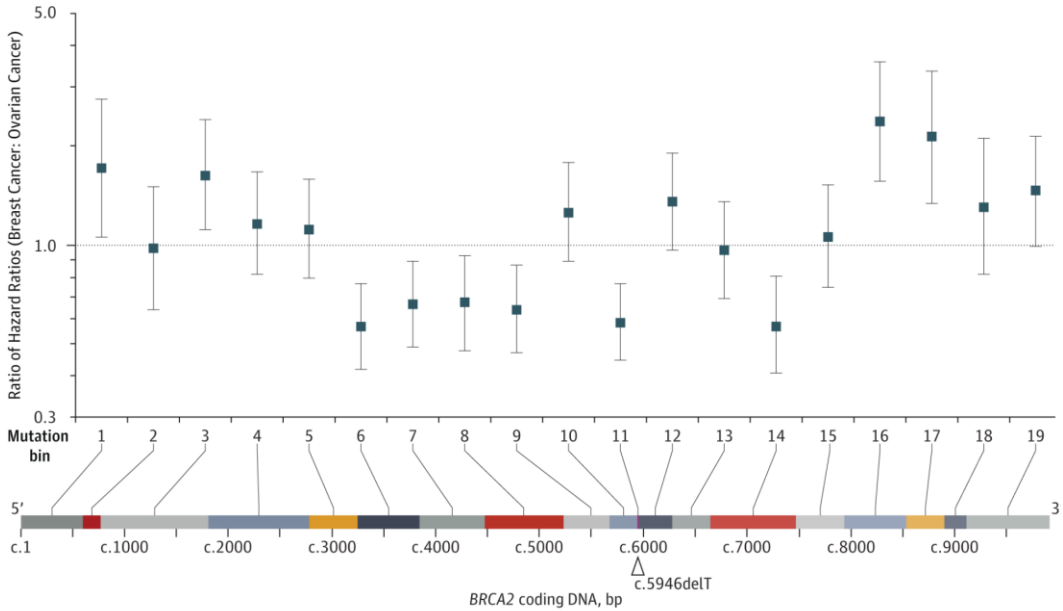
Girardi et al Genet Med 2018

Large variability in risks for *BRCA1/2* carriers

- Risks vary over time
  - Lifestyle, hormonal factors influence risks
- Risks vary by number of affected relatives
  - Other genetic factors influence risks

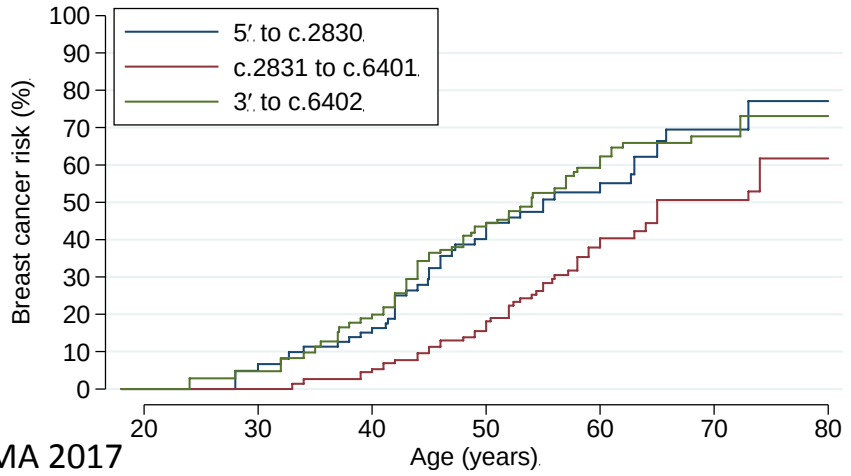
Mutation specific risks

Cancer risks depend on the position of the mutation within the gene



Rebbeck et al, JAMA 2015

BRCA2: Cumulative breast cancer risk by mutation location (wide)



Kuchenbaecker et al, JAMA 2017

BRCA1/2 mutations vs Common genetic variation

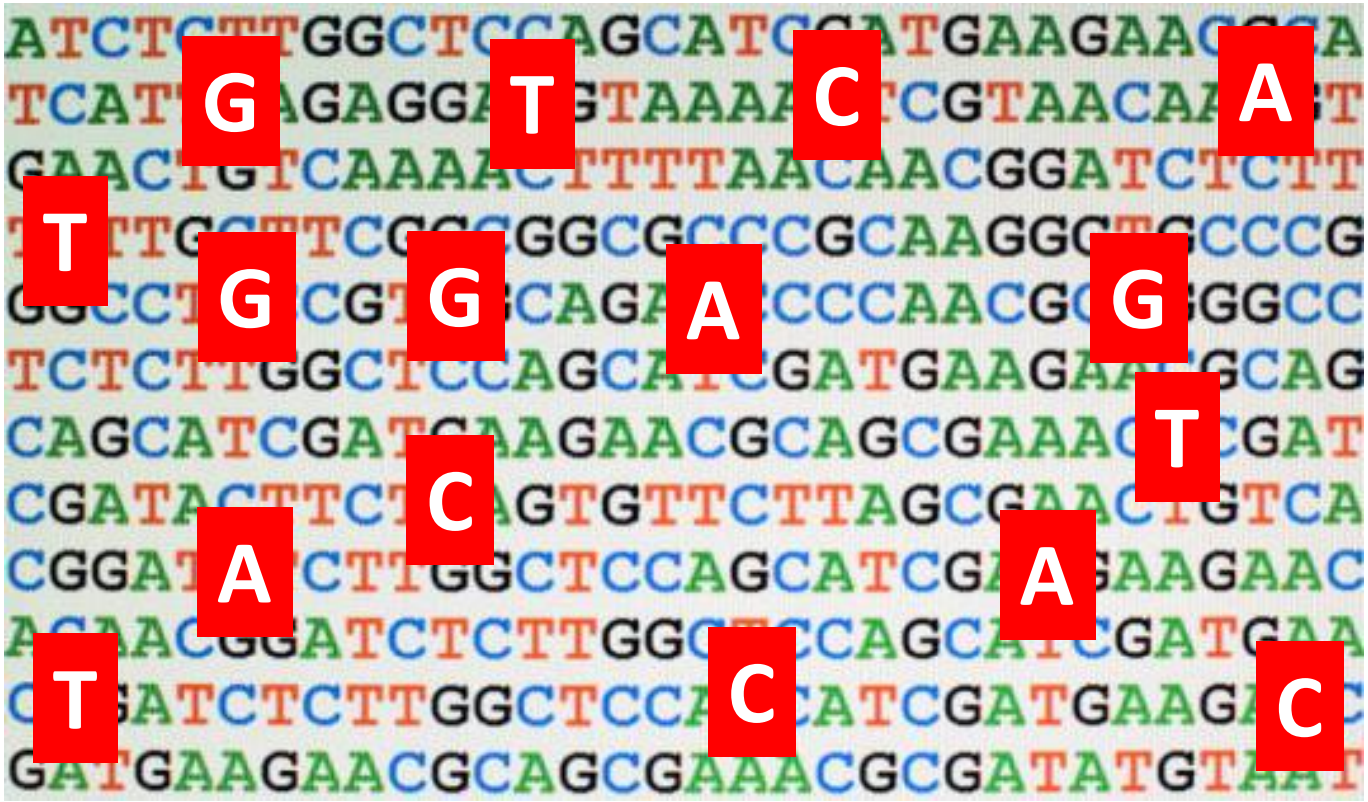
- *BRCA1* and *BRCA2* mutations are rare in the population
- Contribute a lot to an individual's genetic risk

