Dalla Lana School of Public Health

PERSPECTIVE INTEGRATION & IMPLEMENTATION

Application of PRS to Risk Stratified Breast Cancer Screening

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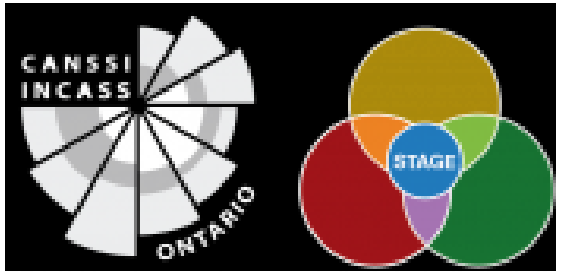
UNIVERSITY OF TORONTO
DALLA LANA SCHOOL OF PUBLIC HEALTH



Breast Cancer in Canada

1/8 WOMEN WILL DEVELOP BREAST CANCER DURING HER LIFE

1/6 CASES

OCCUR IN WOMEN < 50 YEARS OLD

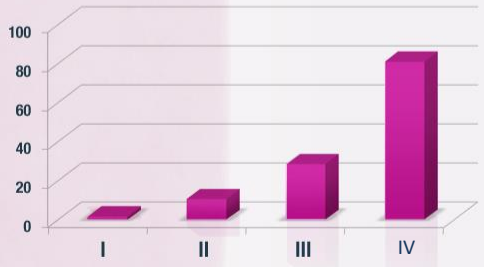
26 300

NEW CASES EACH YEAR

5 000

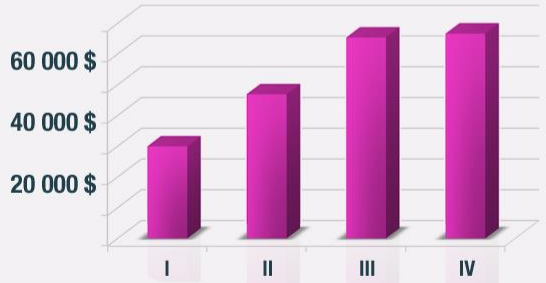
DEATHS ARE ATTRIBUTED TO THIS CANCER EACH YEAR

RELATIVE MORTALITY RATIO (5 YRS)



CANCER STAGES

MEAN COST OF CARE (2 YRS)



CANCER STAGES

Breast Screening in Canada

- Canadian Taskforce on Preventive Health Care recommends screening women 50 to 74 with mammography every 2 to 3 years
- Many screening programs screen outside these guidelines
- Some programs recommend MRI with mammography for women at high risk

Targets women based on age rather than risk

May result in over-screening women at lower risk and underscreening women at higher risk

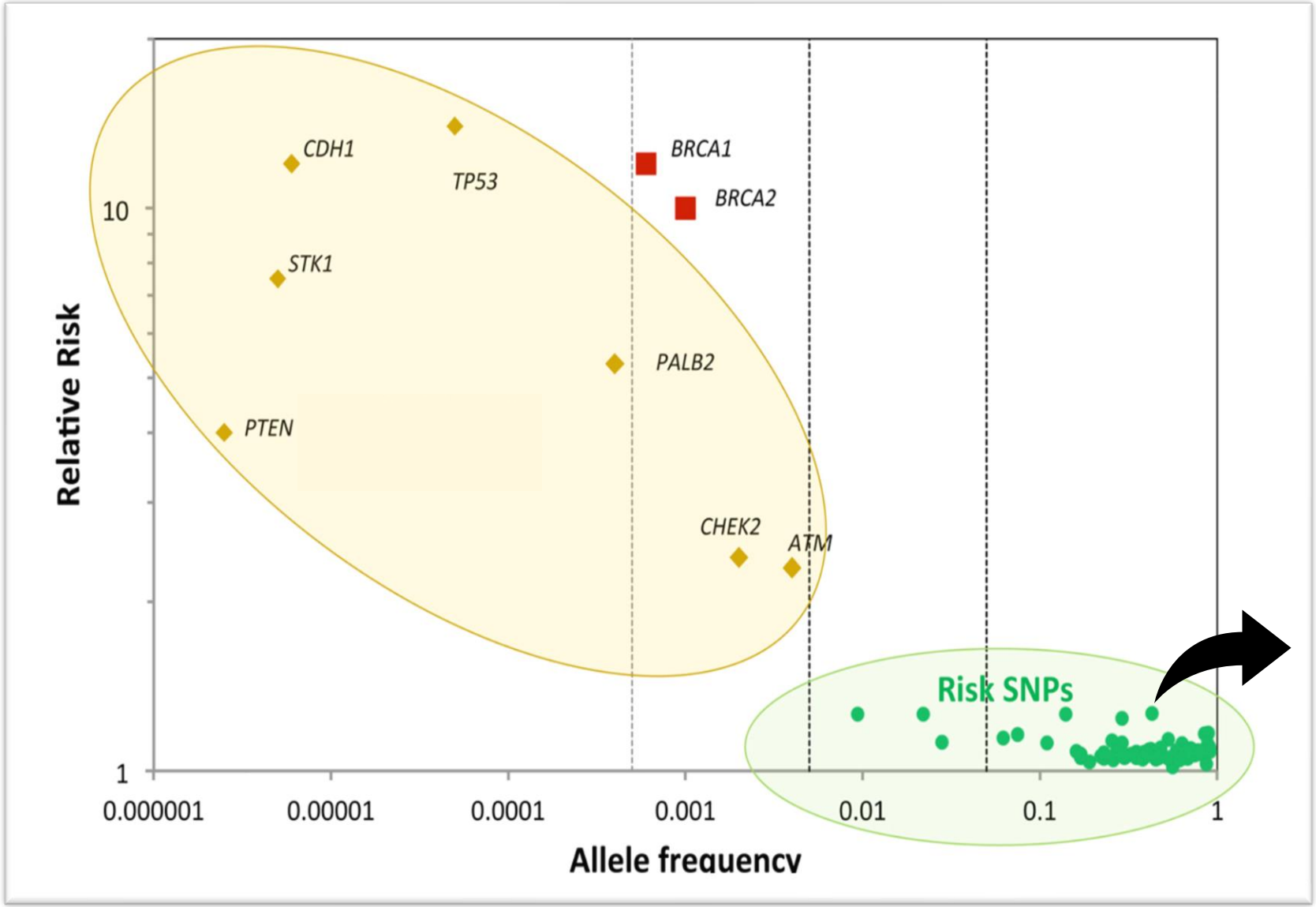
Ontario Breast Screening Programs

Ontario Breast Screening Program (OBSP)
Started in July 1990
50 to 74 years 75+ (referral)
232 screening centers 2 mobile coaches 73 assessment centers
Mammogram every two years or Every year based on family history, density, & benign breast disease

Breast Cancer Risk Assessment

- Many women receive approximate risk estimates based on their family history
- Risk prediction tools (e.g., BOADICEA, IBIS) are used in the context of genetic clinics to assess breast cancer risk and/or risk of carrying a mutation
- **Multi-gene panel tests** often include genes with unproven association
- Significantly limits application of results to inform recommendations for screening and prevention

Genetic architecture of breast cancer



Polygenic
Risk
Score

Slide provided by Dr. Jacques Simard

ARTICLE

Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes

Mavaddat N et al. (2019) Am J Hum Genet. 104:21-34. doi: 10.1016/j.ajhg.2018.11.002.

