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

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CHU de Québec – Université Laval Research Center
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Future of Individualized Medicine XII
Scripps Seaside Forum, La Jolla, CA
March 14-15, 2019

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Santé et Services sociaux Québec · Quebec Breast Cancer Foundation · Canadian Partnership Against Cancer / Partenariat canadien contre le cancer · Canadian Cancer Society · Ontario Cancer Care Ontario Action Cancer Ontario

BREAST CANCER BURDEN IN CANADA

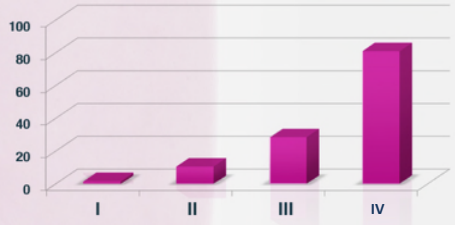
1/8 WOMEN WILL DEVELOP
BREAST CANCER
DURING HER LIFE

1/6 CASES
OCCUR IN WOMEN < 50 YEARS OLD

26 300
NEW CASES EACH YEAR

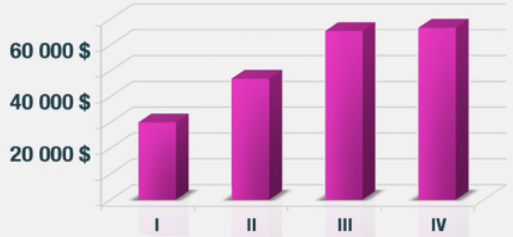
5 000
DEATHS ARE ATTRIBUTED TO
THIS CANCER EACH YEAR

RELATIVE MORTALITY RATIO (5 YRS)



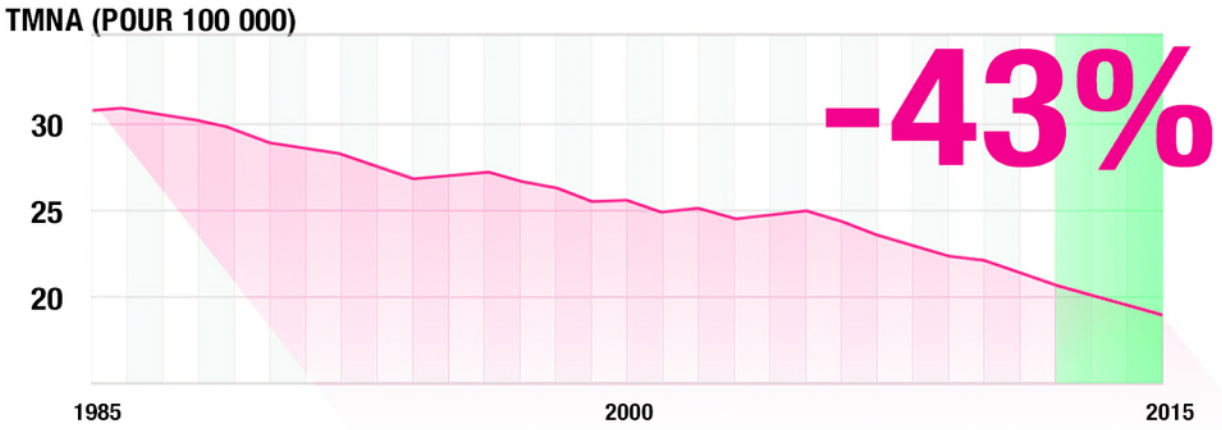
CANCER STAGES

MEAN COST OF CARE (2 YRS)



CANCER STAGES

BREAST CANCER MORTALITY RATES NORMALISED ACCORDING TO AGE, WOMEN, CANADA, 1985-2014



DURING THE LAST 25 YEARS, BREAST CANCER MORTALITY RATES HAVE FALLEN BY 43% DUE TO INCREASED MAMMOGRAPHY SCREENING AND MORE EFFECTIVE THERAPIES

REDUCING BREAST CANCER MORTALITY

Pan-Canadian Study of Mammography Screening and Mortality from Breast Cancer

Andrew Coldman, Norm Phillips, Christine Wilson, Kathleen Decker, Anna M. Chiarelli, Jacques Brisson, Bin Zhang, Jennifer Payne, Gregory Doyle, Rukshanda Ahmad

Coldman A et al. (2014) JNCI 106(11)

DATA WERE OBTAINED ON

2 796 472

SCREENING PARTICIPANTS FROM 1990-2009

THE AVERAGE BREAST CANCER MORTALITY AMONG PARTICIPANTS WAS

40%

LOWER THAN EXPECTED WITH A RANGE ACROSS PROVINCES OF 27% TO 59%

PARTICIPATION IN MAMMOGRAPHY SCREENING PROGRAMS IN CANADA WAS ASSOCIATED WITH SUBSTANTIALLY REDUCED BREAST CANCER MORTALITY.

POLYGENIC SUSCEPTIBILITY TO BREAST CANCER

Polygenic susceptibility to breast cancer and implications for prevention

Nature Genetics 2002 31:33-36

Polygenes, Risk Prediction, and Targeted Prevention of Breast Cancer

New England Journal of Medicine 2008 358:2796-2803

Polygenic susceptibility to prostate and breast cancer: implications for personalised screening

British Journal of Cancer 2011 104:1656-1663

nature genetics

Large-scale genotyping identifies 41 new loci associated with breast cancer risk

Nature Genetics 2013 45:353-61

Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer

Nature Genetics 2015 47:373-80

ARTICLE

Prediction of Breast Cancer Risk Based on Profiling With Common Genetic Variants

J Natl Cancer Inst. 2015 107(5)