BRCA1/2 mutations vs Common genetic variation

An individual's genome

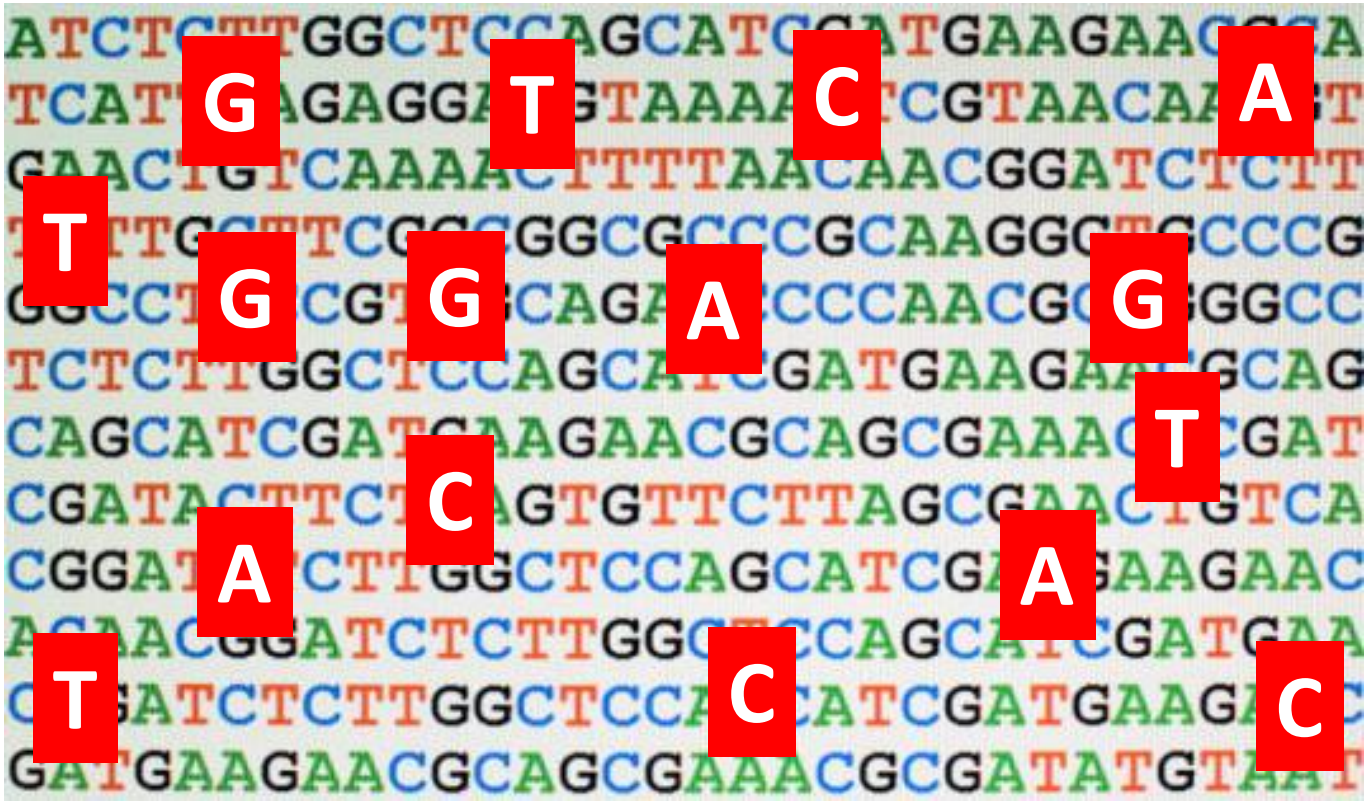
BRCA1/2 mutations vs Common genetic variation

Genetic risk driven by 100's-100,000's of common inherited genetic variations scattered in the genome – **"SNPs"**



BRCA1/2 mutations vs Common genetic variation

Each SNP contributes little to risk of developing breast, ovarian, or prostate cancer



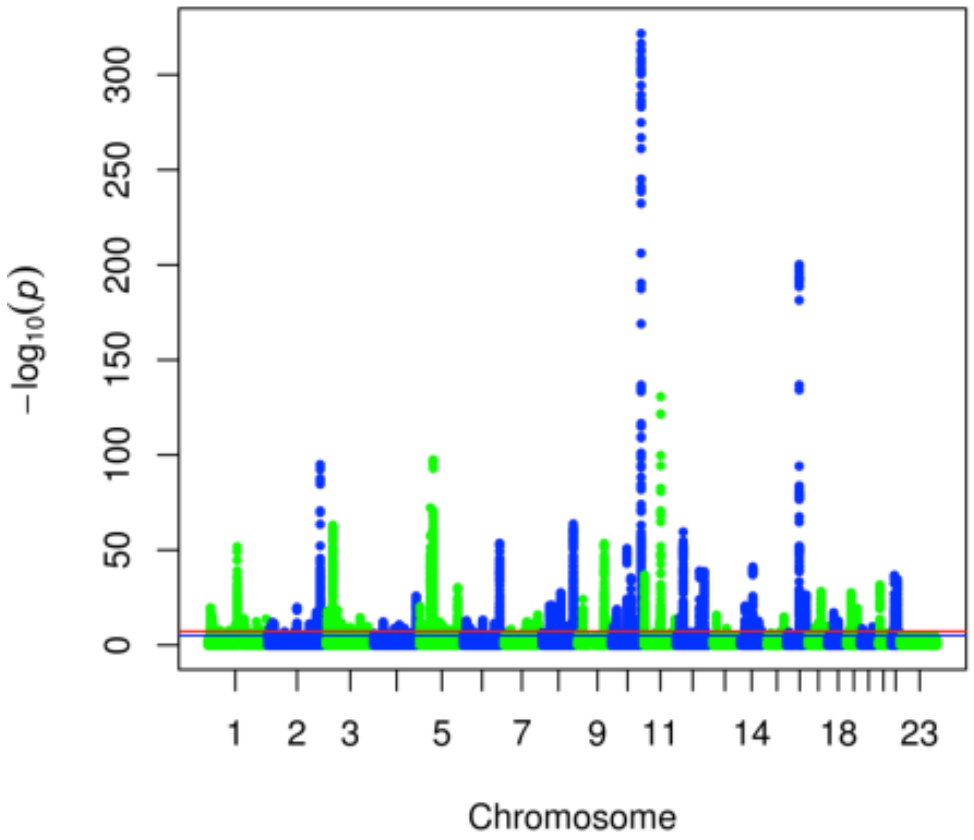
BRCA1/2 mutations vs Common genetic variation