Background

- Building on prior work (77 SNP PRS)
- ~170 identified breast cancer SNPs
- The goal of this analysis was to:
  - Improve discrimination of the PRS by including variants associated at a more liberal significance threshold
  - Consideration of sub-type specific PRS

Study Populations and Data

- Includes data form 79 studies (Breast Cancer Association Consortium)
  - 94,075 cases and 75,017 controls
  - European ancestry
- Genotyped on either iCOGs or OncoArray
- Validation set: randomly selected 10% of cases and controls
  - All on OncoArray
  - Excluding studies of: bilateral breast cancer, those that oversampled for family history
  - Excluding individuals: with in situ disease or unknown ER status
- Additional validation in:
  - 11,428 cases and 18,323 controls, nested case-control studies from 10 cohorts genotyped on OncoArray (e.g., EPIC, PLCO, NHS etc)
  - 190,040 women in UKB including 3,215 incident cases

The PRS

$$PRS = \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k \ldots + \beta_n x_n$$

- β_k is the per-allele odds ratio for SNP *k*
- x_k is the allele dosage for SNP *k*
- *n* is the total number of SNPs in the PRS

What SNPs to included? What weights to use?

Table 1. Comparison of Methods for Deriving the PRS: Results for Overall Breast Cancer in the Validation Set

p Value Cutoff[a]	SNPs Entering Model (n)	SNPs Selected (n)	OR[b]	95% CI	AUC
Published PRS[7]					
	77	77	1.49	1.44–1.56	0.612
Hard-Thresholding Stepwise Forward Regression					
$<5 \times 10^{-8}$	1,817	123	1.59	1.52–1.66	0.626
$<10^{-6}$	2,603	197	1.62	1.55–1.68	0.634
$<10^{-5}$	3,818	305	1.65	1.58–1.72	0.637
$<10^{-4}$	6,743	669	1.62	1.56–1.69	0.631
$<10^{-3}$	14,760	1,707	1.55	1.49–1.62	0.623
Penalized Regression					
Lasso	15,032	3,820	1.71	1.64–1.79	0.647

[a]The p value cut off refers to the SNPs considered based on their marginal associations in the training set; the same p value threshold was used in each case in the stepwise regression. Parameter selection and effect size estimation for derivation of the PRS was carried out in the training set as described in the Material and Methods.

[b]OR per 1 SD for the PRS. OR for association with breast cancer in the validation set was derived using logistic regression adjusting for country and ten PCs. AUCs were adjusted for country. The lasso was carried out after pre-selecting SNPs at $p < 10^{-3}$ based on their marginal association in the training set. For the lasso $\lambda = 0.003$ gave the optimal PRS in the validation set.

Mavaddat N et al. (2019) Am J Hum Genet. 104:21-34. doi: 10.1016/j.ajhg.2018.11.002.

The 313 SNP PRS

- 305 SNP PRS – plus
  - 6 SNPs associated with ER+ disease at $p<10^{-6}$
  - 2 known rare breast cancer susceptibility variants in *BRCA2* and *CHEK2*
- Optimal weights
  - Hybrid approach
  - 196 SNPs case-only p-value <0.025 - subtype-specific weights
  - Remaining SNPs overall breast cancer weights

- Validation for the 77 SNP PRS, 313 SNP PRS and 3820 SNP PRS

Table 2. Association between PRS and Breast Cancer Risk in the Validation Set and Prospective Test Datasets

	Validation Set			Prospective Test Set		
	OR[a]	95% CI	AUC	OR[a]	95% CI	AUC
77 SNP PRS (PRS_{77})						
Overall BC	1.49	1.44–1.56	0.612	1.46	1.42–1.49	0.603
ER-positive	1.56	1.49–1.63	0.623	1.52	1.48–1.56	0.615
ER-negative	1.40	1.30–1.50	0.596	1.35	1.27–1.43	0.584
313 SNP PRS (PRS_{313})						
Overall BC	1.65	1.59–1.72	0.639	1.61	1.57–1.65	0.630
ER-positive	1.74	1.66–1.82	0.651	1.68	1.63–1.73	0.641
ER-negative	1.47	1.37–1.58	0.611	1.45	1.37–1.53	0.601
3,820 SNP PRS (PRS_{3820})						
Overall BC	1.71	1.64–1.79	0.646	1.66	1.61–1.70	0.636
ER-positive	1.81	1.73–1.89	0.659	1.73	1.68–1.78	0.647
ER-negative	1.48	1.37–1.59	0.611	1.44	1.36–1.53	0.600

Parameter selection and effect size estimation for derivation of the PRS was carried out in the training set as described in the Material and Methods. The optimal subtype-specific PRS was obtained by carrying out case-only logistic regression and estimating effect sizes in the relevant subtype for SNPs passing a p value of 0.025 in case-only ordinary logistic regression (ER-positive versus ER-negative disease). OR for association with breast cancer in the validation set derived using logistic regression adjusting for country and ten PCs. AUCs were adjusted for by country. In the prospective test set, logistic regression models were adjusted for study and 15 PCs. AUCs were adjusted for by study.

[a]OR per 1 SD for the PRS.

Mavaddat N et al. (2019) Am J Hum Genet. 104:21-34. doi: 10.1016/j.ajhg.2018.11.002.