LETTER

doi:10.1038/nature24284

Association analysis identifies 65 new breast cancer risk loci

Nature 2017 551:92-94

nature genetics

Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer

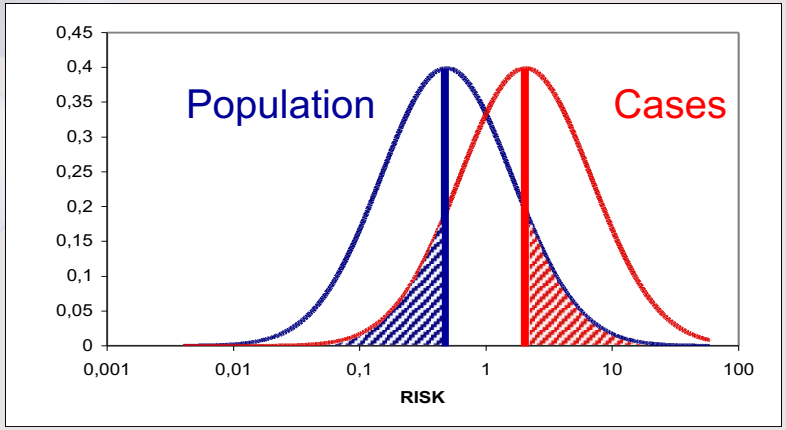
Nature Genetics 2017 49:1767-1778

ARTICLE

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

Am J Hum Genet 2019 104:21-34

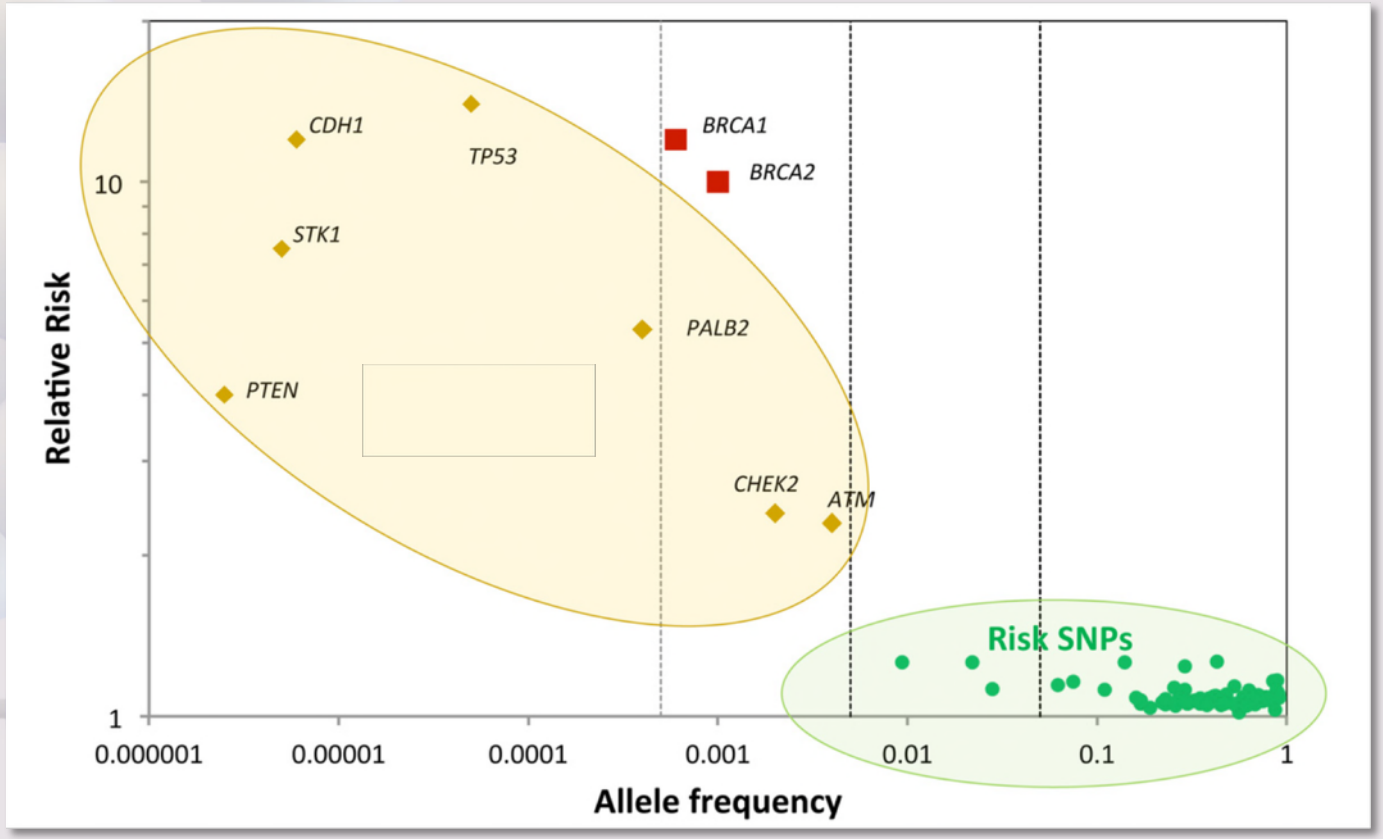
POLYGENIC MODEL OF BREAST CANCER RISK



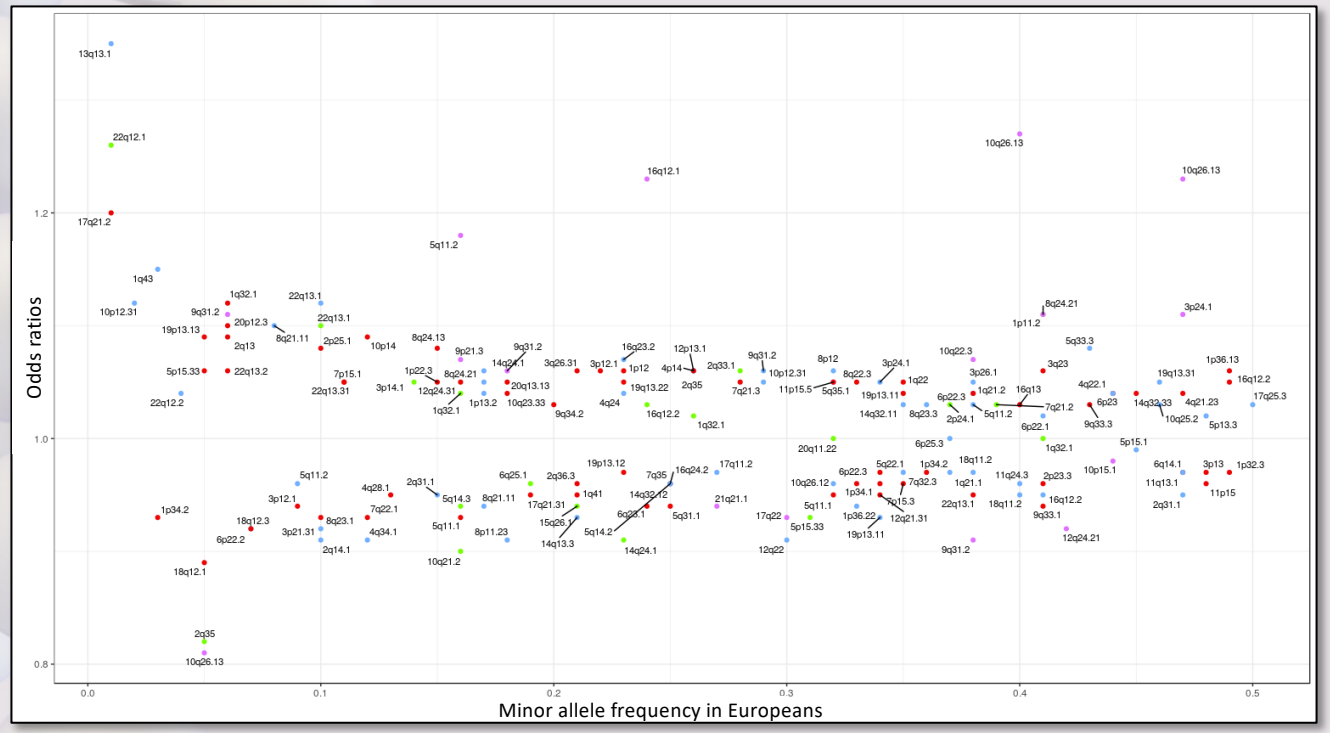
- Although only 12% of the population has a 10% chance or more of developing breast cancer before the age of 70, approximately 50% of all breast cancers are diagnosed in this sub-population.
- On the other hand, 50% of the population has a risk equal to or less than 3% and this subset represents only 12% of all cancers.
- The risk of breast cancer is determined by a combination of genetic and non-genetic factors, such that the majority cases will be diagnosed in the minority of women who are at a relatively high risk.