Adding the SNP effects can have big impact on cancer risk

Polygenic Risk Scores

Genome wide association studies

Included *BRCA1/2* mutation carriers



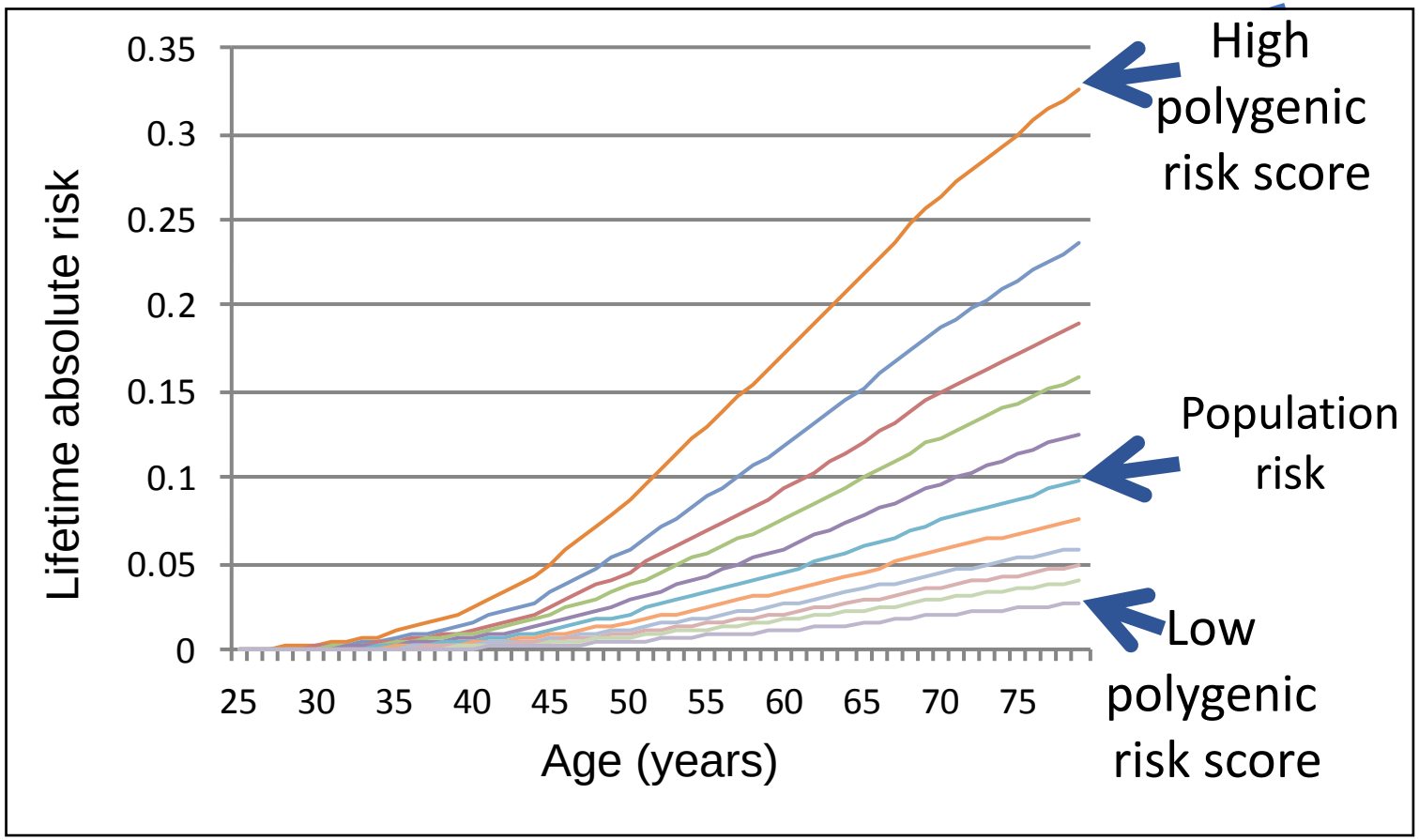
Breast cancer: >180 SNPs

Ovarian cancer: >30 SNPs

Prostate cancer: >140 SNPs

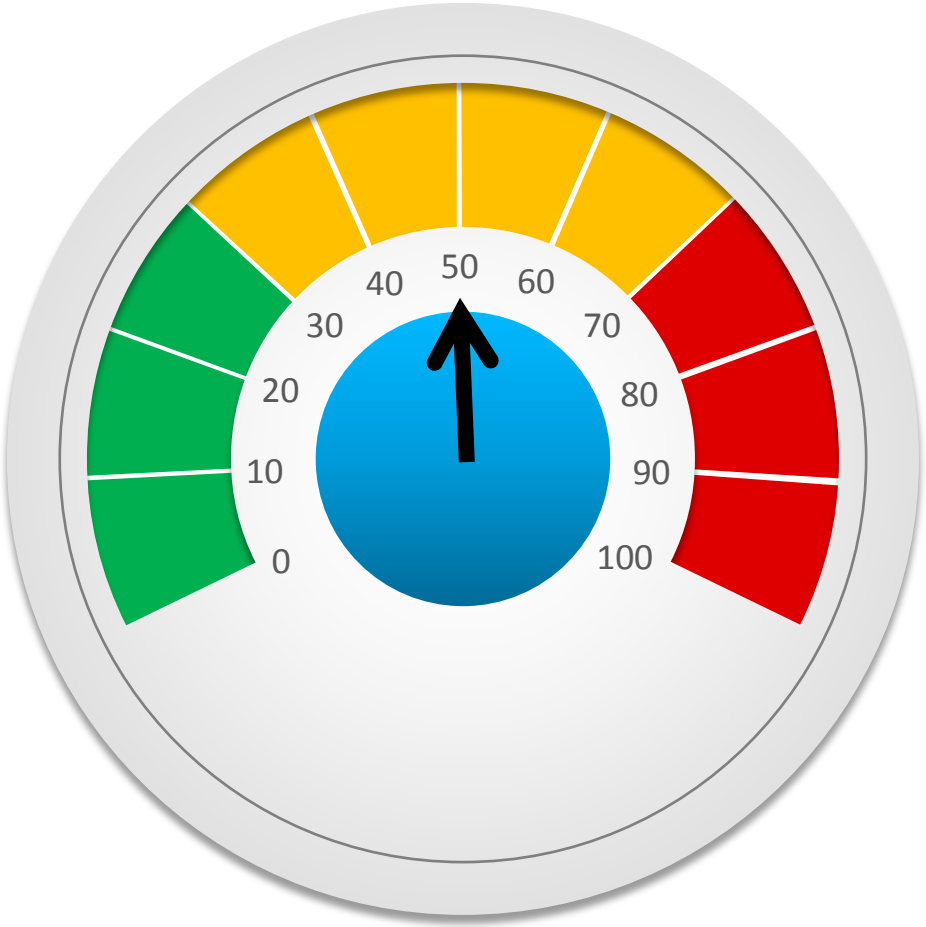
Michailidou et al (Nature 2017), Milne et al (Nat Genet 2017), Phelan et al (Nat Genet 2017)

General population: PRS and breast cancer risk



Mavaddat et al AJHG 2019

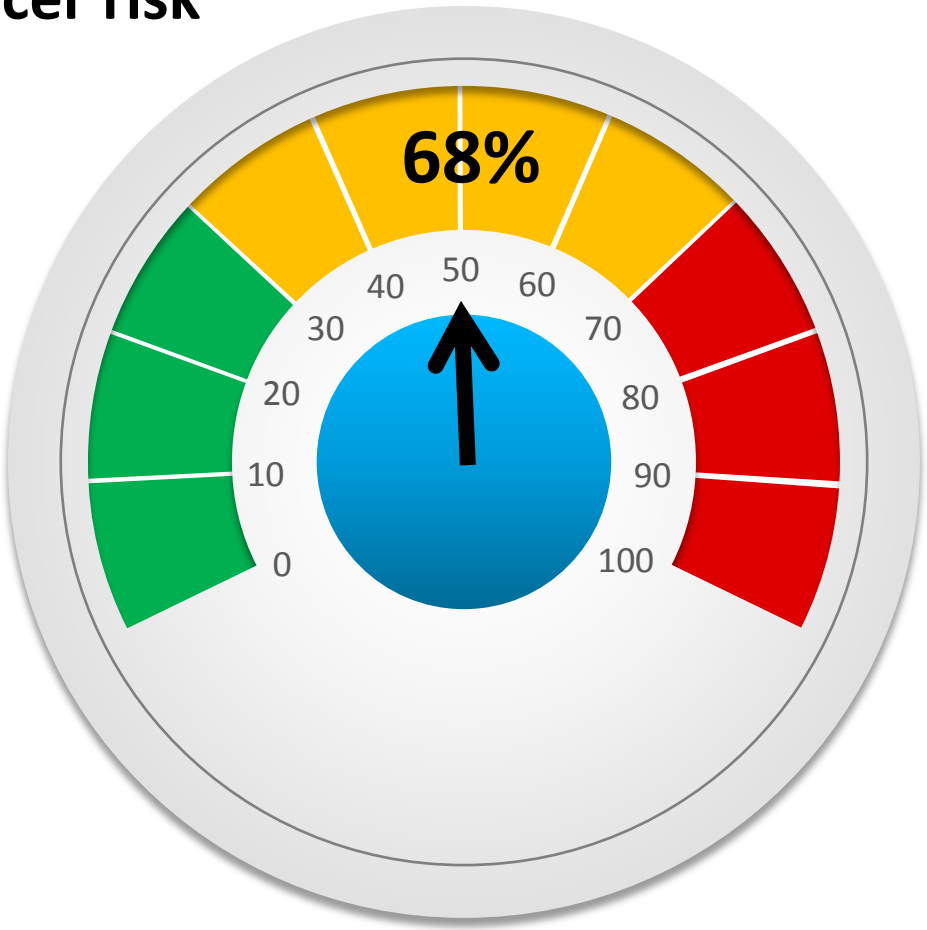
Polygenic Risk Scores in *BRCA1, BRCA2* mutation carriers: act like volume control



