KØBENHAVNS UNIVERSITET

Herlev og Gentofte Hospital

PRSONAL

(Population-based Randomized Study Of a Novel breast cancer risk ALgorithm and stratified screening)

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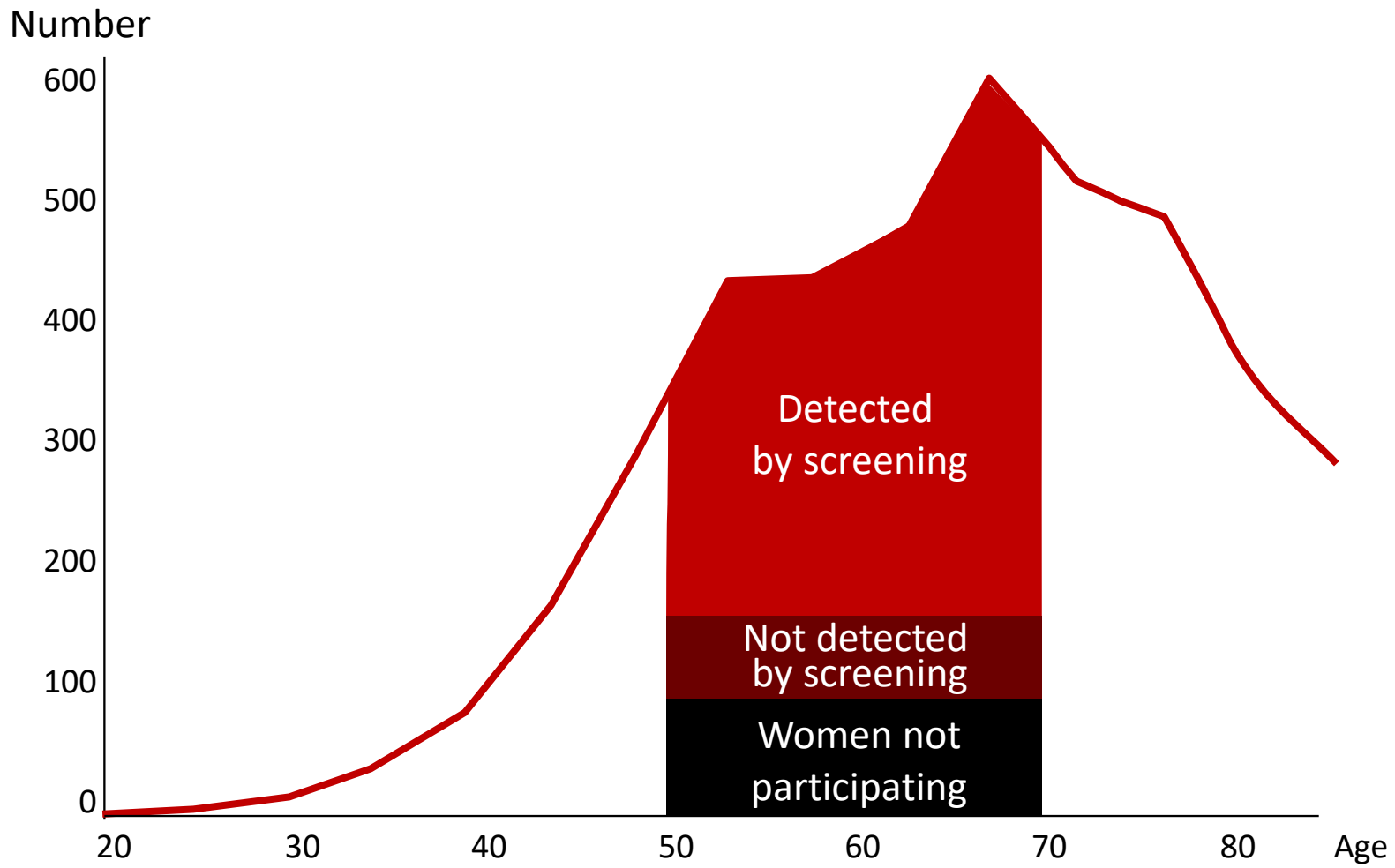
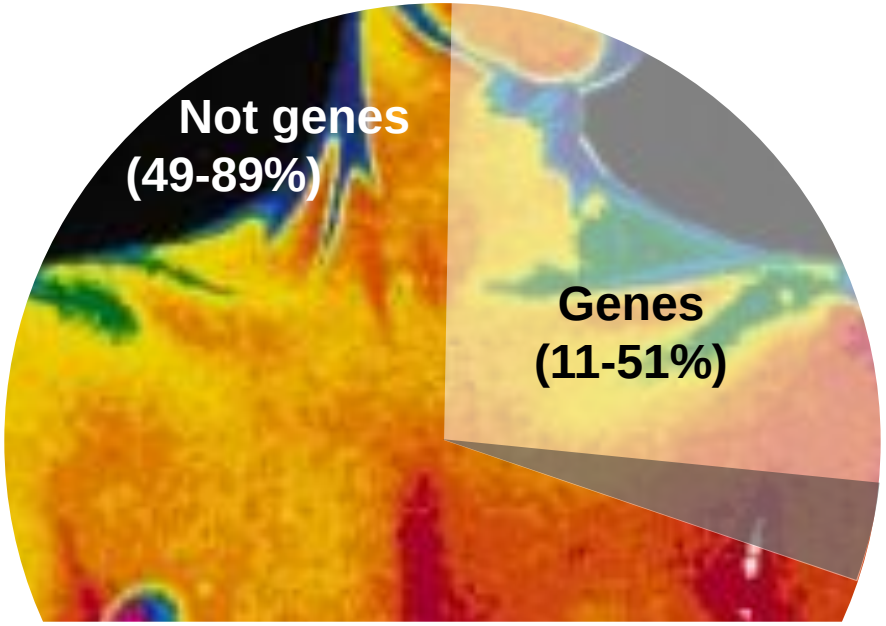
Funding of PRSONAL

No other conflicts of interests (unfortunately…)

Breast cancer in Denmark, 2020.
Nationwide screening since 2008:
Biennial mammography of 50-69-year aged women

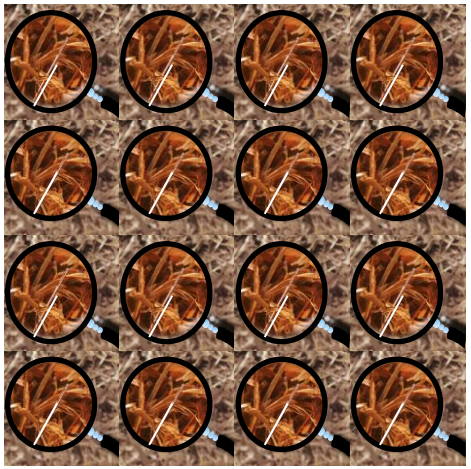


Genetic variation and breast cancer – a brief history



What about the rest?