Pharoah, P.D. et al Nature Genetics 31: 33-56, 2002

GENETIC LOCI IDENTIFIED FOR BREAST CANCER BY RISK ALLELE FREQUENCY AND RISK CONFERRED



ALLELIC ARCHITECTURE OF SNPS ASSOCIATED WITH BREAST CANCER



PERSPECTIVE PROJECT (2013-2018)

(Personalized Risk Stratification for Prevention and Early Detection of Breast Cancer)

THIS PROJECT IS DESIGNED TO INCREASE EARLY DETECTION OF BREAST CANCER BY EXTENDING CURRENT MAMMOGRAPHY SCREENING PROGRAMS IN AN **OPTIMALLY COST-BENEFICIAL** AND TARGETED MANNER ESPECIALLY FOR **YOUNGER WOMEN (35 TO 49)** AT HIGHER RISK.

THIS WILL BE ACHIEVED THROUGH THE **DETERMINATION OF A GENETIC RISK PROFILE** WHICH WILL BE INCORPORATED INTO THE RISK PREDICTION MODEL (BOADICEA) IN ORDER TO **INCREASE THE PROPORTION OF WOMEN IDENTIFIABLE IN THE HIGH-RISK CATEGORY**.

GenomeCanada

QUEBEC BREAST CANCER FOUNDATION

IRSC CIHR
Instituts de recherche en santé du Canada
Canadian Institutes of Health Research

NATIONAL CANCER INSTITUTE

GenomeQuébec

PERSONALISED RISK STRATIFICATION FOR PREVENTION AND EARLY DETECTION OF BREAST CANCER

GenomeCanada

2013-2017

GenomeQuébec

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Ottawa, Canada

NATIONAL CANCER INSTITUTE

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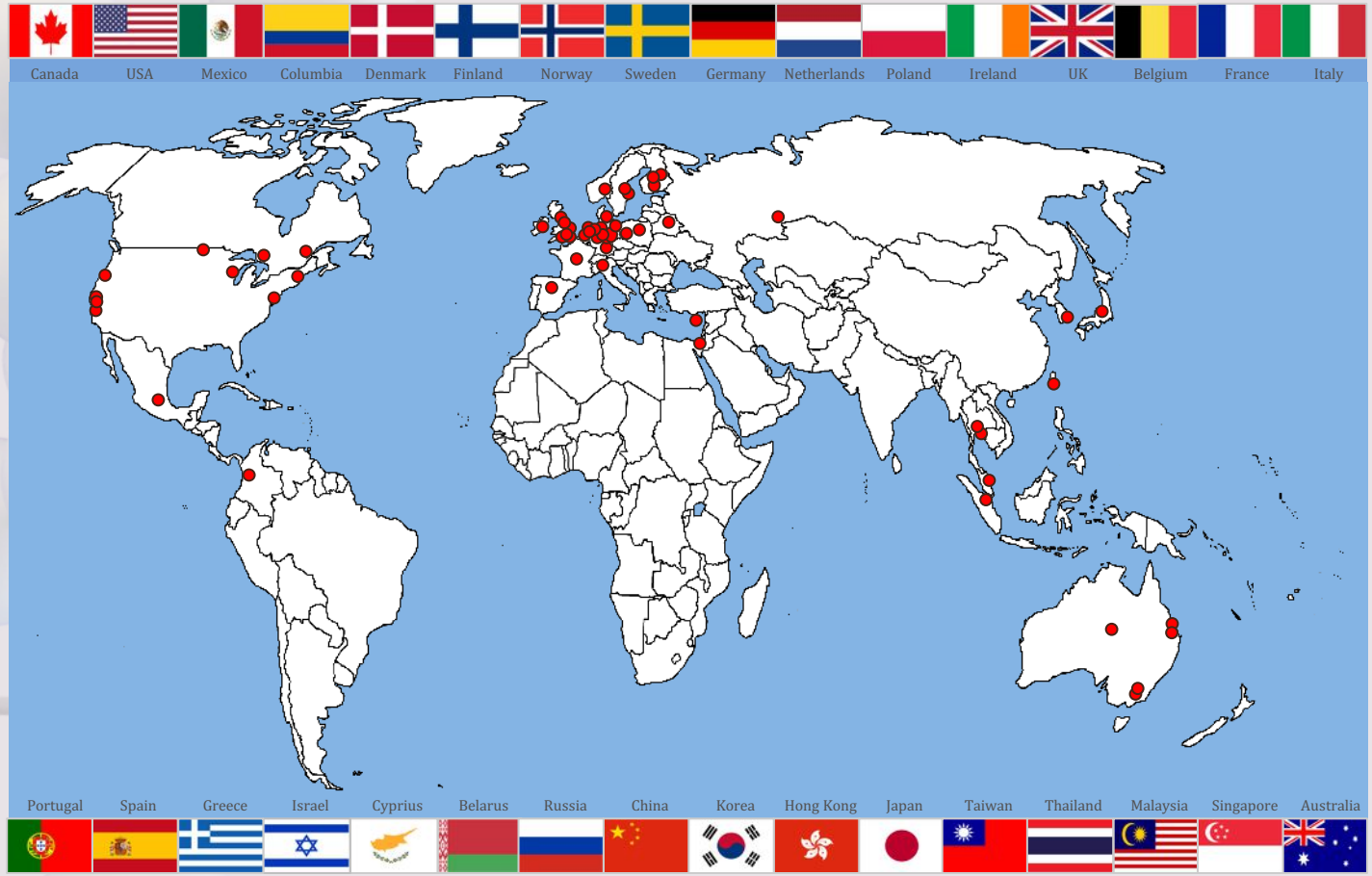
QUEBEC BREAST CANCER FOUNDATION