Kuchenbaecker et al JNCI 2017
LeCarpentier et al JCO 2017

Polygenic Risk Scores in *BRCA1, BRCA2* mutation carriers: act like volume control

***BRCA2* breast cancer risk**



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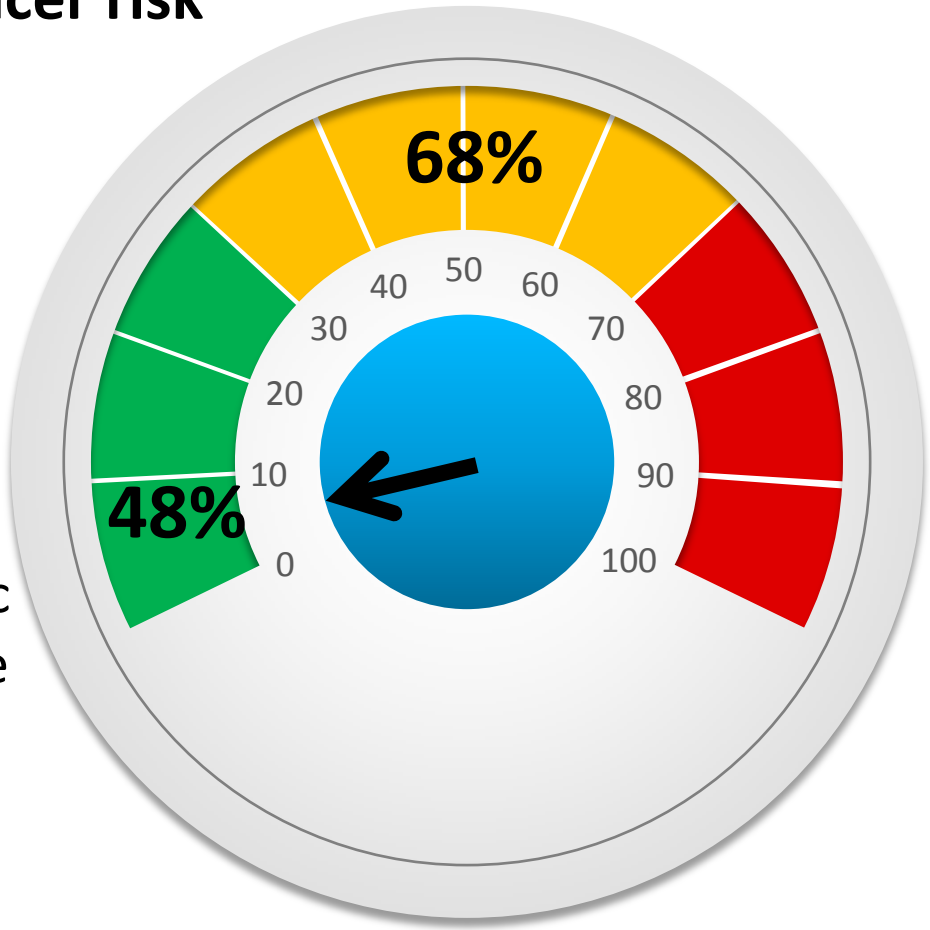
Polygenic Risk Score in *BRCA1, BRCA2* mutation carriers: act like volume control

***BRCA2* breast cancer risk**



Low polygenic risk score

Kuchenbaecker et al JNCI 2017
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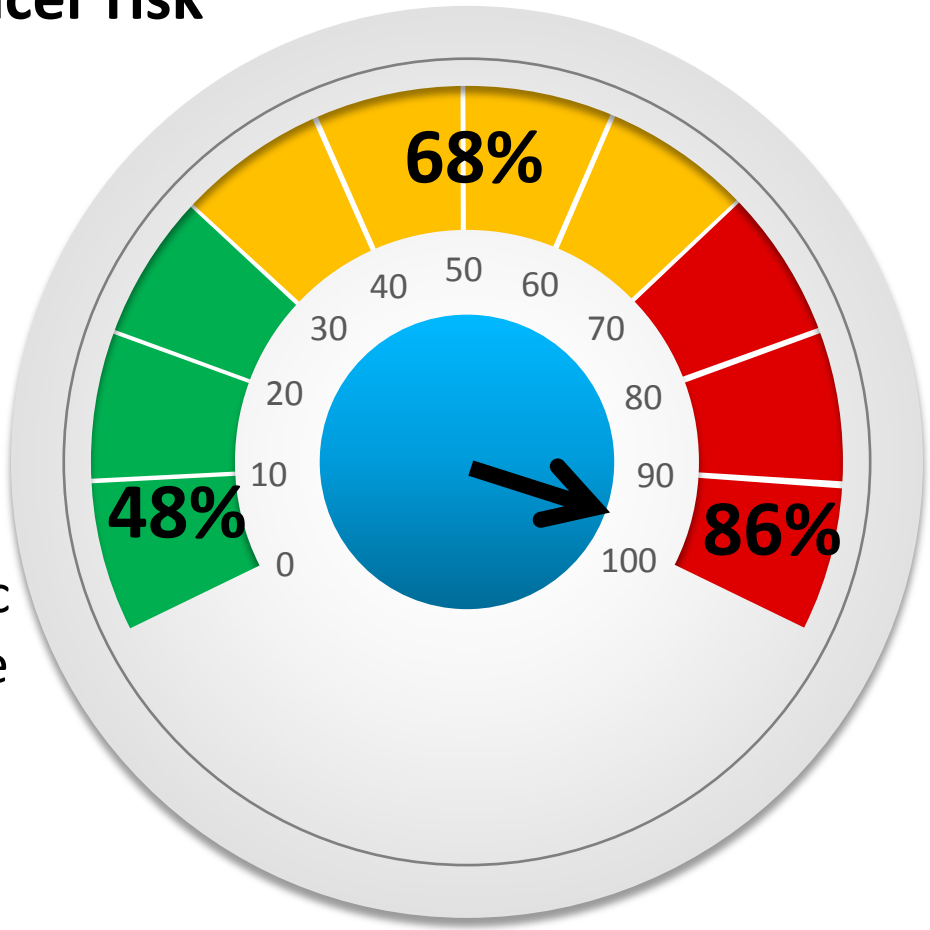
Polygenic Risk Scores in *BRCA1, BRCA2* mutation carriers: act like volume control