BRCA1+BRCA2
(1993, 1995)

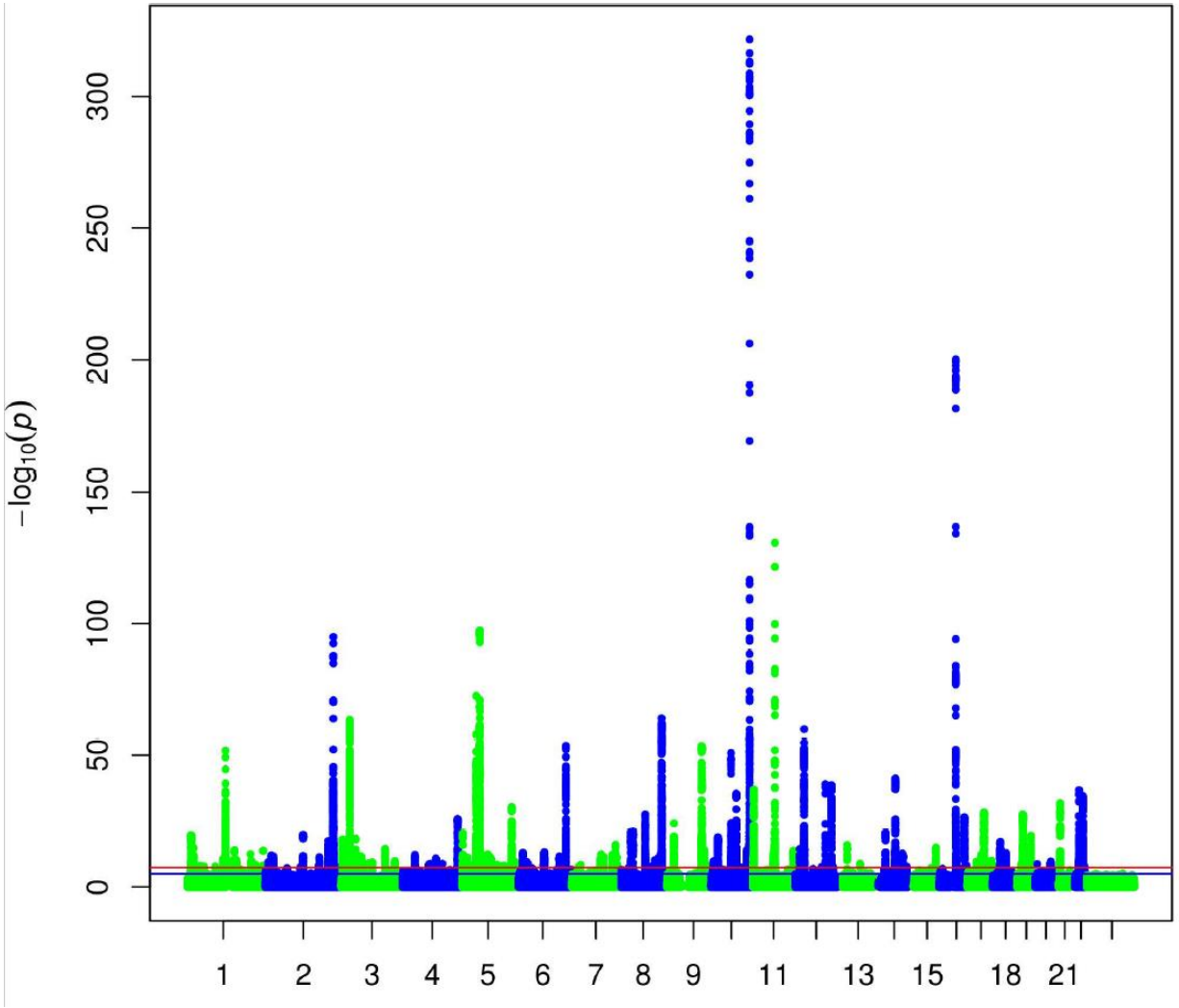


Statistical power!

LETTER

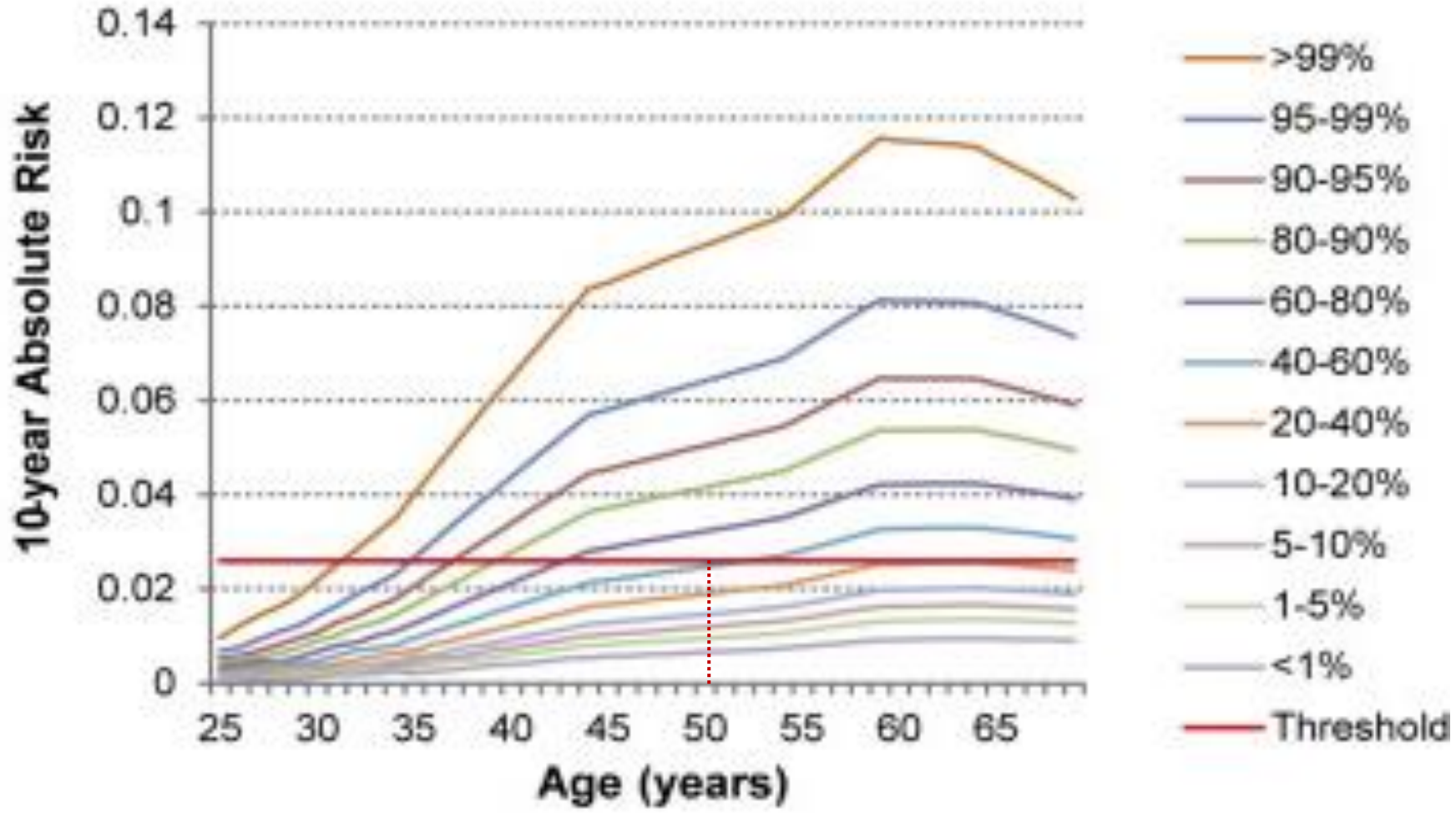
doi:10.1038/nature24284

Association analysis identifies 65 new breast cancer risk loci



Michailidou K. et al. Nature 551:92-94 (2017).