FONDATION CHU de Québec

CHU de Québec

BREAST CANCER ASSOCIATION CONSORTIUM
> 105 STUDIES - ~393,000 SAMPLES - 36 COUNTRIES



GENETIC RISK PROFILE

HUNDREDS OF RESEARCH TEAMS FROM

50

COUNTRIES

“ONCOARRAY”

INTEGRATION OF

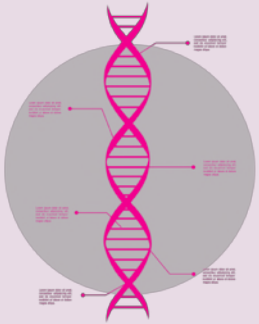
DATA

MEDICAL HISTORY
TUMOR PATHOLOGY
TREATMENT RESPONSE
ENVIRONMENT
FAMILY HISTORY

600 000

PARTICIPANTS

BREAST
PROSTATE
LUNG
OVARY
COLORECTAL

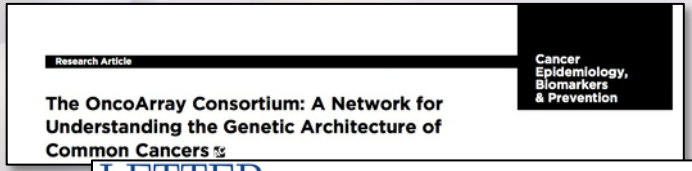


ANALYSIS OF

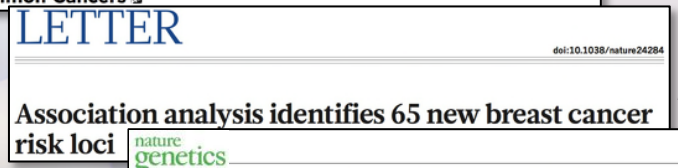
GENOMIC

DATA

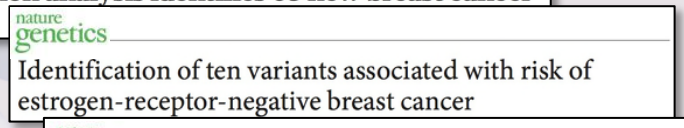
ONCOARRAY NETWORK



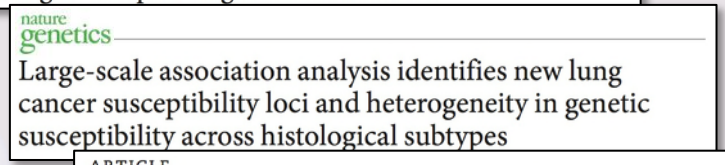
Cancer Epidemiol Biomarkers Prev. 2017 26(1):126-135