BRCA2 breast cancer risk



Low polygenic risk score

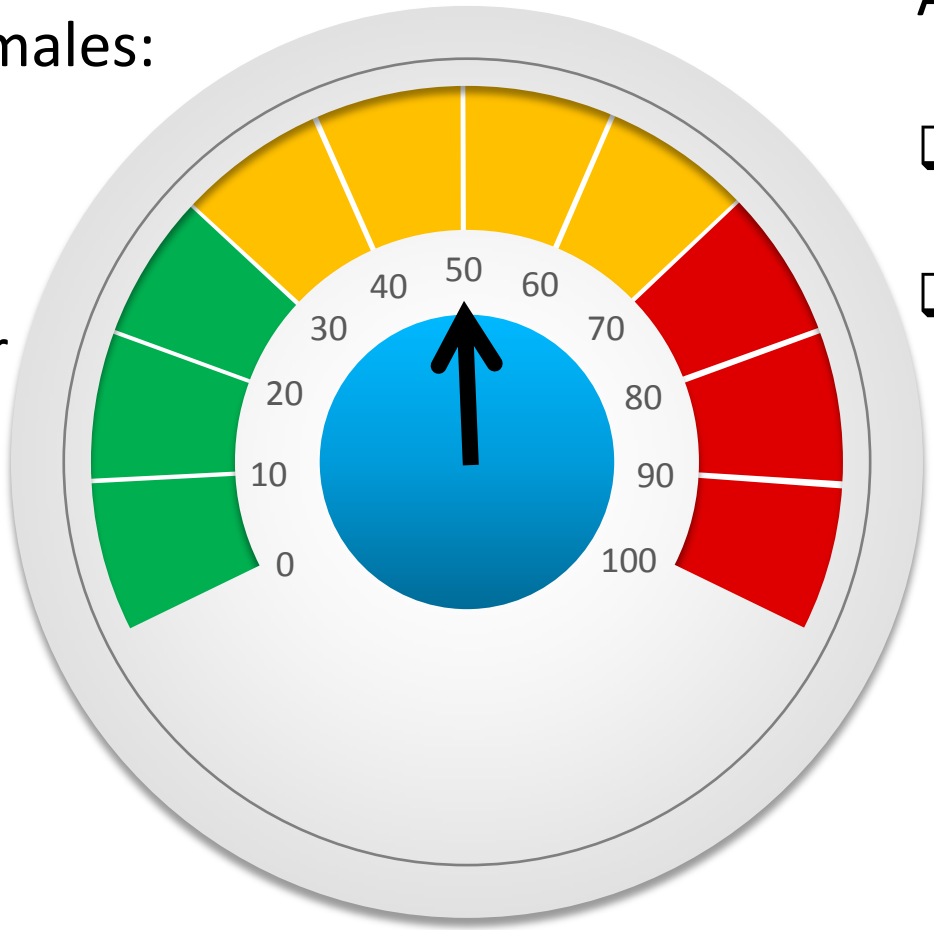
High polygenic risk score

Kuchenbaecker et al JNCI 2017
LeCarpentier et al JCO 2017

Polygenic Risk Scores in *BRCA1, BRCA2* mutation carriers: act like volume control

Applicable to females:

- ❑ Breast Cancer
- ❑ Ovarian Cancer



Applicable males:

- ❑ Breast Cancer
- ❑ Prostate Cancer

Kuchenbaecker et al JNCI 2017
LeCarpentier et al JCO 2017

Lifestyle and hormonal risk modifiers: IBCCS studies

Breast Cancer Risk factor	BRCA1	BRCA2
Age at menarche	✔	✔
Parity (Y/N)	✗	✗
Number of children	✔	✔
Breastfeeding	✔	✔
Oral Contraceptive Prep use	✔(ever)*	✔(ever)*
Alcohol consumption,	✗	✗
Smoking	✔**	✔**
Body Mass Index	✔	✔
Height	✔	✔
Mammographic Density	✔	✔

* Evidence inconsistent
**>5 years prior to fftp

Schrijver et al, JNCI Cancer Spect 2019; Andrieu et al JNCI Cancer Spect 2019; Qian et al JNCI 2019; Mitchell et al Can Res 2006;

Lifestyle and hormonal risk modifiers: IBCCS studies

Ovarian Cancer Risk factor	BRCA1	BRCA2
Number of children	✔	consistent
Oral contraceptive use	✔	✔
Tubal ligation	✔	consistent

Studies ongoing

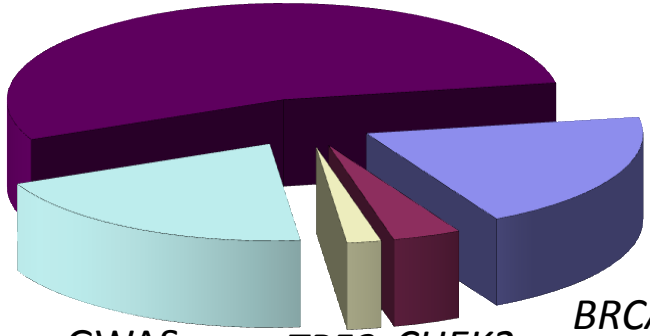
Schrijver et al, submitted; Antoniou et al CEPB 2008

Susceptibility to breast cancer in 2019

- Reproductive
- Menstrual
- Hormonal
- Lifestyle
- Physiological
- Mammographic density
- Family history