Polygenic risk score of breast cancer. 313 SNPs



”…A powerful and reliable predictor of breast cancer risk that may improve breast cancer prevention programs”

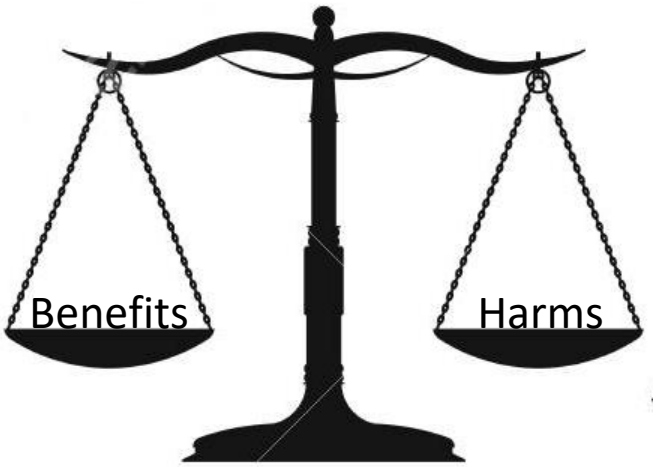
Mavaddat N et al. Am J Hum Genet. 104: 21-34 (2019).

“Listen: You are all individuals. You are all different!”

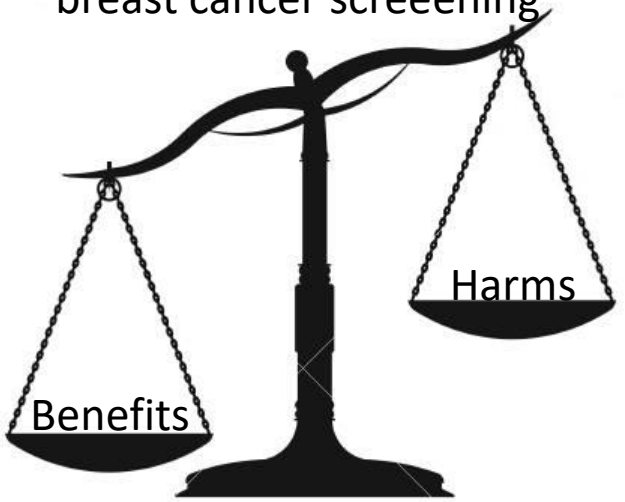
Life of Brian, Monty Python, 1980

Allocate Resources by Risk

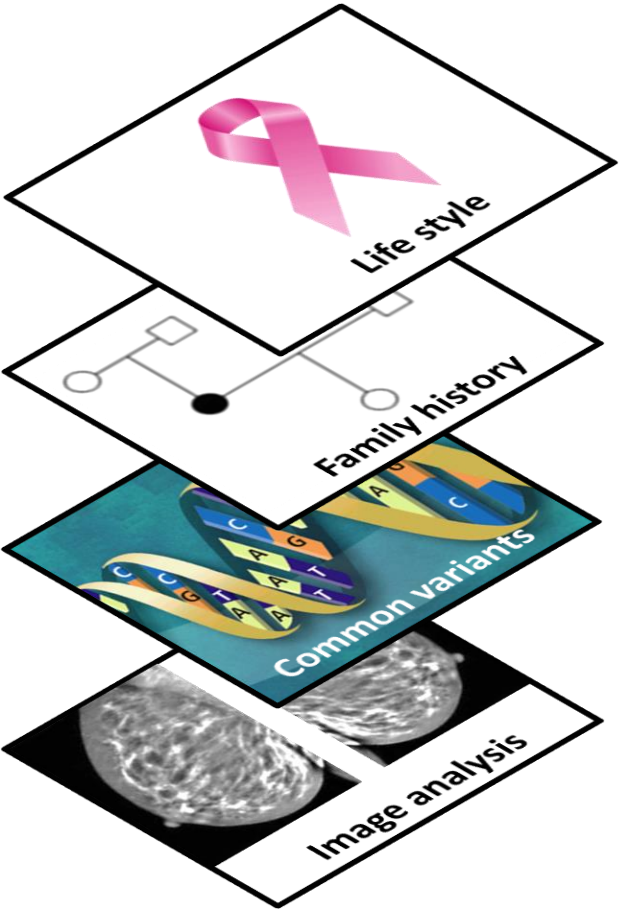
One-size-fits-all:
50-69-year olds have
mammography every 2nd year

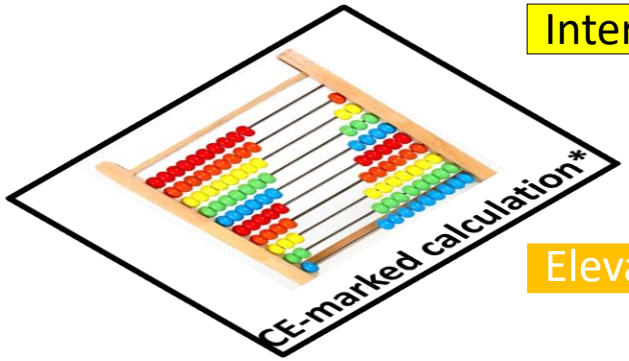


Personalized
breast cancer screeening



Vision for risk stratified breast cancer screening





Low → Mammography every 4. year

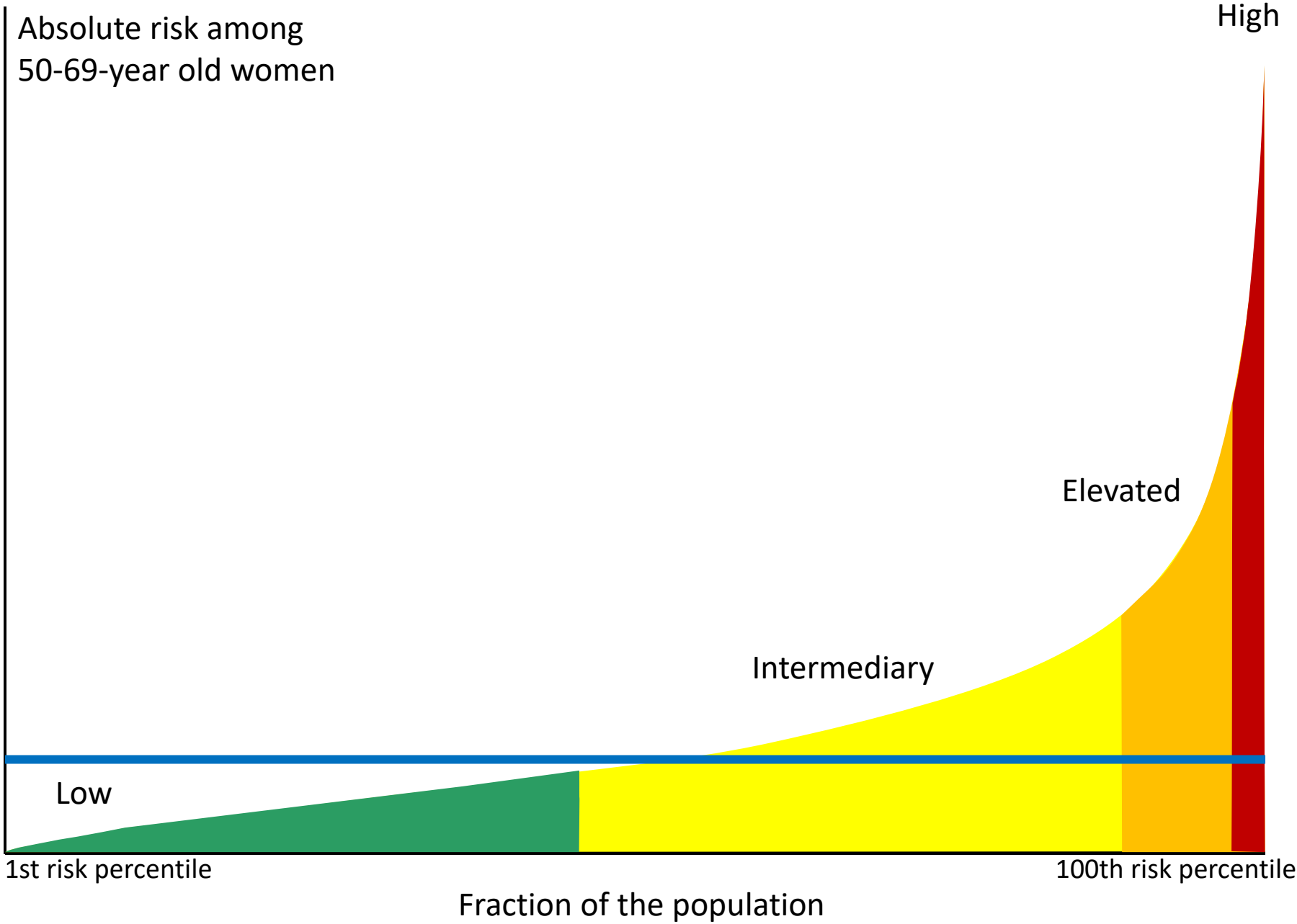
Intermediary → Mammography every 2. year