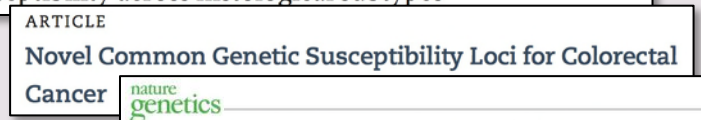
Nature 2017 551:92-94



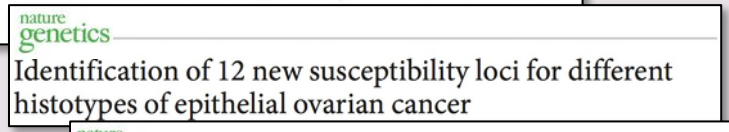
Nature Genetics 2017 49:1767-1778



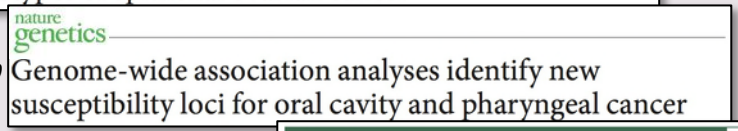
Nature Genetics 2017 49(7):1126-1132



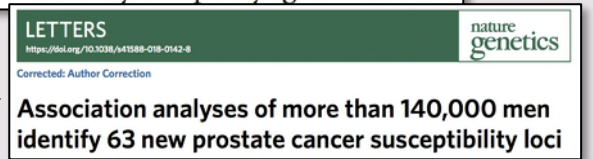
JNCI 2019 111(2):146-157



Nat Genet. 2017 49(5):680-691



Nat Genet. 2016 48(12):1544-1550



Nat Genet. 2018 50(7):928-936

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-018-08054-4 OPEN

Shared heritability and functional enrichment across six solid cancers

Xia Jiang et al.#

Nat Commun. 2019 10(1):431

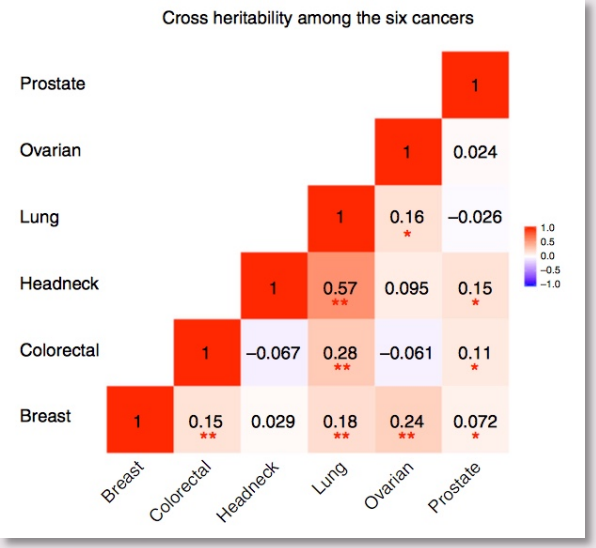
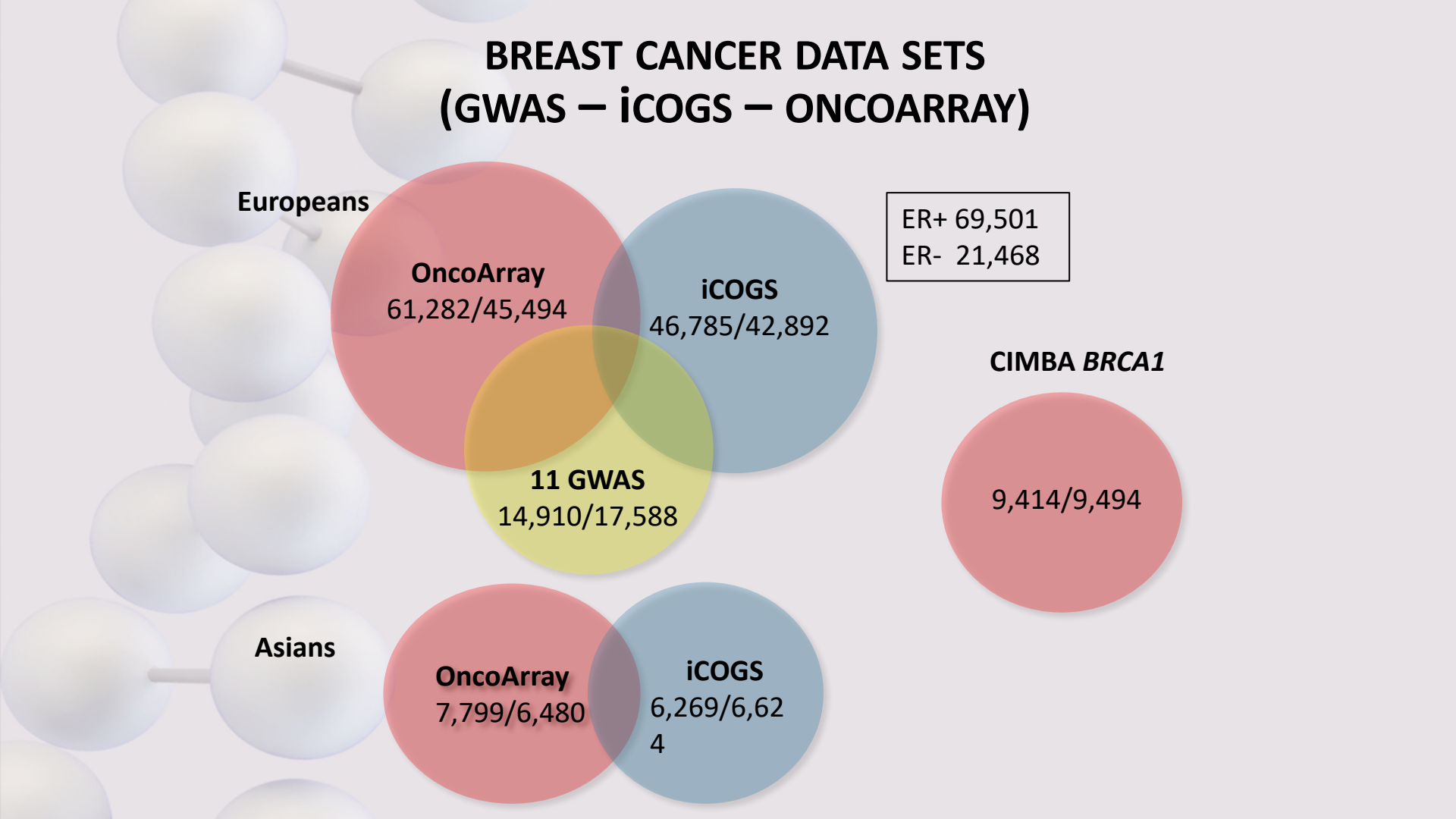


Table 1 Significant enrichment estimates of genomic functional categories, meta-analyzed across six cancer sites

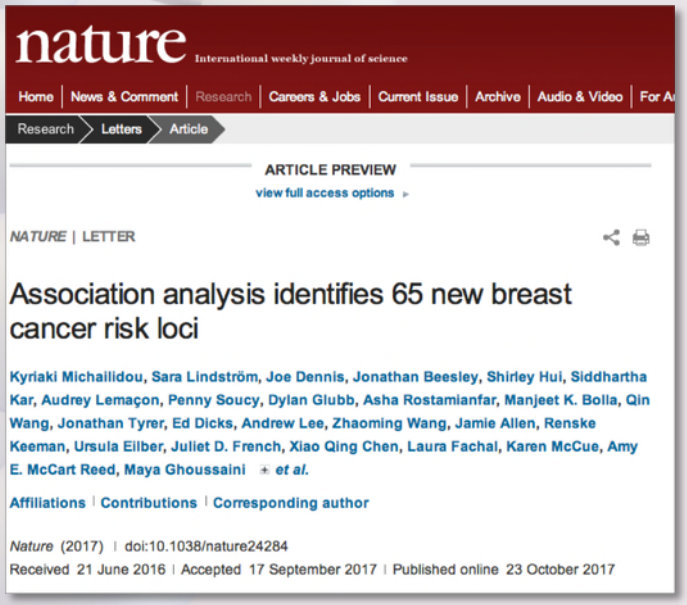
Category	Enrichment (95% CI)	*P*-value
Conserved region	9.78 (5.72–13.84)	2.28×10^{-5}
TFBS	4.04 (2.91–5.17)	1.43×10^{-7}
H3K9ac	3.41 (2.14–4.69)	2.04×10^{-4}
H3K4me3	3.23 (2.47–4.00)	8.91×10^{-9}
Super Enhancer	2.56 (2.23–2.89)	1.99×10^{-20}
H3K27ac (PGC)	2.36 (1.91–2.80)	2.12×10^{-9}
H3K27ac (Hnisz)	1.90 (1.65–2.15)	1.86×10^{-12}
H3K4me1	1.84 (1.56–2.12)	2.57×10^{-9}
Repressed region	0.34 (0.07–0.61)	1.15×10^{-6}

The meta-analysis was performed based on the enrichment estimates and standard errors calculated using LD score regression in each individual cancer type. *P*-values were significant after Bonferroni correction ($P < 0.05/24$)
TFBS transcription factor binding sites

BREAST CANCER DATA SETS
(GWAS – iCOGS – ONCOARRAY)



ASSOCIATIONS ANALYSES – BREAST CANCER



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NATURE | LETTER

Association analysis identifies 65 new breast cancer risk loci

Kyriaki Michailidou, Sara Lindström, Joe Dennis, Jonathan Beesley, Shirley Hui, Siddhartha Kar, Audrey Lemaçon, Penny Soucy, Dylan Glubb, Asha Rostamianfar, Manjeet K. Bolla, Qin Wang, Jonathan Tyrer, Ed Dicks, Andrew Lee, Zhaoming Wang, Jamie Allen, Renske Keeman, Ursula Eilber, Juliet D. French, Xiao Qing Chen, Laura Fachal, Karen McCue, Amy E. McCart Reed, Maya Ghoussaini ✳ *et al.*

Affiliations | Contributions | Corresponding author

Nature (2017) | doi:10.1038/nature24284

Received 21 June 2016 | Accepted 17 September 2017 | Published online 23 October 2017

nature genetics

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NATURE GENETICS | LETTER

Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer

Roger L Milne, Karoline B Kuchenbaecker, Kyriaki Michailidou, Jonathan Beesley, Siddhartha Kar, Sara Lindström, Shirley Hui, Audrey Lemaçon, Penny Soucy, Joe Dennis, Xia Jiang, Asha Rostamianfar, Hilary Finucane, Manjeet K Bolla, Lesley McGuffog, Qin Wang, Cora M Aalfs, ABCTB Investigators, Marcia Adams, Julian Adlard, Simona Agata, Shahana Ahmed, Habibul Ahsan, Kristiina Aittomäki, Fares Al-Ejeh ✳ *et al.*