Breast Cancer Familial Aggregation

Unexplained: ~55%



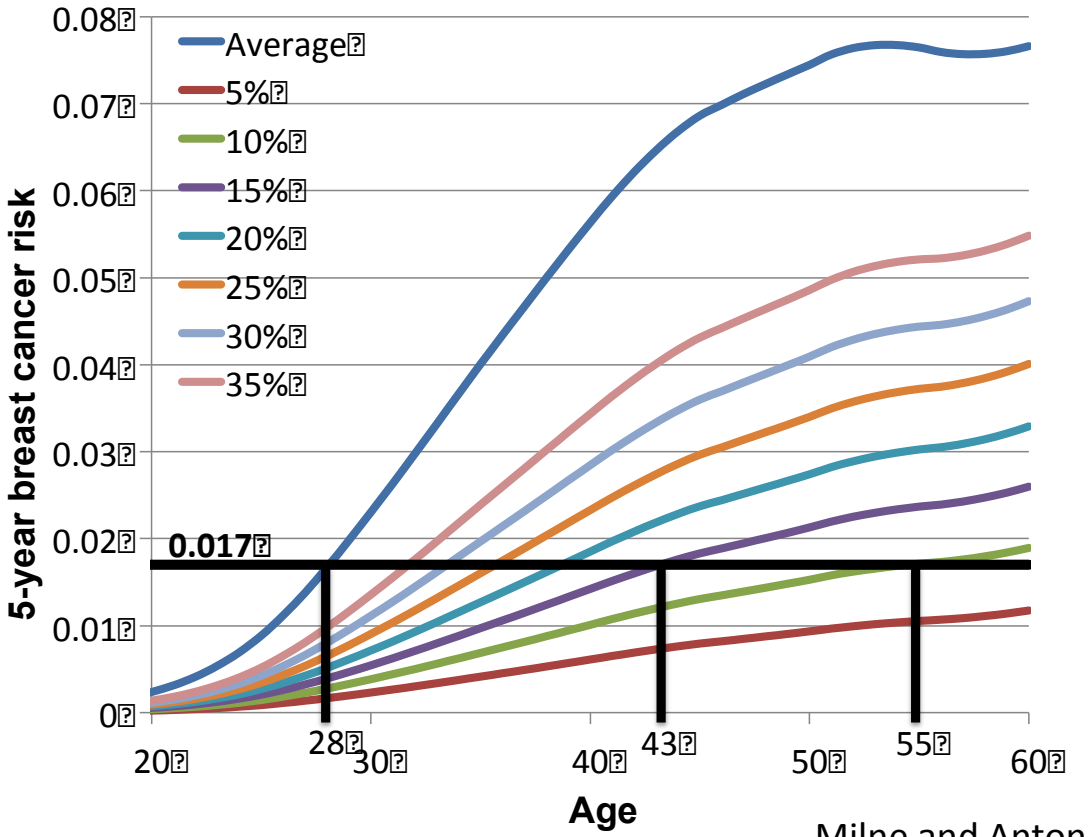
GWAS identified: >180 loci

TP53 *CHEK2*
PTEN *ATM*
CDH1 *PALB2*
STK11 *NBN*
NF1

BRCA1
BRCA2

Integrating all risk modifiers

Predicted 5-year BC risks by different risk factor combinations



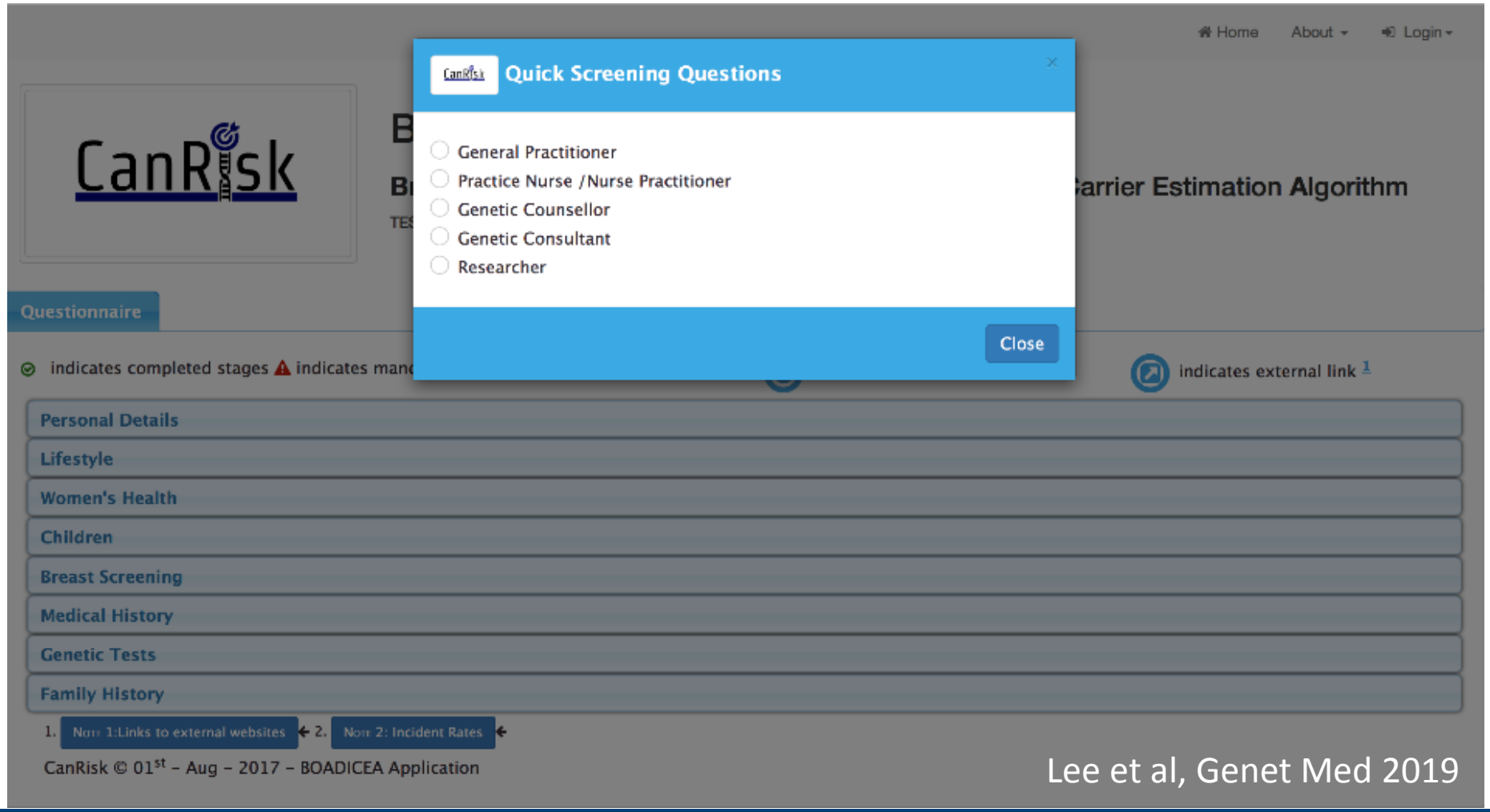
"High risk factors"

"low risk factors"

Milne and Antoniou, Endocr Relat Cancer. 2016

BOADICEA model

https://www.canrisk.org



Lee et al, Genet Med 2019

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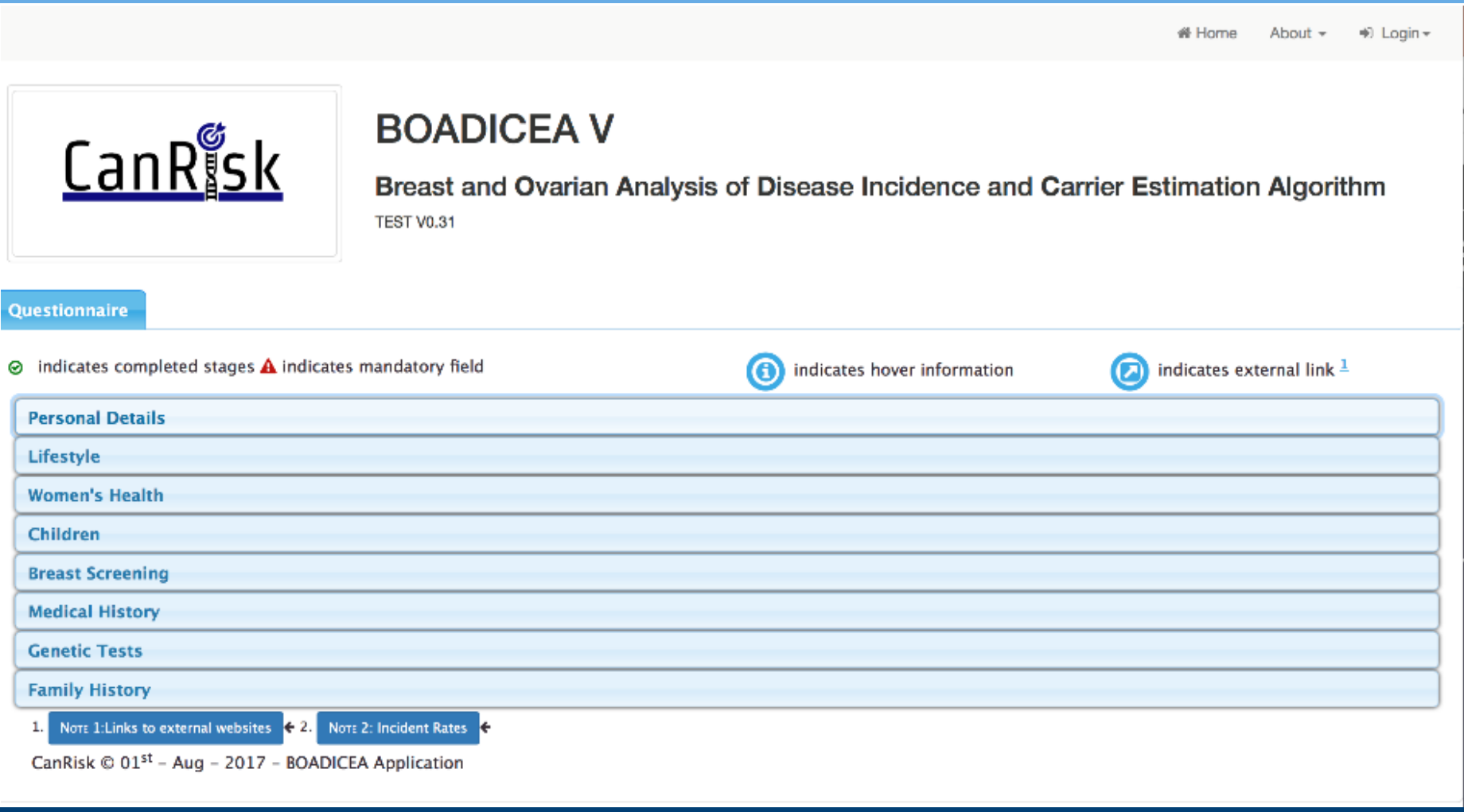