ARTICLE | Genetics inMedicine

Open

Corrected: Author Correction

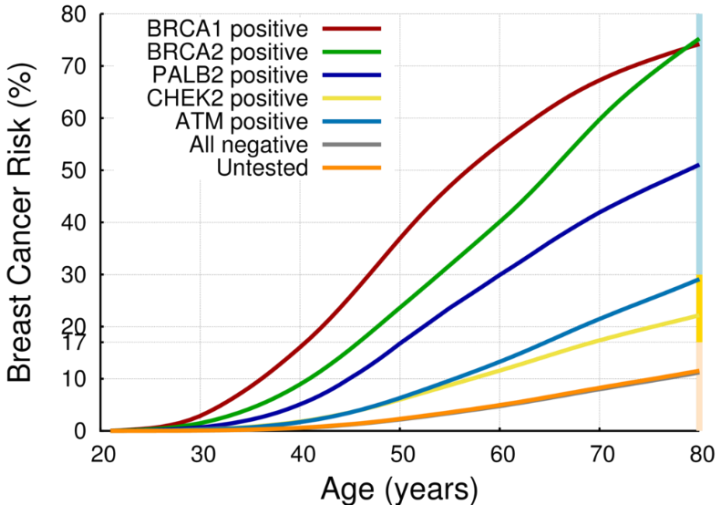
BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors

Andrew Lee, MSci, CASM[1], Nasim Mavaddat, MBBS, PhD[1], Amber N. Wilcox, MPH[2], Alex P. Cunningham, MSc, PhD[1], Tim Carver, PhD[1], Simon Hartley, MSc, PhD[1], Chantal Babb de Villiers, PhD[3], Angel Izquierdo, MD[4], Jacques Simard, PhD[5], Marjanka K. Schmidt, PhD[6], Fiona M. Walter, MD, FRCGP[3], Nilanjan Chatterjee, PhD[7,8], Montserrat Garcia-Closas, MPH, DrPH[2], Marc Tischkowitz, MD, PhD[9], Paul Pharoah, PhD[1,10], Douglas F. Easton, PhD[1,10] and Antonis C. Antoniou, PhD[1]

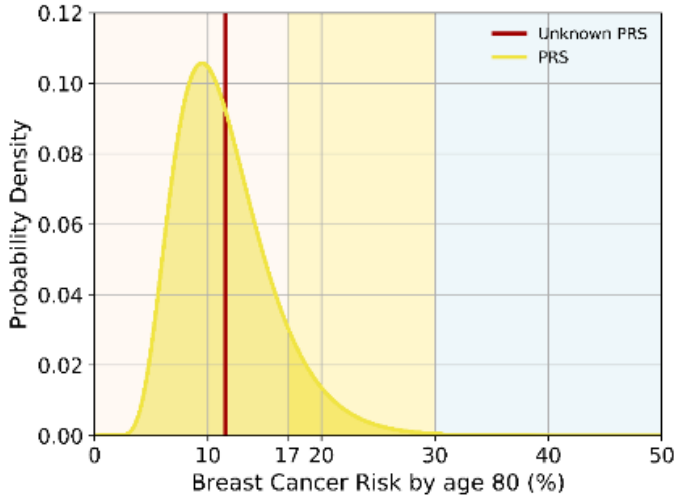
Lee et al, Genet Med. 2019 Jan 15. doi: 10.1038/s41436-018-0406-9

BOADICEA breast cancer model: comprehensive risk prediction

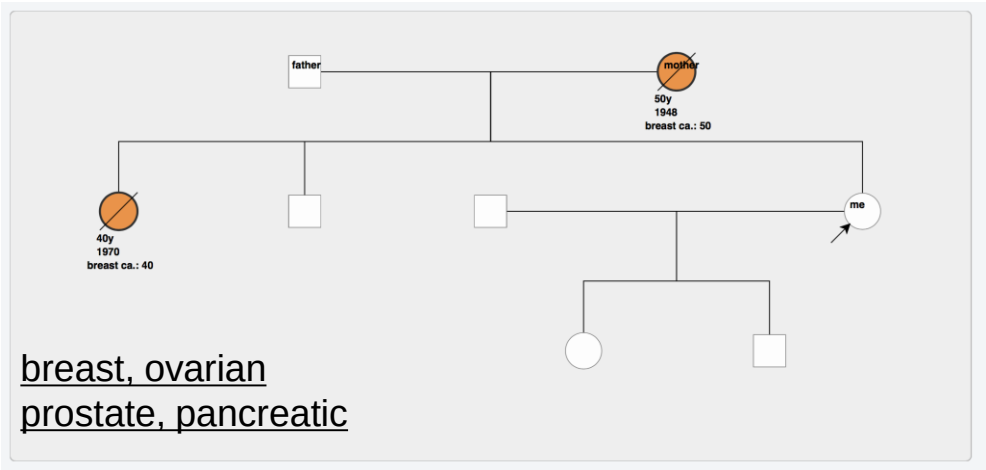
Rare genetic Variants



Polygenic Risk Score



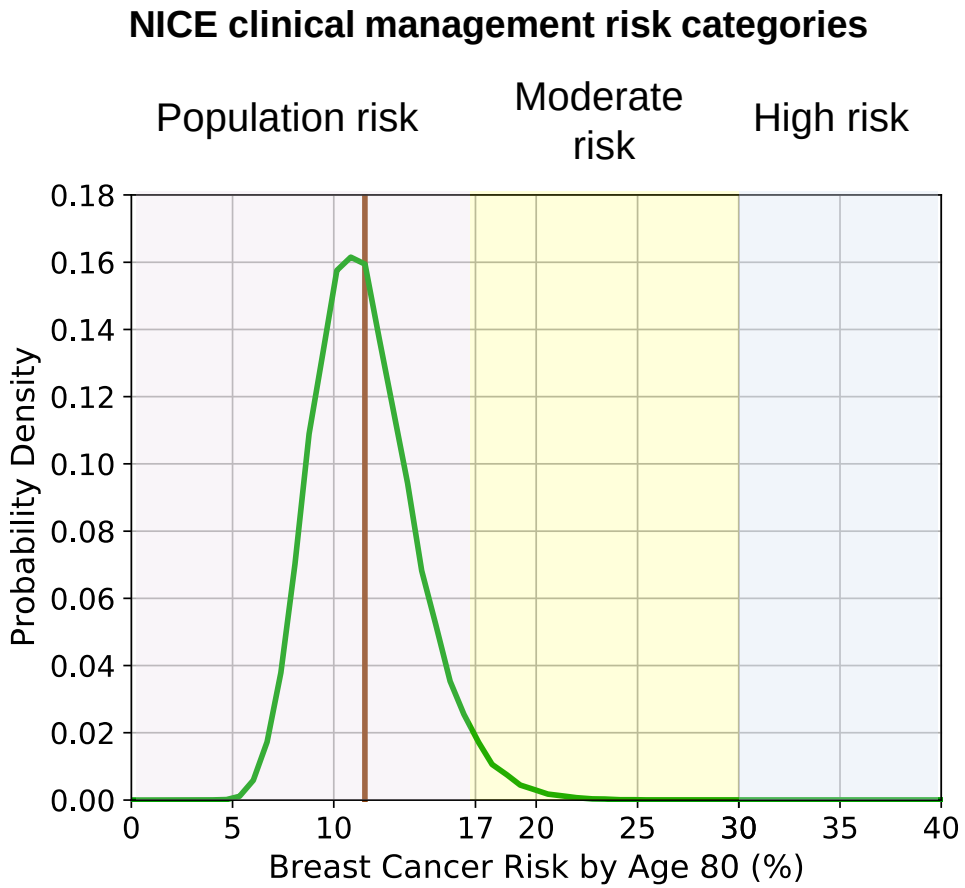
Family history



- Other unobserved genetic effects
- Lifestyle/hormonal/reproductive risk factors, mammographic density
- Breast tumour characteristics: ER/PR/HER2
- Population demographics