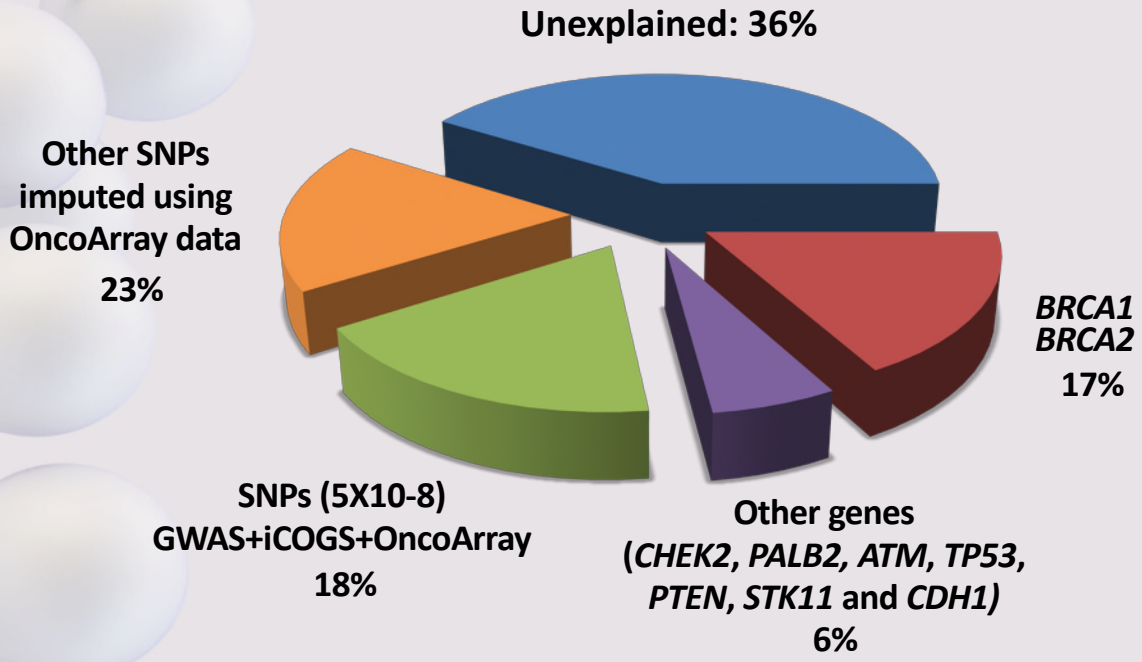
Affiliations | Contributions | Corresponding author

Nature Genetics (2017) | doi:10.1038/ng.3785

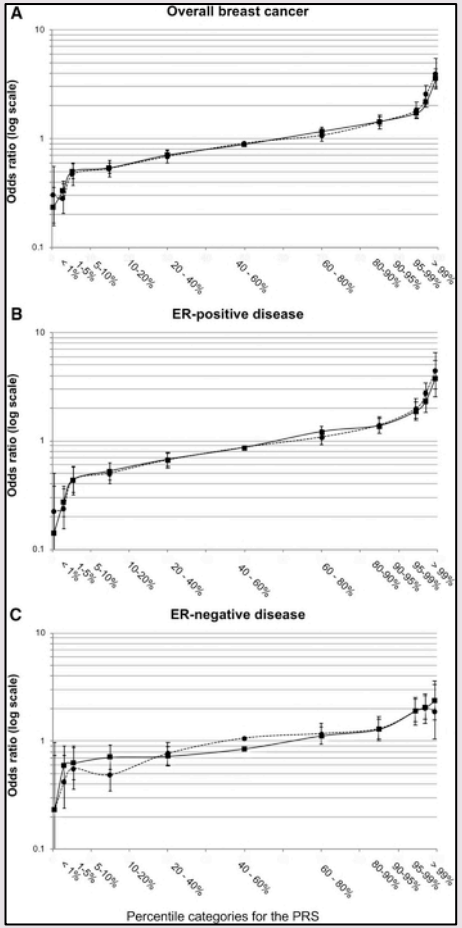
Received 30 May 2016 | Accepted 11 January 2017 | Published online 23 October 2017

- Identification of **75** new breast cancer risk loci, including **9** associated with **estrogen-receptor negative** disease.
- In total, common risk variants now explain **18% of the familial relative risk** (FRR).
- We estimate that variants imputable from the OncoArray explain ~41% of the FRR, and thus, **the new risk SNPs account for ˜44% of the FRR that can be explained by all imputable SNPs**.
- Enrichment analyses of **genomic features** and **pathway analyses** have shed light on the underlying biological processes involved in breast cancer susceptibility.

GENETIC VARIANCE OF BREAST CANCER RISK (AFTER iCOGS AND ONCOARRAY)