Elevated → Yearly mammog./ Tomosynthesis

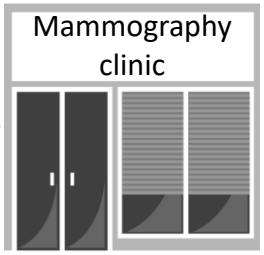
High → Yearly MRI/ Risk reduction

*BOADICEA in CanRisk

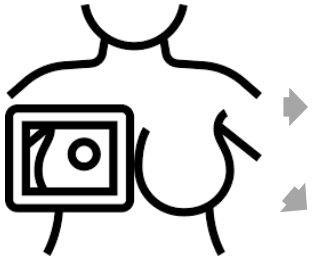
Risk Stratified Screening



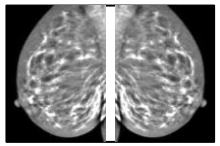
PRSONAL – Randomized Clinical Trial



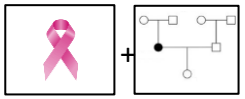
Information and consent



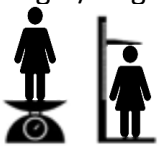
Mammogram

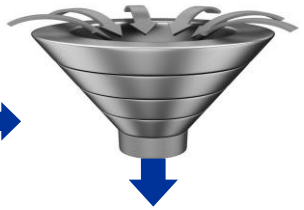


Questionnaire



Weight/height

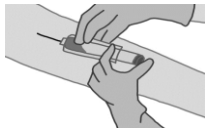




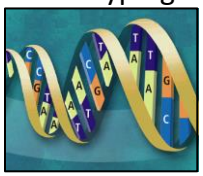
Randomization

Intervention group

Blood sampling



Genotyping



Control group: Standard program

Follow-up

Communicate risk, advice and suggested screening programme

Follow-up

PRSONAL - Sample size and power

Primary outcome	Measure	Recording time point	Previously	Reference/ Country	Number of women needed
Acceptance	Mammography in low-risk women within 2 years <30%	Day 730	41% would be unhappy or very unhappy to have less intensified screening if they had lower risk.	Meisel SF, Pashayan N, Rahman B, et al: Adjusting the frequency of mammography screening on the basis of genetic risk: Attitudes among women in the UK. Breast 24:237-41, 2015/**UK**	90% statistical power and significance level of 0.05: 1:1 Randomization of **962 women**. Assumptions: 95% eligible, 50% agree to be randomized; randomization will last 2½ months.

A clear criterium of success:
If more than 30% of the women in the low-risk group opt out of the de-escalated screening and have their mammography within 2 years from baseline, PRSONAL will not have achieved its goals, in terms of acceptance and projected economic sustainability

Secondary outcomes	Measure	Recording time points	Expected in the control group	Reference/ Country	Detectable change in PRSONAL, 90% power
Anxiety	PROMIS anxiety scale	Day 1, 180, 365 , 800	Mean=52.4, SD=8.2	Xie Z, Wenger N, Stanton AL, et al: Risk estimation, anxiety, and breast cancer worry in women at risk for breast cancer: A single-arm trial of personalized risk communication. Psychooncology 28:2226-2232, 2019/**US**	+1.7 in all +7.7 in high-risk women
Breast cancer worry	Lerman breast cancer worry scale	Day 1, 180, 365, 800	Mean=7, SD=1	Xie Z, Wenger N, Stanton AL, et al: Risk estimation, anxiety, and breast cancer worry in women at risk for breast cancer: A single-arm trial of personalized risk communication. Psychooncology 28:2226-2232, 2019/**US**	+0.4 in all +1.9 in high-risk women
Quality of life	EQ-5D-5L	Day 1, 180, 365, 800	Mean=0.86, SD=0.17	Sorensen J, Davidsen M, Gudex C, et al: Danish EQ-5D population norms. Scand J Public Health 37:467-74, 2009/**DK**	-0.04 in all -0.16 in high-risk women

Potential Benefits

Breast cancer at screening visits: +10%

Breast cancer after screening visits: -24%

Number of screening visits: -15%

Fewer breast cancers detected at advanced stage

Reduced screening costs

Reduced treatment costs

Fewer breast cancer deaths?