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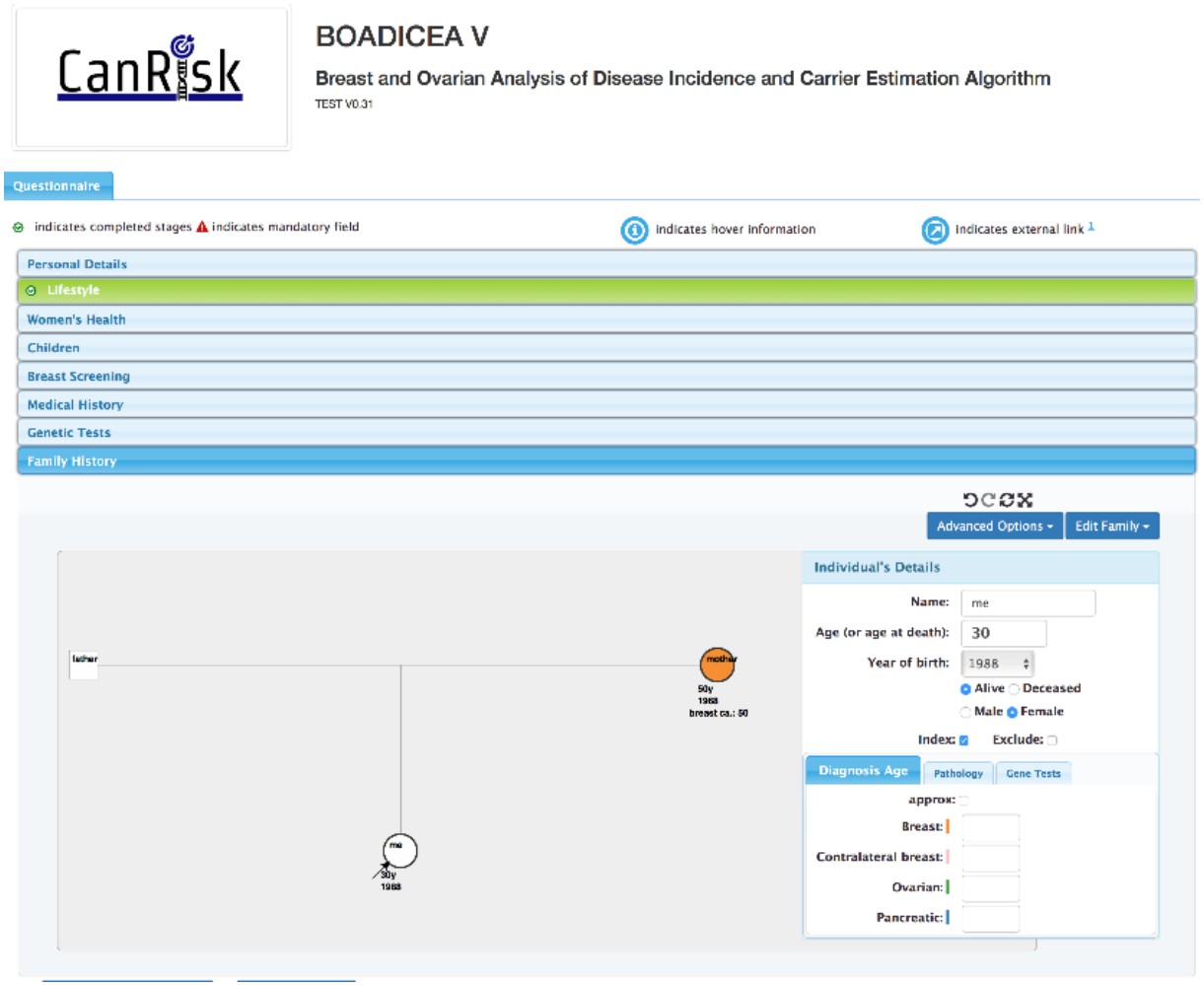

CanRisk
BOADICEA V
Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
TEST V0.31
Questionnaire
indicates completed stages
indicates mandatory field
indicates hover information
indicates external link
Personal Details
Lifestyle
Women's Health
Children
Breast Screening
Medical History
Genetic Tests
Family History
Advanced Options
Edit Family
father
mother
50y
1968
breast ca.: 50
me
30y
1988
Individual's Details
Name:
me
Age (or age at death):
30
Year of birth:
1988
Alive
Deceased
Male
Female
Index:
Exclude:
Diagnosis Age
Pathology
Gene Tests
approx:
Breast:
Contralateral breast:
Ovarian:
Pancreatic:

Absolute Risk of Breast Cancer

The woman's risk of developing **breast cancer over the next 5 years is 0.5%**. In other words, about 5 out of 1000 women with these risk factors will develop cancer over the next 5 year period.

The woman's risk of developing **breast cancer over the next 10 years is 1.4%**. In other words, about 14 out of 1000 women with these risk factors will develop cancer over the next 10 year period.

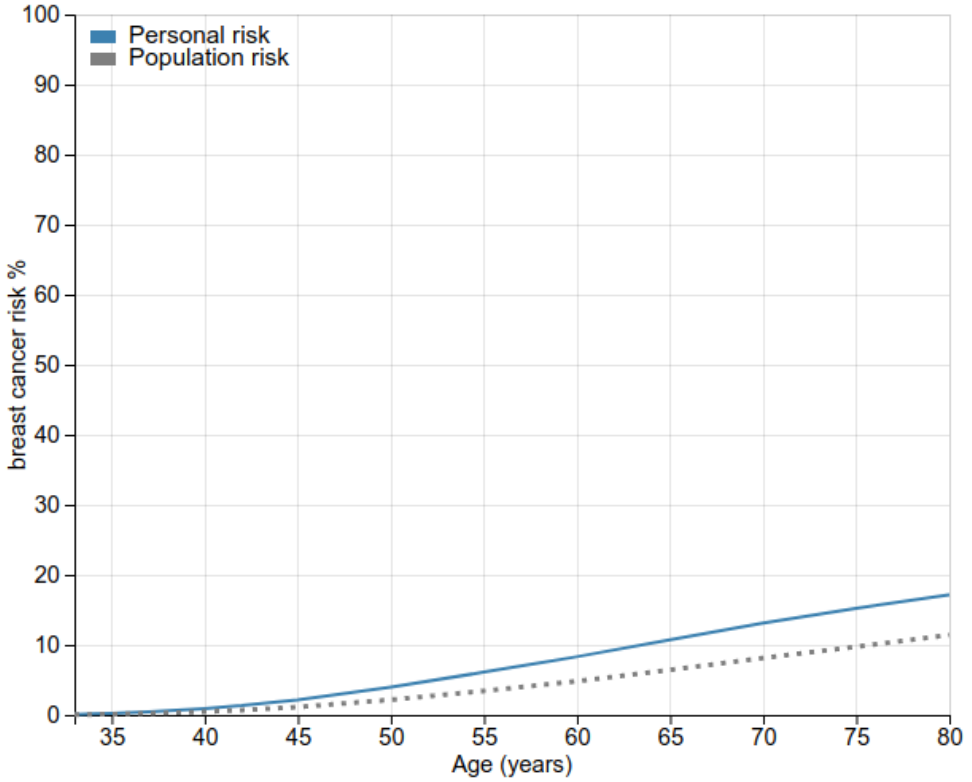
The woman's risk of developing **breast cancer by the age of 80 is 17.2%**. In other words, about 172 out of 1000 women with these risk factors will develop breast cancer by the age of 80.

Risk values

Personal Risk of Developing Breast Cancer Compared to the Population

The woman's risk of developing **breast cancer by the age of 80 is 17.2%**, compared to the **average population risk of 11.4%**.

In other words, about 172 out of 1000 women with these risk factors will develop breast cancer by the age of 80, compared to an average woman where 114 in 1000 will develop breast cancer.



Icon Array to Show Breast Cancer Risk after 5 years, 10 years and at the Age of 80

☐ Next 5 Year Risk ☑ Next 10 Year Risk ☑ Risk by Age 80

Breast Cancer 10 Year Risk

The woman's risk of developing **breast cancer over the next 10 years is 1.4%**. In other words, about 14 out of 1000 women with these risk factors will develop cancer over the next 10 year period.