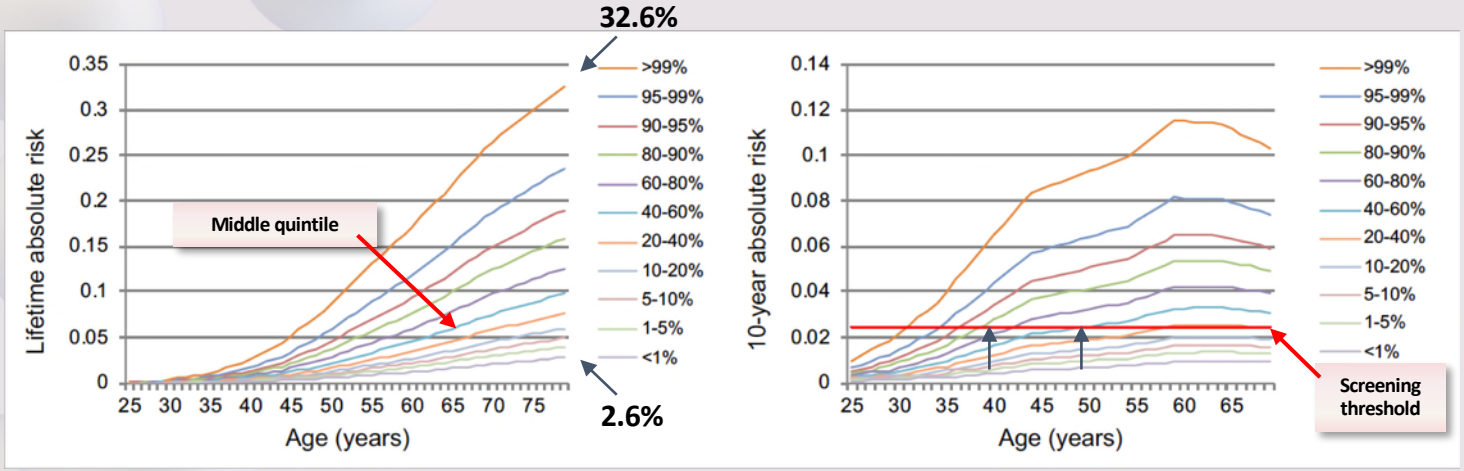


ASSOCIATION BETWEEN THE 313 SNP POLYGENIC RISK SCORE (PRS) AND BREAST CANCER RISK IN WOMEN OF EUROPEAN ORIGIN



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

CUMULATIVE AND 10-YEAR ABSOLUTE RISK OF DEVELOPING BREAST CANCER BY PERCENTILES OF THE POLYGENIC RISK SCORE (PRS) (313 SNPs)

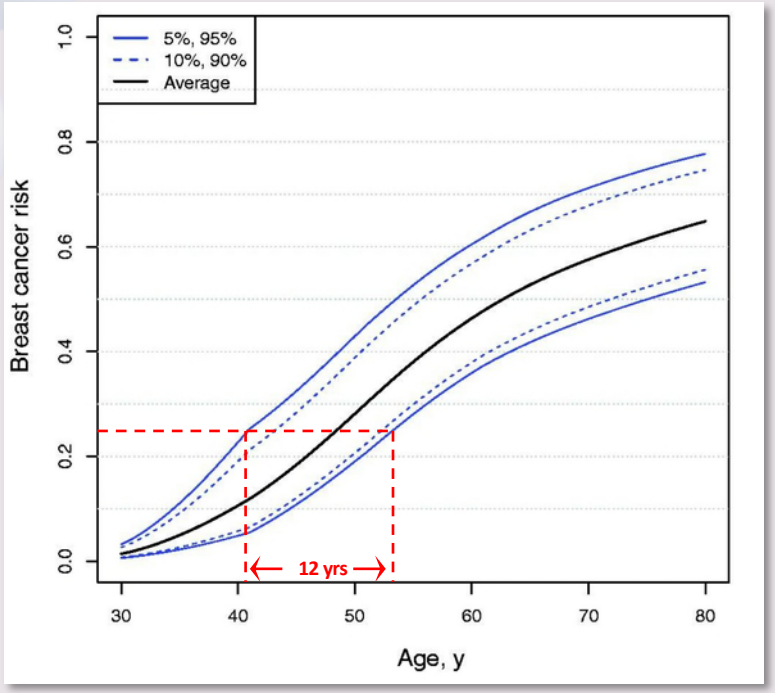


- The average 10-year absolute risk of breast cancer for a 47 year old woman (i.e. the age at which women become eligible to enter the UK breast cancer screening program) in the general population is 2.6%.

- However, the 19% of women with the highest PRS will attain this level of risk by age 40 years.

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

PREDICTED BREAST CANCER RISKS IN BRCA1 MUTATION CARRIERS BY PERCENTILE OF THE POLYGENIC RISK SCORE



The estrogen receptor–negative breast cancer PRS comprised of 53 SNPs was used for *BRCA1* carriers

J Natl Cancer Inst. 2017 Jul 1;109(7). doi: 10.1093/jnci/djw302

ARTICLE Genetics inMedicine

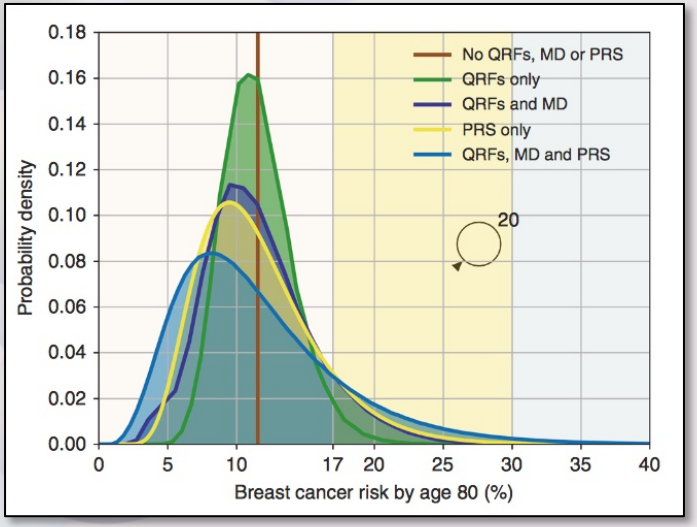
Open

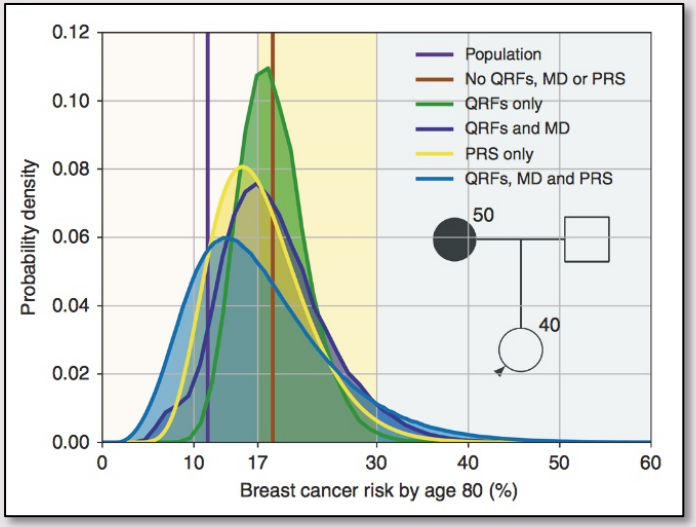
BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors

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]

Genet Med. 2019 Jan 15. doi: 10.1038/s41436-018-0406-9

BOADICEA PREDICTED LIFETIME BREAST CANCER RISK FOR A WOMEN WITH UNKNOWN FAMILY HISTORY OR WITH A MOTHER AFFECTED AT AGE 50





Risk categories

Pink=near population risk ($< 17\%$)