Lee et al, Genet Med 2019

Combining risk factors altogether: risk stratification example



Risk factors only

Risk categories

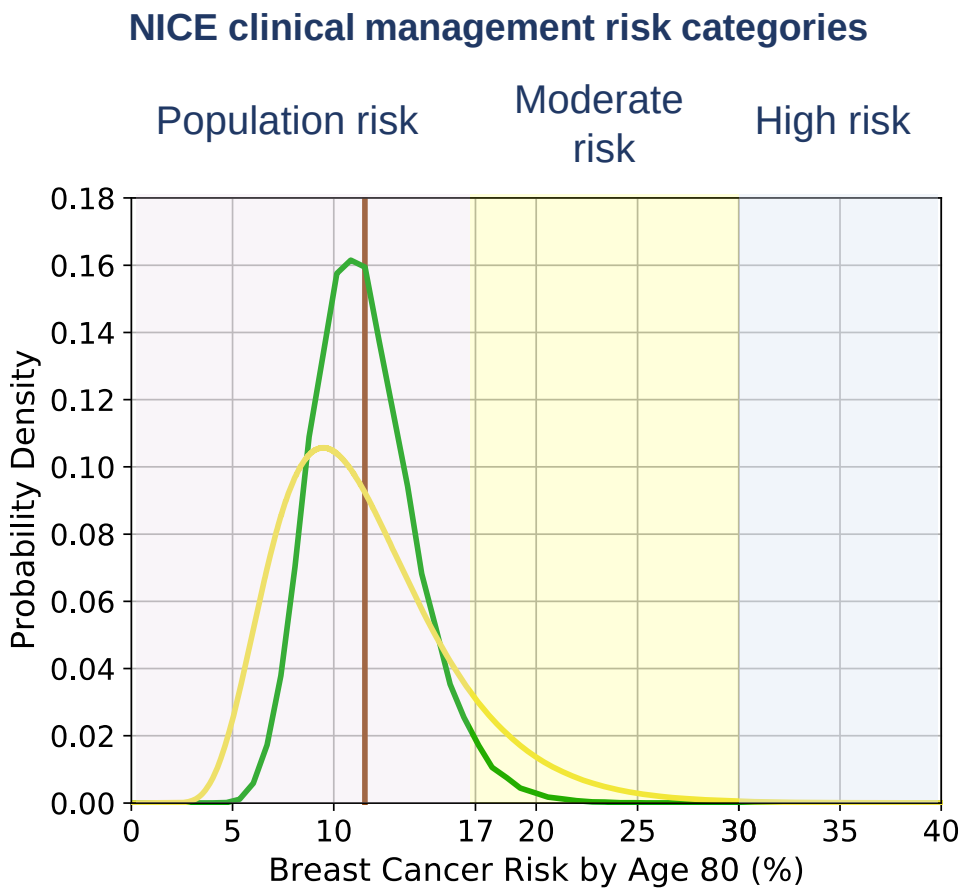
Population risk $< 17\%$

Moderate risk $\geq 17\%$ and $< 30\%$

High risk $\geq 30\%$

Lee et al Genet Med 2019

Combining risk factors altogether: risk stratification example

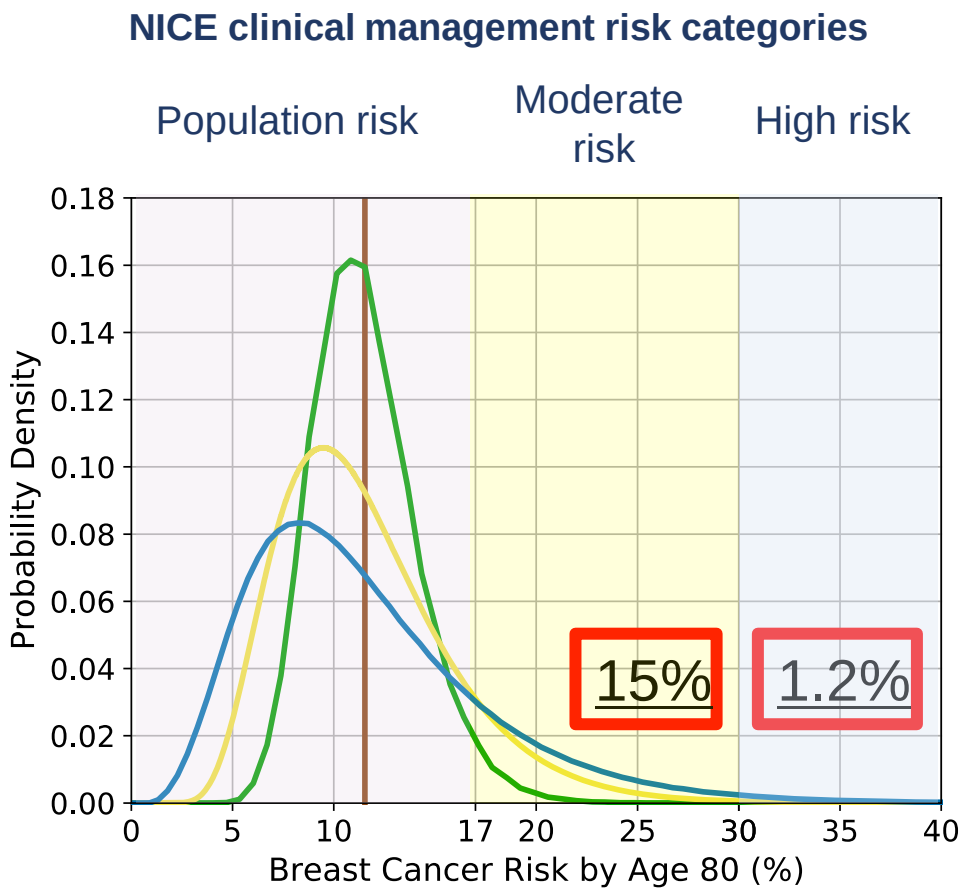


Risk factors only

Genetics (SNPs, PRS) only

Lee et al Genet Med 2019

Combining risk factors altogether: risk stratification example



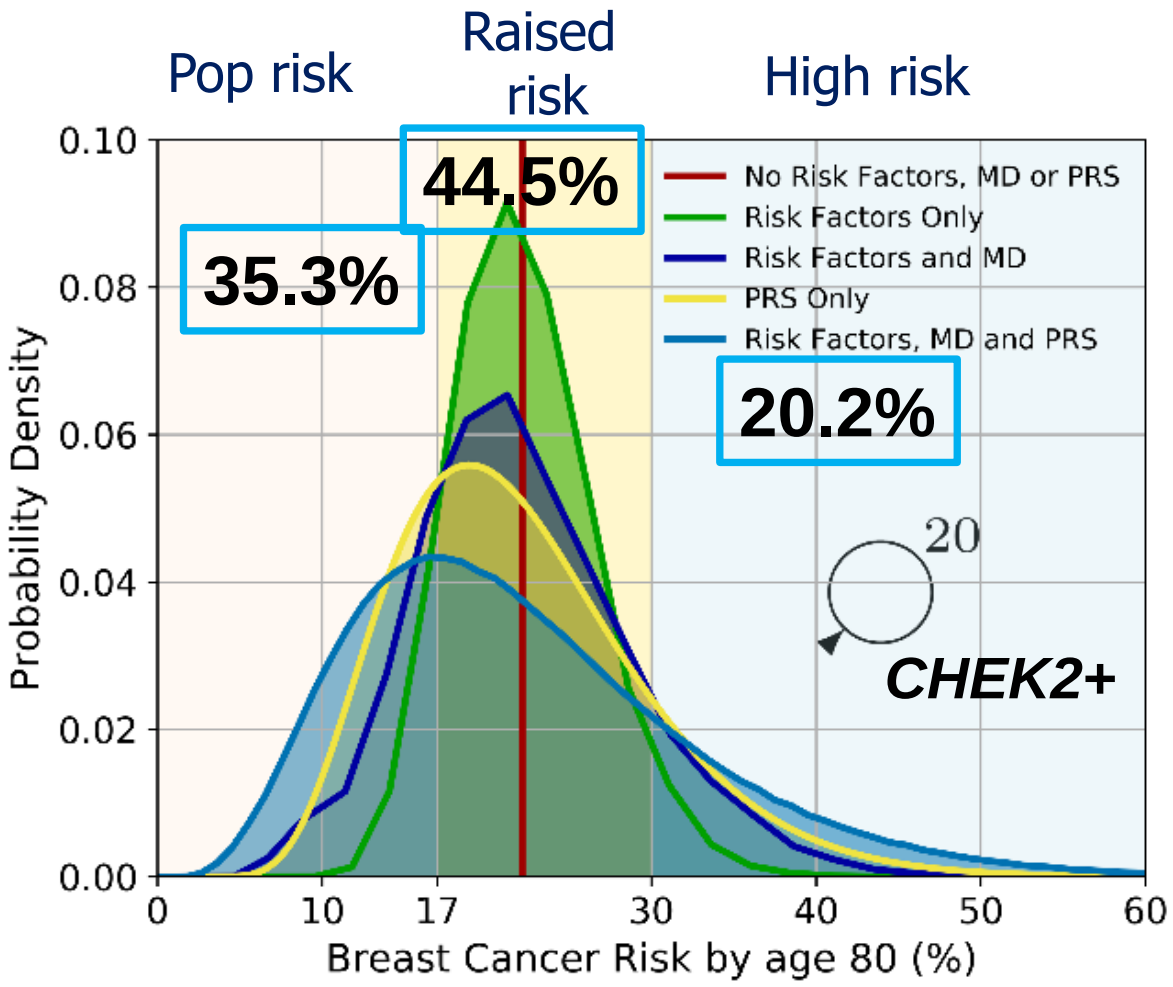
Risk factors only

Genetics (SNPs, PRS) only

Combined – full model

Lee et al Genet Med 2019

Combining risk factors altogether: risk stratification example



Lee et al Genet Med 2019

PERSPECTIVE
INTEGRATION & IMPLEMENTATION

Personalized Risk Assessment for the Prevention and Early Detection of Breast Cancer: Integration & Implementation (PERSPECTIVE I&I)

Co-Leads: Jacques Simard & Anna M. Chiarelli

GenomeCanada
CIHR IRSC
GenomeQuébec
Fondation cancer du sein du Québec
FONDATION CHU DE QUÉBEC
Économie et Innovation Québec
CHU de Québec Université Laval Centre de recherche
Ontario Health Cancer Care Ontario

PERSPECTIVE I&I

OVERARCHING GOALS:

- To improve personalized risk assessment to offer cost-effective risk-based screening and prevention of breast cancer to women most likely to benefit
- To determine the optimal implementation approaches within the Canadian healthcare system

***Patient-oriented*:** Improve genetic counselling of high-risk women about screening and risk reduction strategies

***Population-oriented*:** Develop evidence for shifting to a risk-based screening approach to improve the balance of benefits to harms