Partners of PRSONAL

midt regionmidtjylland

Liaison to Central Region, DK

Coordinating, Genotyping

Mammography screening

REGION H Region Hovedstaden

Sponsor

Transplantation of BOADICEA to DK

UNIVERSITY OF CAMBRIDGE

Joint development of Tool for risk communication

Joint development of Tool for risk communication

Incorporating risk model in the Tool

Melatech™

Construction of Tool for risk communication

Joint development of Tool for risk communication

Danish Cancer Society

Focus groups, surveys and tests

PRSONAL – Risk data flow

Collection of data used for risk calculation and data for safety monitoring

Day 1, day of attendance

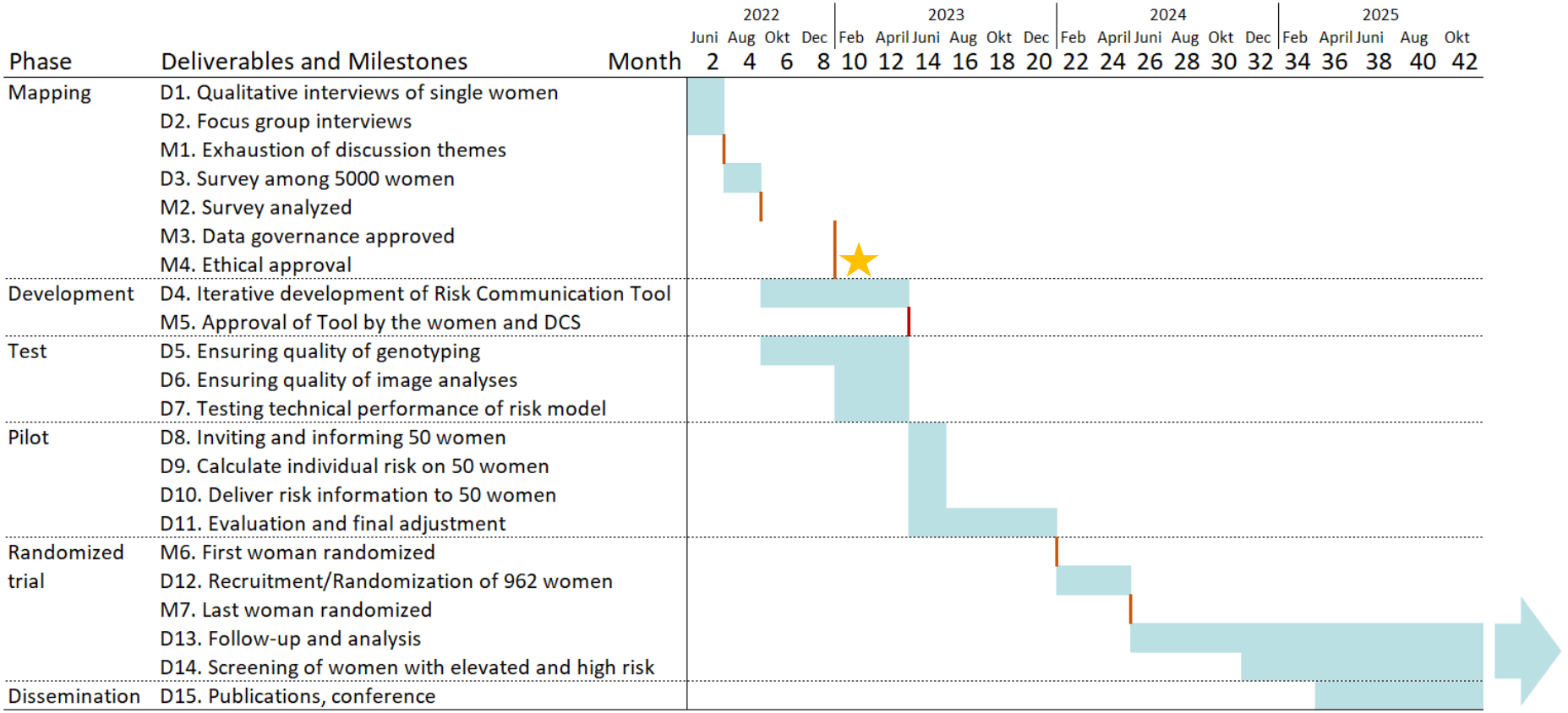
Mammography
BIRADS breast density
Lifestyle etc. (a.m. BOADICEA)
Family history (a.m. BOADICEA)
Height, weight
Education
Own risk assessment
Quality of Life (EQ-5D-5L)
PROMIS anxiety scale
Lerman breast cancer worry scale

Blood test for genetic analysis

	Day 90	Day 180	Day 365	Day 800
Control	No contact	Quality of Life (EQ-5D-5L) PROMIS anxiety scale Lerman breast cancer worry scale	Quality of Life (EQ-5D-5L) PROMIS anxiety scale Lerman breast cancer worry scale	Quality of Life (EQ-5D-5L) PROMIS anxiety scale Lerman breast cancer worry scale Screening mammography
Intervention	Adapted risk communi-cation and suggestion for future screening	Quality of Life (EQ-5D-5L) PROMIS anxiety scale Lerman breast cancer worry scale	Quality of Life (EQ-5D-5L) PROMIS anxiety scale Lerman breast cancer worry scale Mammogram/tomosyn-thesis and MRI for women with elevated and high risk at year 1.	Quality of Life (EQ-5D-5L) PROMIS anxiety scale Lerman breast cancer worry scale Screening mammography (intermediary risk) **Fraction of low-risk women with a mammography after baseline***

***Primary outcome**

PRSONAL – Status



Phase	Deliverables and Milestones	Month
Mapping	D1. Qualitative interviews of single women	
	D2. Focus group interviews	
	M1. Exhaustion of discussion themes	
	D3. Survey among 5000 women	
	M2. Survey analyzed	
	M3. Data governance approved	
	M4. Ethical approval	
Development	D4. Iterative development of Risk Communication Tool	
	M5. Approval of Tool by the women and DCS	
Test	D5. Ensuring quality of genotyping	
	D6. Ensuring quality of image analyses	
	D7. Testing technical performance of risk model	
Pilot	D8. Inviting and informing 50 women	
	D9. Calculate individual risk on 50 women	
	D10. Deliver risk information to 50 women	
	D11. Evaluation and final adjustment	
Randomized trial	M6. First woman randomized	
	D12. Recruitment/Randomization of 962 women	
	M7. Last woman randomized	
	D13. Follow-up and analysis	
	D14. Screening of women with elevated and high risk	
Dissemination	D15. Publications, conference	

DCS: Danish Cancer Society

Challenges

Complex data vs. comprehension

Strong communication vs. no staff

Reduce invisible inequality in health (One-size-fits-all is inequality…)

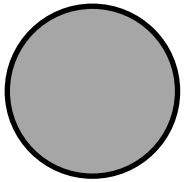
Don’t loose socioeconomic disadvantaged citizens

Probably more…

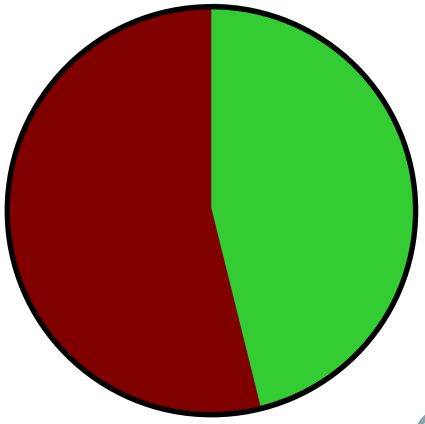
Relevant risk communication

HOTLINE: XXXX XXXX

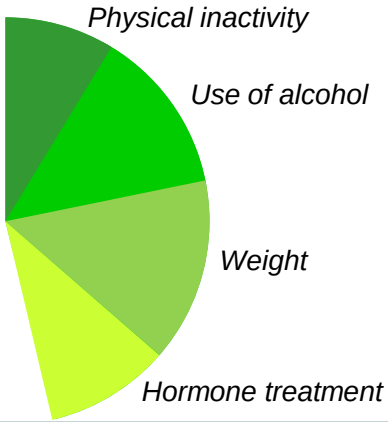
Average for all women at your age



Your risk to get breast cancer within the next 5 years is 8.2%.



Risk factors you can change:



A women like you, but with average scores for these factors, will have a risk of 5.2%

What does this mean?

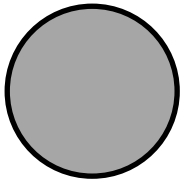
I wish another risk description

We suggest that next screening examination will be an MRI and will take place between 01-MM-ÅÅÅÅ and 01-MM-ÅÅÅÅ. You will be invited by electronic mail as usual.

Relevant risk communication

HOTLINE: XXXX XXXX

Average for all women at your age



Your risk to get breast cancer within the next 5 years is 0.8%.