14 women are likely to develop breast cancer

986 women are unlikely to develop breast cancer

Breast Cancer Remaining Lifetime Risk

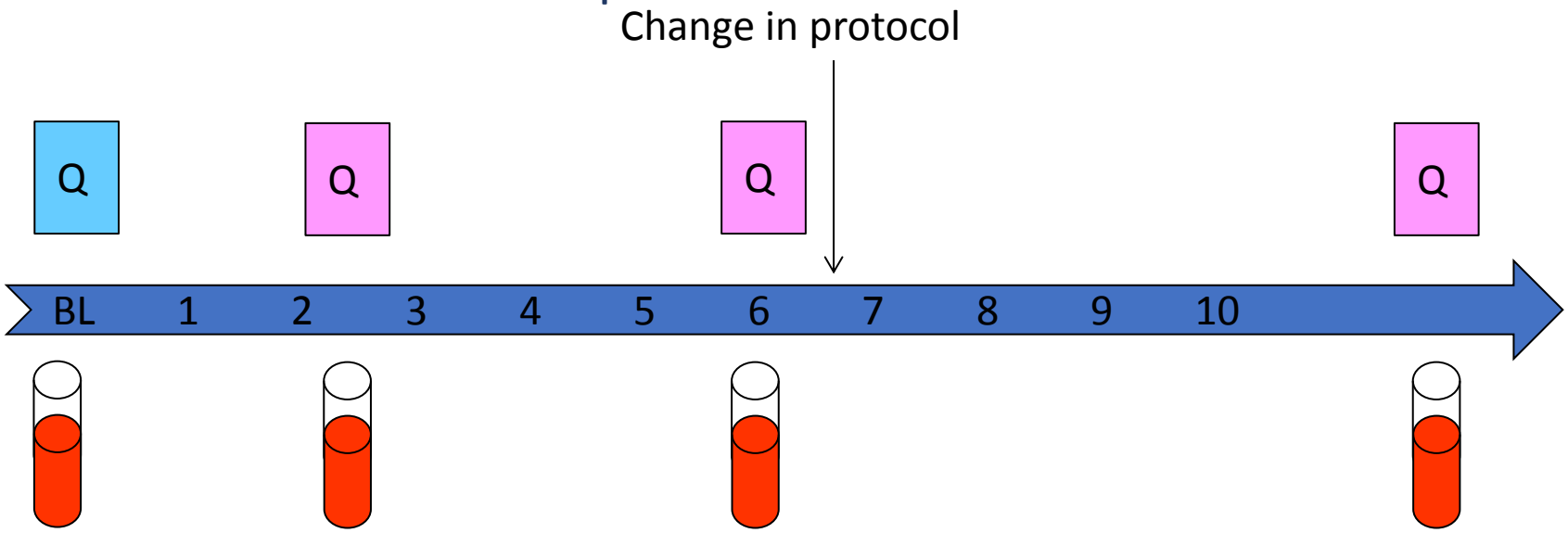
The woman's risk of developing **breast cancer by the age of 80 is 17.2%**. In other words, about 172 out of 1000 women with these risk factors will develop breast cancer by the age of 80.

172 women are likely to develop breast cancer

828 women are unlikely to develop breast cancer

Future Plans: Early detection of cancer in *BRCA1/2*

- New CR–UK Early Detection Grant, (Easton and Rosenfeld)
- *PALB2, CHEK2, ATM, RAD51C, RAD51D* mutation carriers
- Increased annual sample collection
  - Annual blood samples



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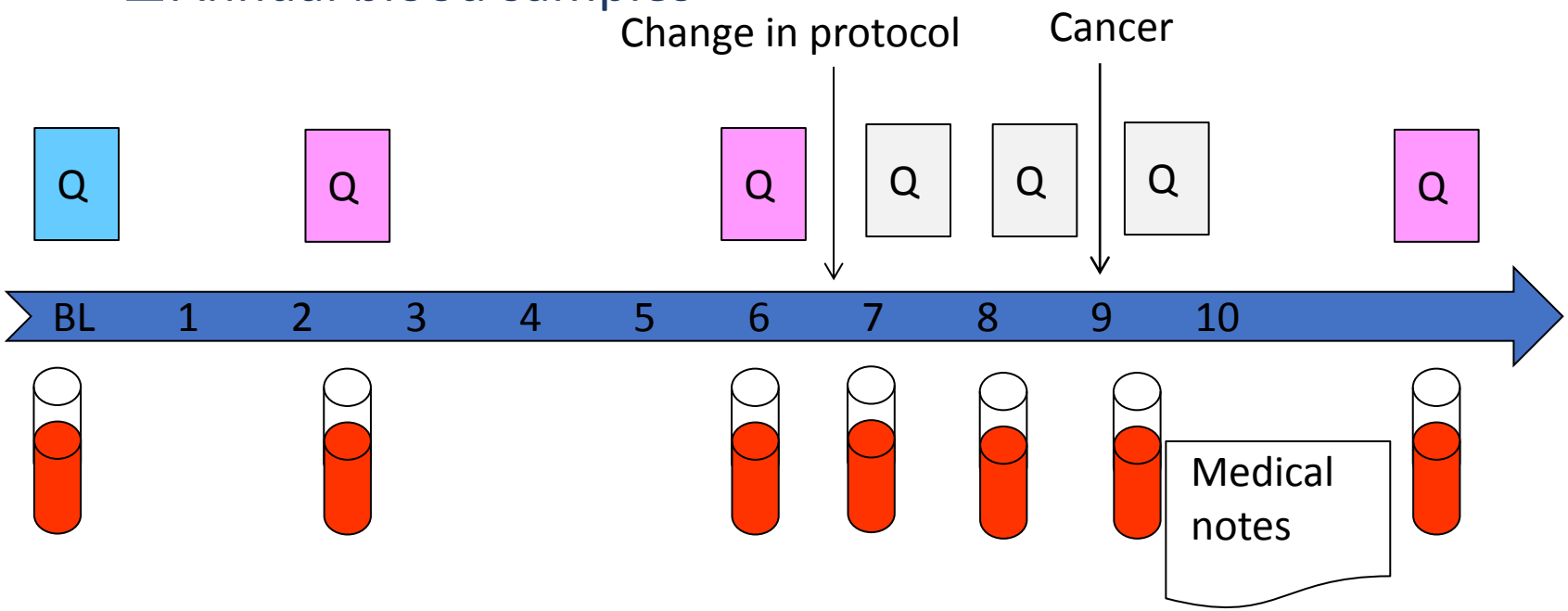

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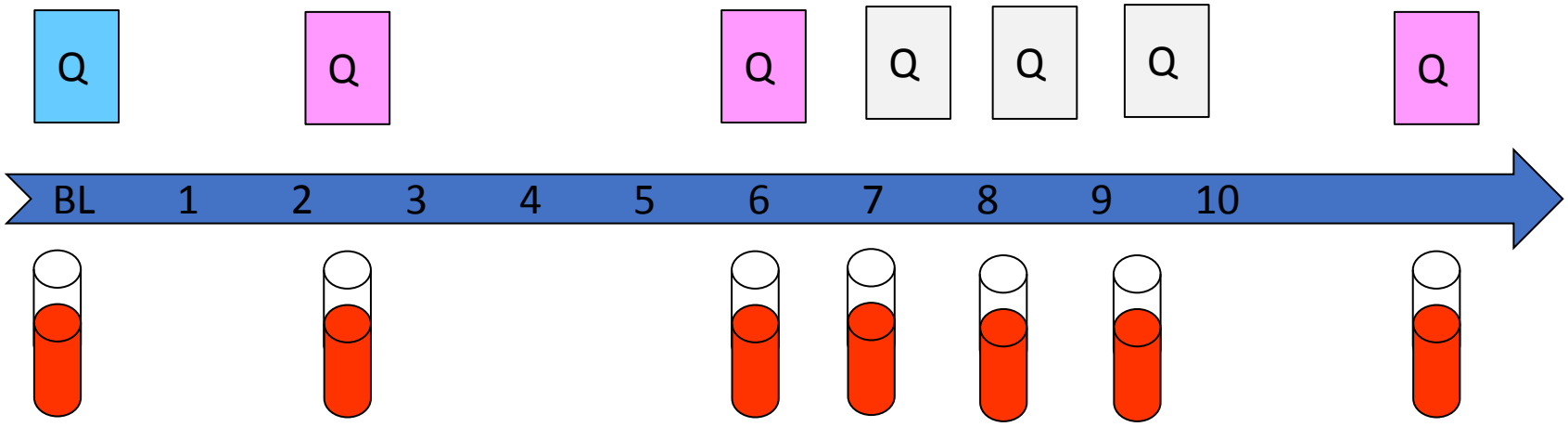

- Evaluate ED assays: ctDNA, methylation, proteins etc

Acknowledgments

- All EMBRACE study participants
- All recruiting clinical genetics centres
- Cambridge University coordinating team

  Doug Easton
  Debra Frost
  Daniel Barrowdale
  Jo Perkins
  Sabrina Cano-Morales
  Nitzan Rosenfeld
  Wendy Cooper

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