PERSPECTIVE
INTEGRATION & IMPLEMENTATION

PERSPECTIVE I&I

ACTIVITY 1

IDENTIFICATION OF NOVEL BREAST CANCER SUSCEPTIBILITY GENES

10 000 CASES | 10 000 CONTROLS

WHOLE-EXOME SEQUENCING*

50 000 | 50 000

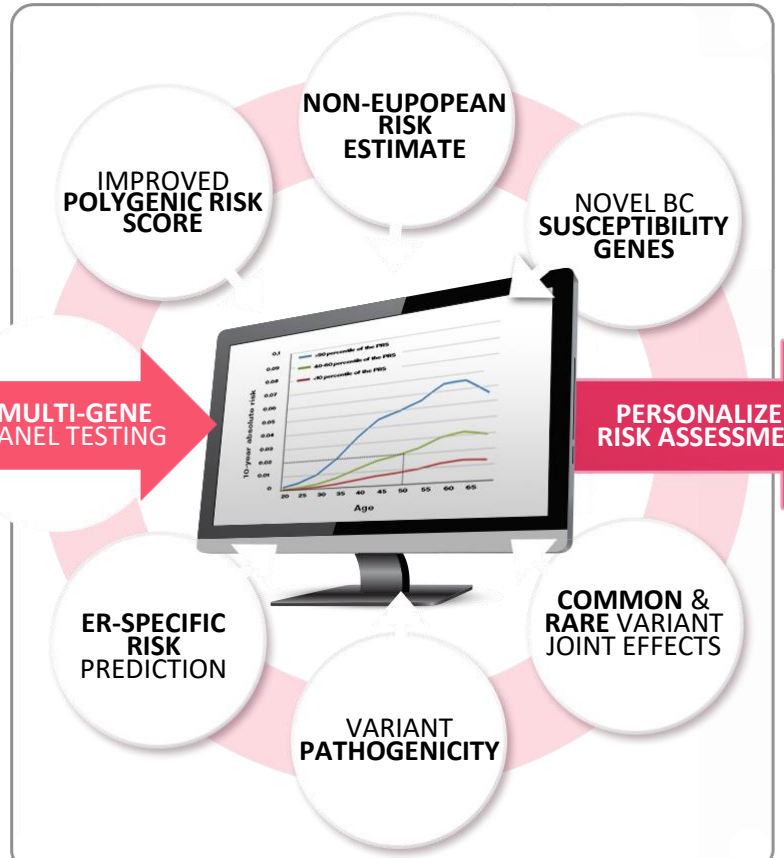
CANDIDATE GENE MUTATION SCREENING

PRECISE RISK ESTIMATES OF VALIDATED BREAST CANCER GENES

* **FUNCTIONAL ASSESSMENT OF RARE VARIANTS**

MULTI-GENE PANEL TESTING

ACTIVITY 2



PERSONALIZED RISK ASSESSMENT

MORE ACCURATE RISK PREDICTION

IMPROVE:

- GENETIC COUNSELLING
- SHARED DECISION PROCESS **ABOUT SCREENING AND RISK REDUCTION STRATEGIES**
- EFFECTIVENESS OF **PRIMARY PREVENTION**

* In collaboration with the international BRIDGES project

Slide provided by Dr. Jacques Simard

PERSPECTIVE I&I

RISK STRATIFICATION TOOLS

- **CLINICAL-GRADE POLYGENIC RISK SCORE GENETIC TEST**
- **COMPREHENSIVE RISK PREDICTION WEB-TOOL**
- **WEB-BASED RISK COMMUNICATION TOOL**
- **ECONOMIC MICROSIMULATION MODEL**

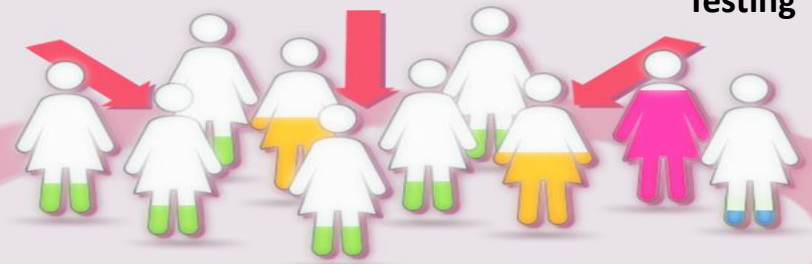
5 000 women enrolled through mammography centers

ACTIVITY 3

Knowledge, Attitudes & Beliefs

Acceptability & Feasibility

Uptake of Genetic Testing



RISK-BASED SREENING APPROACH

Screening Behaviors & Outcomes

Organizational Readiness

Costing Data

Socio-Ethical & Legal Issues

ACTIVITY 4

REAL WORLD COSTS FROM POPULATION-LEVEL DATABASES

EVIDENCE-BASED ACTIONABLE AND COST-EFFECTIVE STRATEGIES FOR IMPLEMENTION

PROVIDE REAL-LIFE EVIDENCE

ACTIONABLE FRAMEWORK TO SUPPORT THE TRANSITION FROM AGE-BASED TO RISK-BASED SCREENING

Activity 3: The Pre-implementation Study

- About 5,000 women 40 to 69 will be recruited in Ontario and Quebec through summer 2021

INCLUSION CRITERIA:

Women 40 to 69 years of age
Had a recent mammogram
Within or outside ON or QC screening programs
Have a family doctor or nurse practitioner (Quebec only)

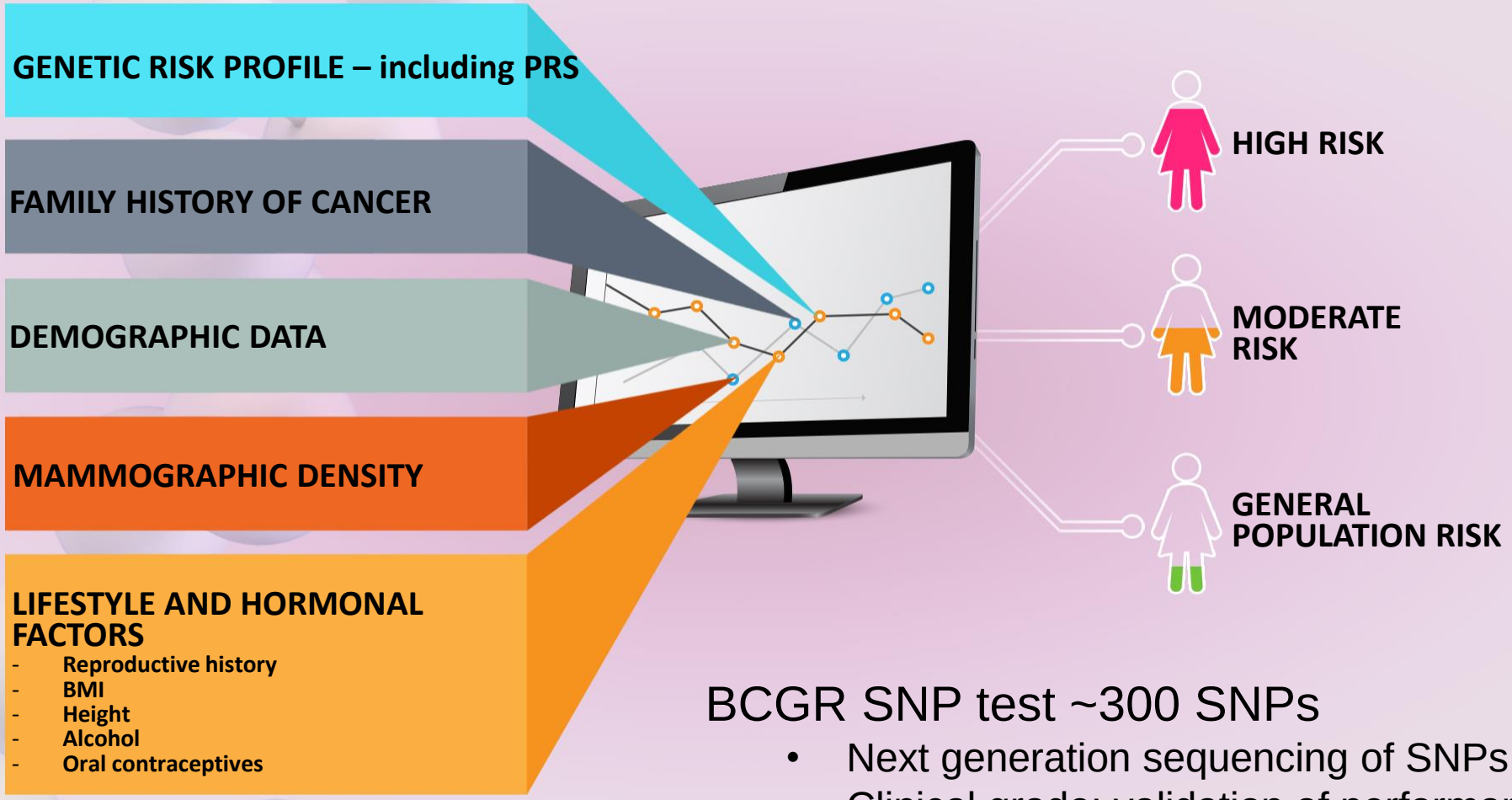
EXCLUSION CRITERIA:

Prior history of breast cancer or DCIS, ovarian or pancreatic cancer
Had a mastectomy, breast implants
Known high-risk women (e.g., *BRCA* or other high-risk mutation, ≥25% lifetime risk, prior chest radiation)
Had genetic testing and/or counselling for breast cancer

PERSPECTIVE
INTEGRATION & IMPLEMENTATION

Risk Assessment: CanRisk (BOADICEA)

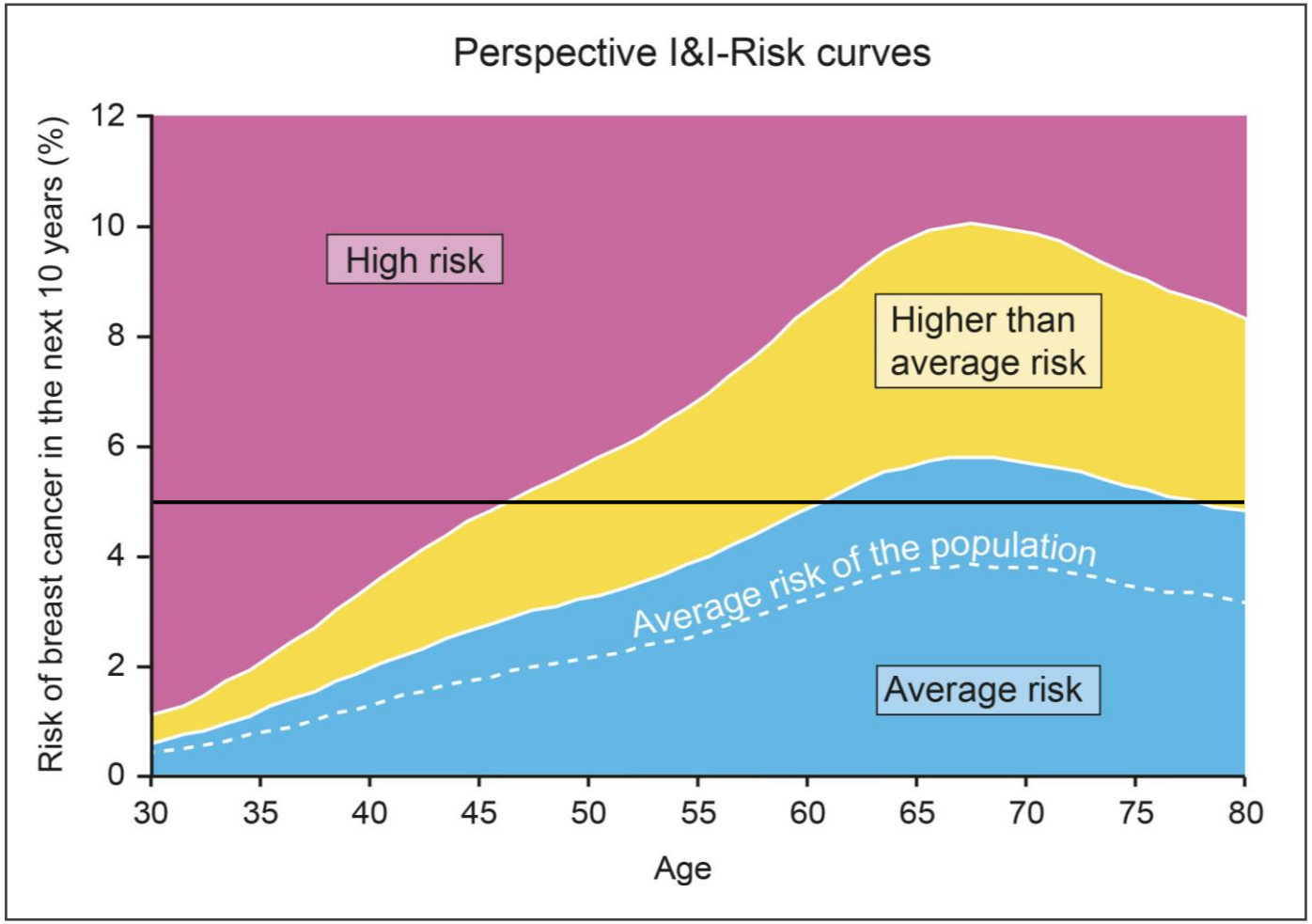
PERSPECTIVE
INTEGRATION & IMPLEMENTATION



BCGR SNP test ~300 SNPs

- Next generation sequencing of SNPs
- Clinical grade: validation of performance metrics, QC, standard operating procedures
- Assay designed for high volume/low-cost