Risk factors you can change:

Physical inactivity

Weight

A women like you, but with average scores for these factors, will have a risk of 0.6%

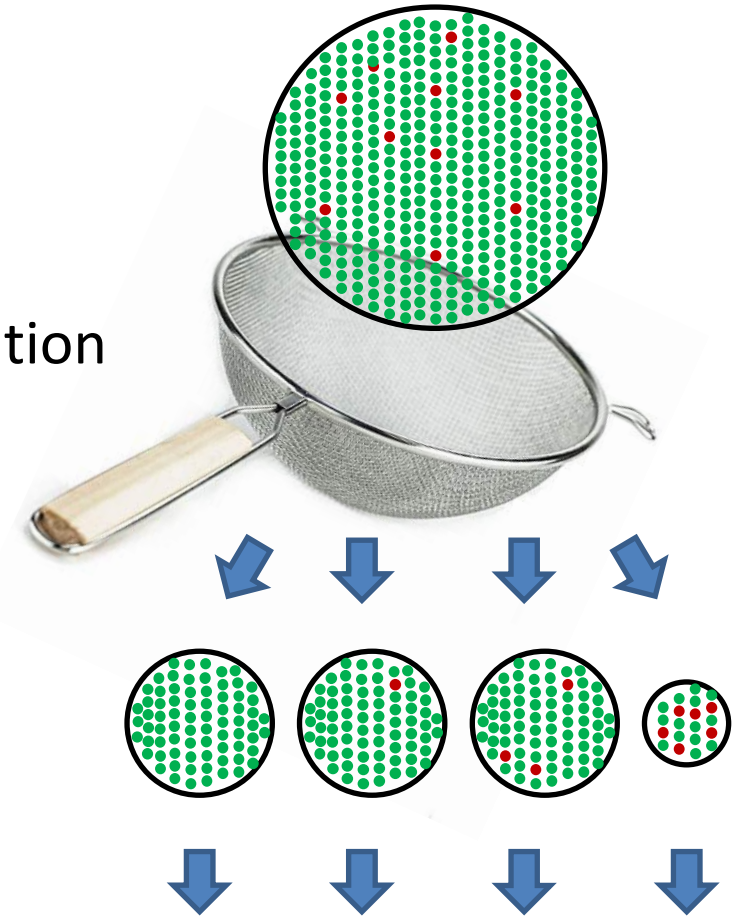
What does this mean?

I wish another risk decription

We suggest that the screening mammography will take place between 01-MM-ÅÅÅÅ and 01-MM-ÅÅÅÅ. You will be invited by electronic mail as usual. Please note that you have the right according to the law to have a screening mammography already in 2 years. For the group of women with your risk, however, we estimate that the harms will the exceed the benefits.

Future screening programmes are multidimensional and multistep

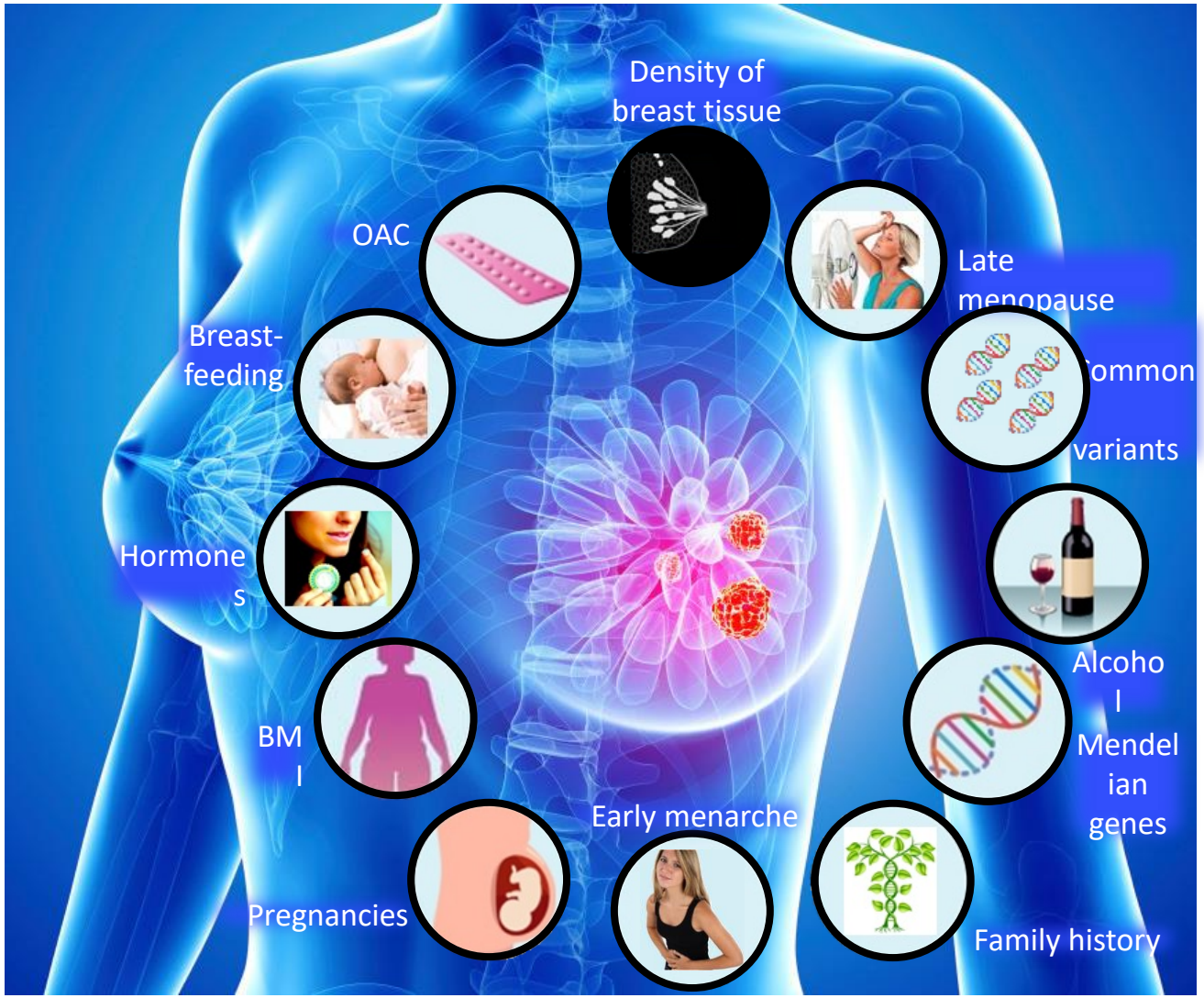
Risk stratification



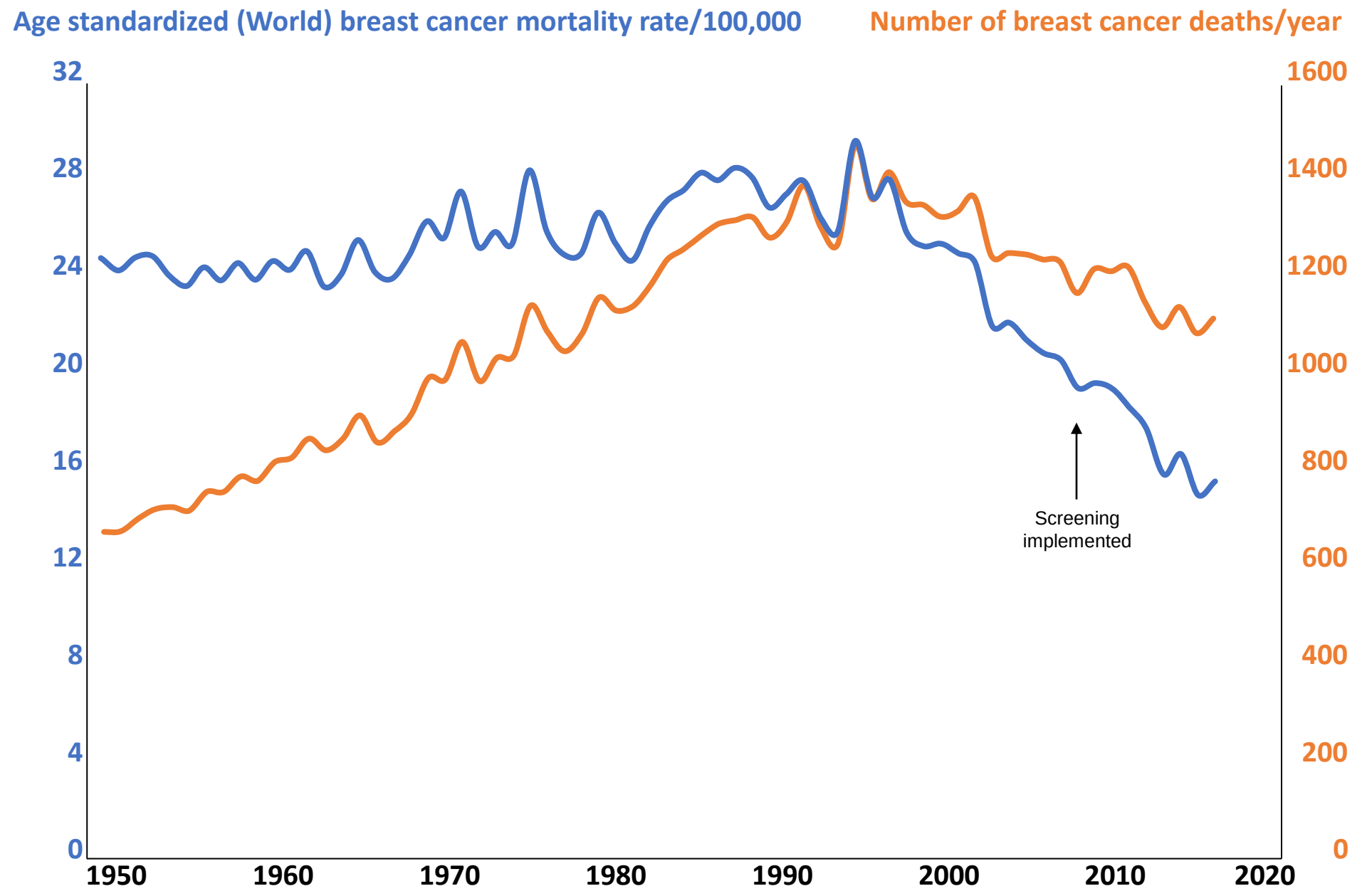
Diversified interventions

We know the risk factors

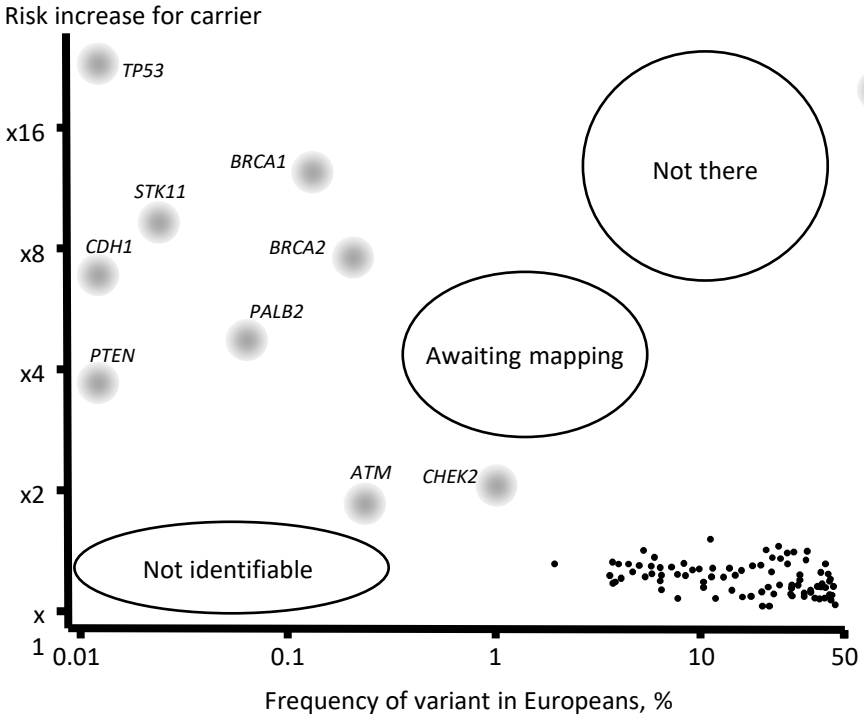
…and now we know have to combine them.



Breast cancer mortality in Denmark



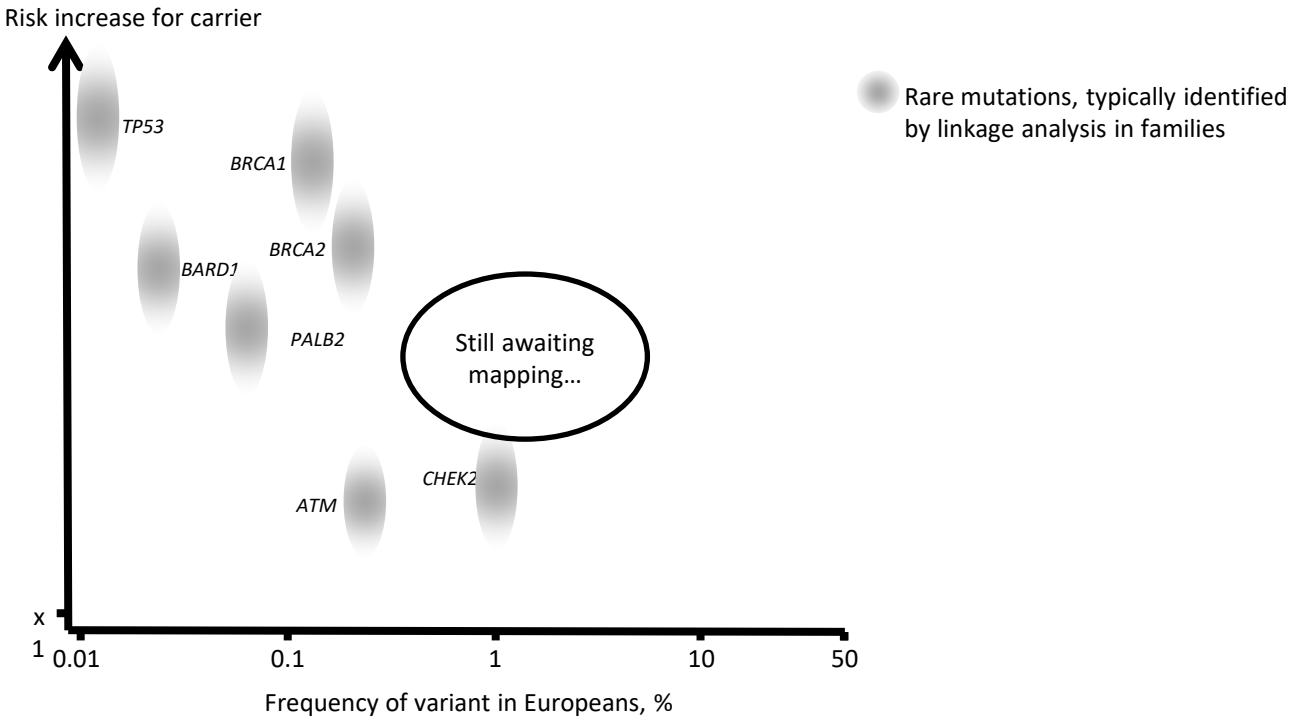
Breast cancer and genetics



- Rare mutations, typically identified by linkage analysis in families
- Frequent variants, typically identified by genome-wide association studies

Bojesen, *UfL* 2019 and Ghoussaini M. *et al*. Am J Pathol. 2013

Better description of risk by each mendelian variant



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Breast Cancer Risk Genes — Association Analysis in More than 113,000 Women

Breast Cancer Association Consortium*

ABSTRACT

BACKGROUND

Genetic testing for breast cancer susceptibility is widely used, but for many genes, evidence of an association with breast cancer is weak, underlying risk estimates are imprecise, and reliable subtype-specific risk estimates are lacking.