Risk Categories: 10-year absolute risk



SCREENING ACTION PLAN

40-69 years: Annual mammogram and MRI

40-49 years: Talk to doctor about screening

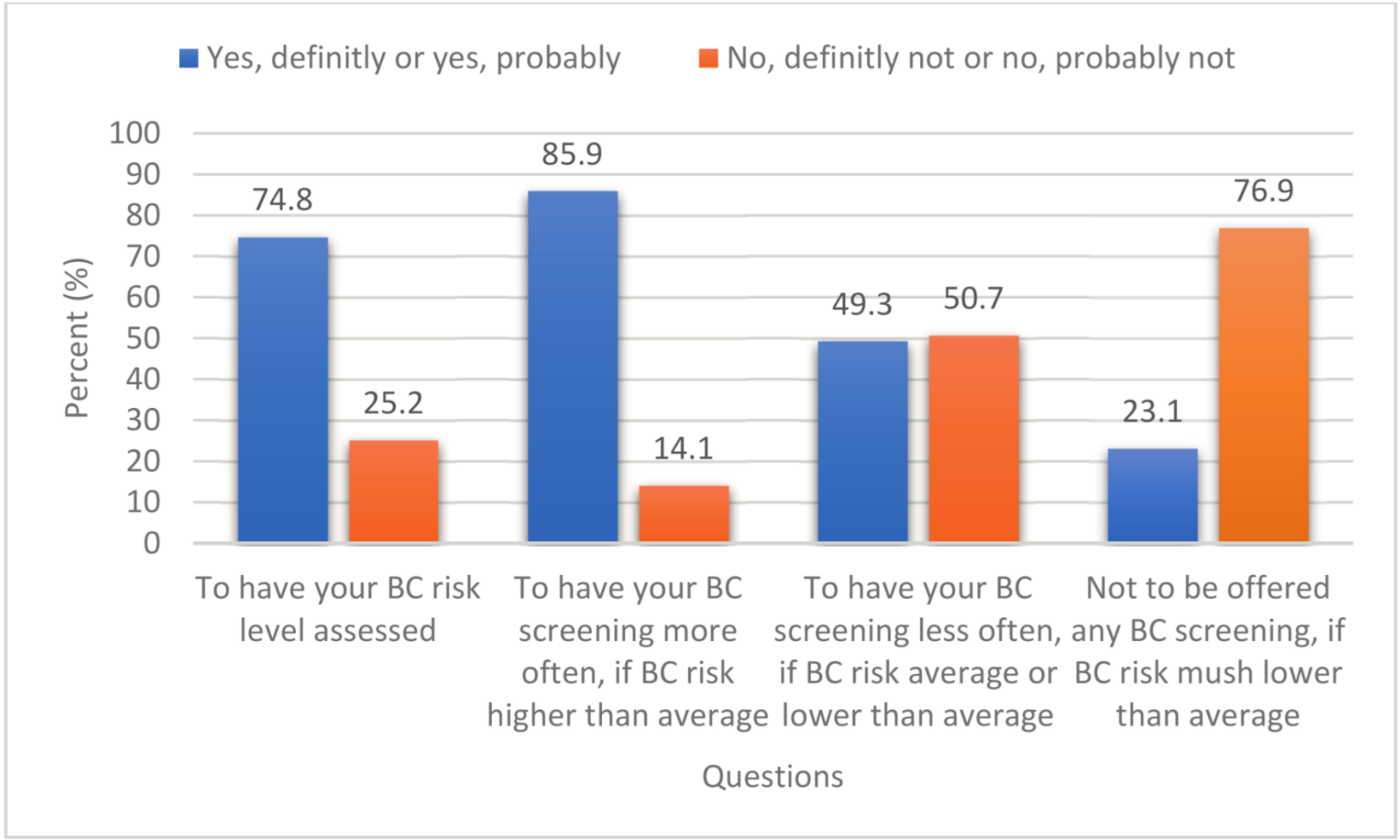
50-69 years: Annual mammogram

40-49 years: No regular screening

50-69 years: Biennial mammogram

PERSPECTIVE
INTEGRATION & IMPLEMENTATION

*10 year absolute risk scaled to remaining lifetime risk (RLR) at age 30 (the anchor) to age 80.



Panel C: Willingness to have BC risk assessment and tailored screening frequency.

Nabi et al, 2021

ACTIVITY 3

RISK STRATIFICATION TOOLS

- CLINICAL-GRADE POLYGENIC RISK SCORE GENETIC TEST
- COMPREHENSIVE RISK PREDICTION WEB-TOOL
- WEB-BASED RISK COMMUNICATION TOOL
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5 000 women enrolled through mammography centers

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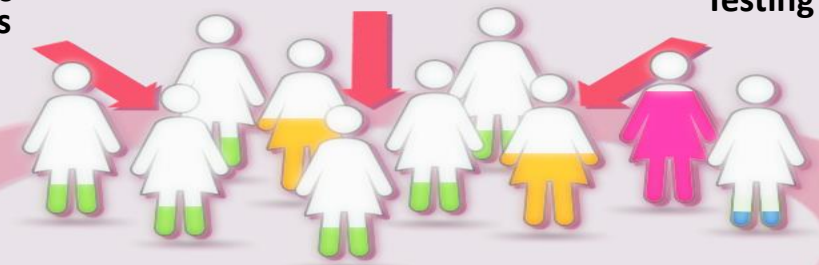

RISK-BASED SREENING APPROACH

Screening Behaviors & Outcomes

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Costing Data

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ACTIVITY 4

REAL WORLD COSTS FROM POPULATION-LEVEL DATABASES

EVIDENCE-BASED ACTIONABLE AND COST-EFFECTIVE STRATEGIES FOR IMPLEMENTION

PROVIDE REAL-LIFE EVIDENCE

ACTIONABLE FRAMEWORK TO SUPPORT THE TRANSITION FROM AGE-BASED TO RISK-BASED SCREENING

Using OncoSim-BC and BOADICEA to estimate the impact of population-wide application of BOADICEA
Individual and population-level cost-effectiveness analysis versus current age-based screening guidelines

International Collaborative Efforts

MyPeBS compares personalised risk-based screening to standard screening.

- A multi-centre, international, randomised clinical study that will recruit **85,000 women from Belgium, France, Israel, Italy and the United Kingdom**.
- Involves 26 partners from 7 different countries.
- Will investigate whether the personalised approach is at least equally or maybe more acceptable than the age based one.

Women Informed to Screen Depending on Measures of Risk (WISDOM)

- Recruiting **100,000 women** from throughout **California, Minnesota, Iowa, North Dakota, South Dakota.**
- Will evaluate if personalized screening is as safe as annual screening, if it causes fewer harms such as unnecessary follow-up screenings, biopsies or other procedures, and whether women accept the approach.

Summary

- Risk prediction tools are already used to inform screening (e.g., High Risk OBSP)
- CanRisk (the web tool that uses BOADICEA to estimate risk) is being used in High Risk Clinics in Ontario (since ~spring 2021)
- Application of PRS to inform breast cancer screening is being investigated
- International efforts to understand the benefits, costs and approach to implementation are on-going

PERSONALIZED RISK ASSESSMENT FOR PREVENTION AND EARLY DETECTION OF BREAST CANCER:

INTEGRATION & IMPLEMENTATION

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