METHODS

We used a panel of 34 putative susceptibility genes to perform sequencing on samples from 60,466 women with breast cancer and 53,461 controls. In separate analyses for protein-truncating variants and rare missense variants in these genes, we estimated odds ratios for breast cancer overall and tumor subtypes. We evaluated missense-variant associations according to domain and classification of pathogenicity.

RESULTS

Protein-truncating variants in 5 genes (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*) were associated with a risk of breast cancer overall with a P value of less than 0.0001. Protein-truncating variants in 4 other genes (*BARD1*, *RAD51C*, *RAD51D*, and *TP53*) were associated with a risk of breast cancer overall with a P value of less than 0.05 and a Bayesian false-discovery probability of less than 0.05. For protein-truncating variants in 19 of the remaining 25 genes, the upper limit of the 95% confidence interval of the odds ratio for breast cancer overall was less than 2.0. For protein-truncating variants in *ATM* and *CHEK2*, odds ratios were higher for estrogen receptor (ER)–positive disease than for ER-negative disease; for protein-truncating variants in *BARD1*, *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, and *RAD51D*, odds ratios were higher for ER-negative disease than for ER-positive disease. Rare missense variants (in aggregate) in *ATM*, *CHEK2*, and *TP53* were associated with a risk of breast cancer overall with a P value of less than 0.001. For *BRCA1*, *BRCA2*, and *TP53*, missense variants (in aggregate) that would be classified as pathogenic according to standard criteria were associated with a risk of breast cancer overall, with the risk being similar to that of protein-truncating variants.

CONCLUSIONS

The results of this study define the genes that are most clinically useful for inclusion on panels for the prediction of breast cancer risk, as well as provide estimates of the risks associated with protein-truncating variants, to guide genetic counseling. (Funded by European Union Horizon 2020 programs and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Easton at the University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, United Kingdom, or at dfe20@medschl.cam.ac.uk.

*A complete list of collaborators and investigators is provided in the Supplementary Appendix, available at NEJM.org.

Dr. Dorling, Dr. Carvalho, and Mr. Allen and Drs. Teo, Devilee, and Easton contributed equally to this article.

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2021

Cancer diseases are heterogenous

Strategies to detect them while small, must be diverse

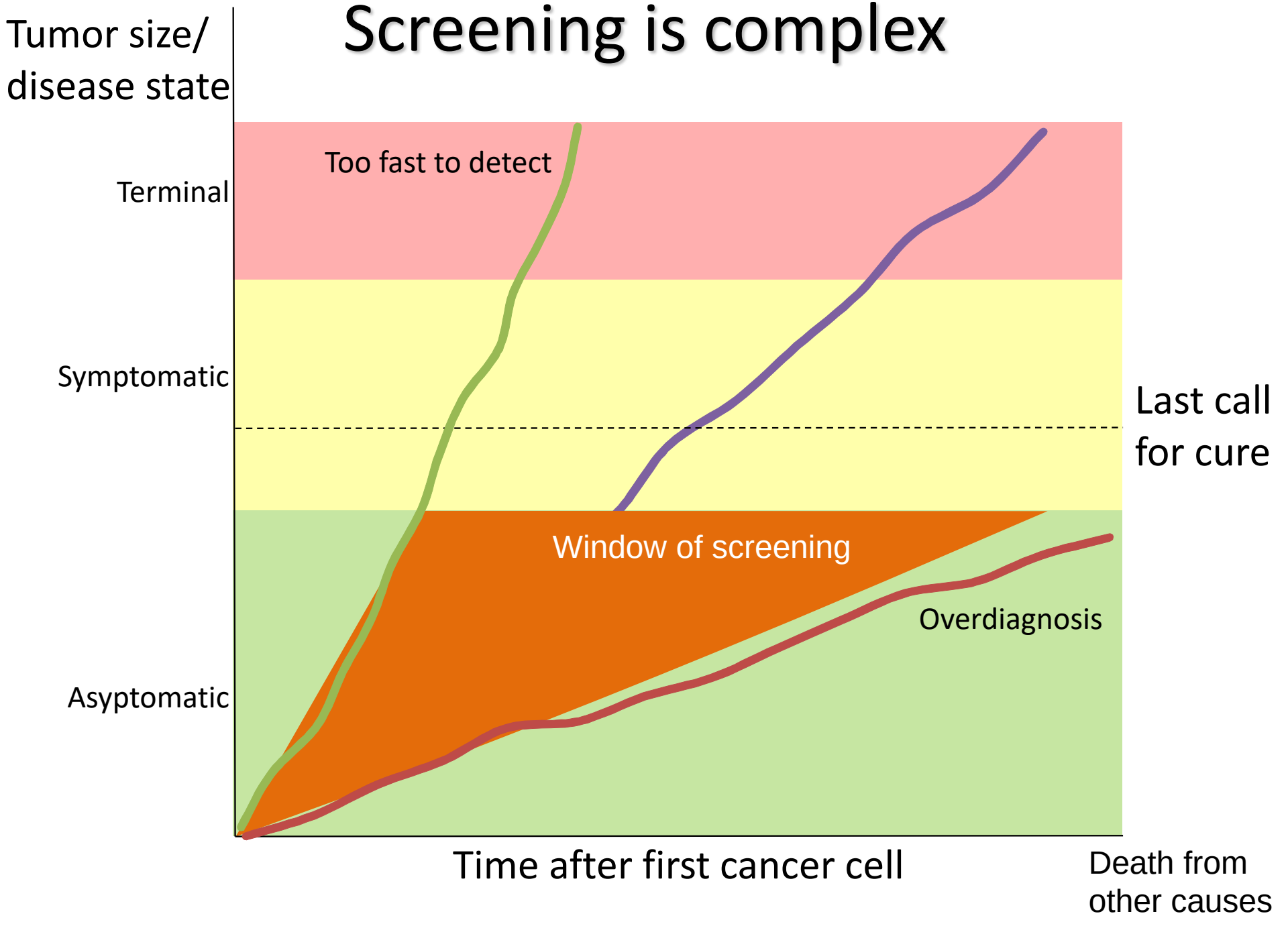
Cancer is caused by infections
Cancer is inherited

Cancer is caused by mutations
Cancer is caused by environment

Cancer is frequent
(50% of the population)
Cancer is rare
(for a cell)

Cancer is an
old-age disease
Cancer is a
stochastic event

Screening is complex



Three solutions

1) Stop smoking
   (Reduces likelihood of first cancer cell)
2) Improve treatment
   (Increases threshold for last call for cure)
3) Early detection/screening
   (But not too early)

Cancer screening

Pro

With screening
we find tumors while they
are small and treatable

Con

We cannot use scarce ressources on healthy individuals