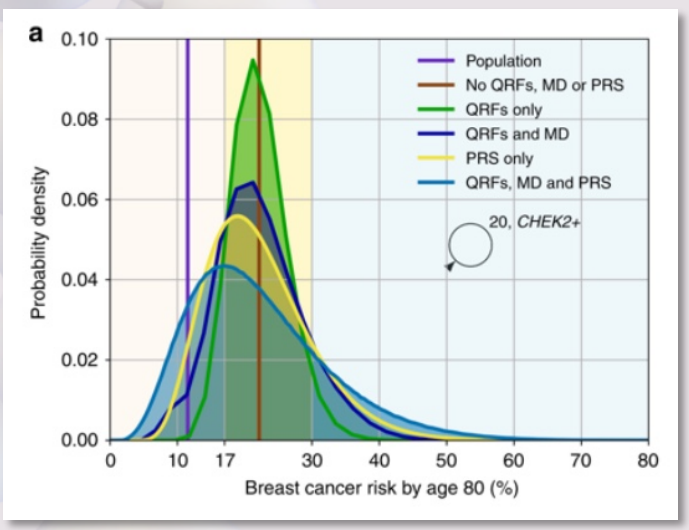
Yellow=moderate risk ($\geq 17\%$ and $< 30\%$)

Blue=high risk ($\geq 30\%$)

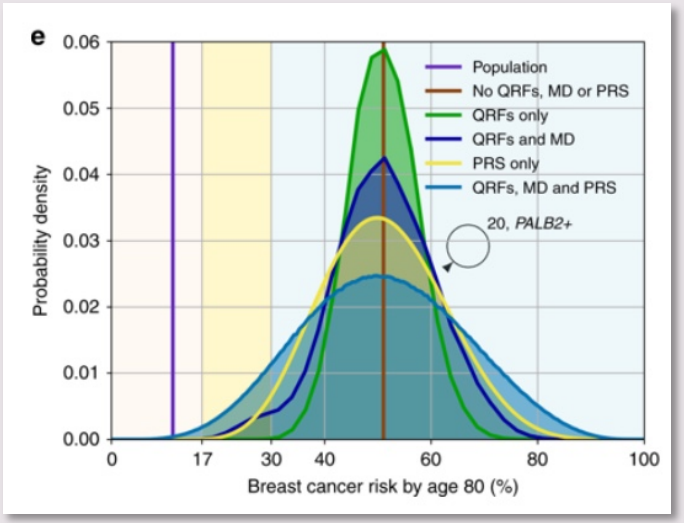
Genet Med. 2019 Jan 15. doi: 10.1038/s41436-018-0406-9

BOADICEA PREDICTED LIFETIME BREAST CANCER RISK FOR A FEMALE INTERMEDIATE-RISK RARE PATHOGENIC VARIANT CARRIER WITH UNKNOWN FAMILY HISTORY

CHEK2



PALB2



Risk categories

Pink=near population risk ($< 17\%$)

Yellow=moderate risk ($\geq 17\%$ and $< 30\%$)

Blue=high risk ($\geq 30\%$)

Genet Med. 2019 Jan 15. doi: 10.1038/s41436-018-0406-9

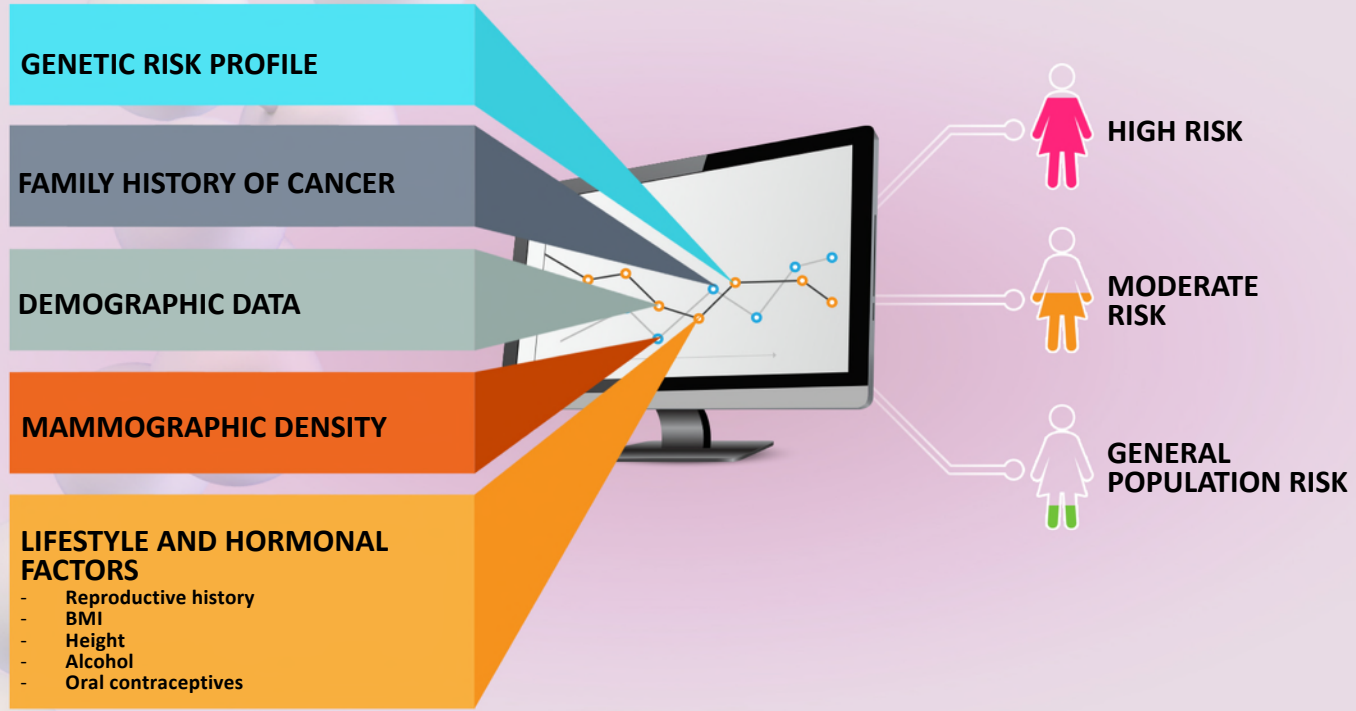
PREDICTED DISTRIBUTIONS OF WOMEN IN THE POPULATION IN DIFFERENT RISK CATEGORIES (based on NICE guidelines)

Family history		Lifetime (20-80)			
		QRF Only	QRF and MD	PRS Only	QRF, MD and PRS
Unknown Family history	Average population risk (%)	11.5			
	% at near population risk	97.0	90.5	89.2	84.2
	% at moderate risk	**3.0**	**9.5**	**10.6**	**14.7**
	% at high risk	**0.0**	**0.0**	**0.2**	**1.1**
Mother affected at age 50	% at near population risk	35.1	42.3	52.3	55.1
	% at moderate risk	**64.4**	**53.6**	**45.6**	**38.0**
	% at high risk	**0.5**	**4.1**	**2.1**	**6.8**

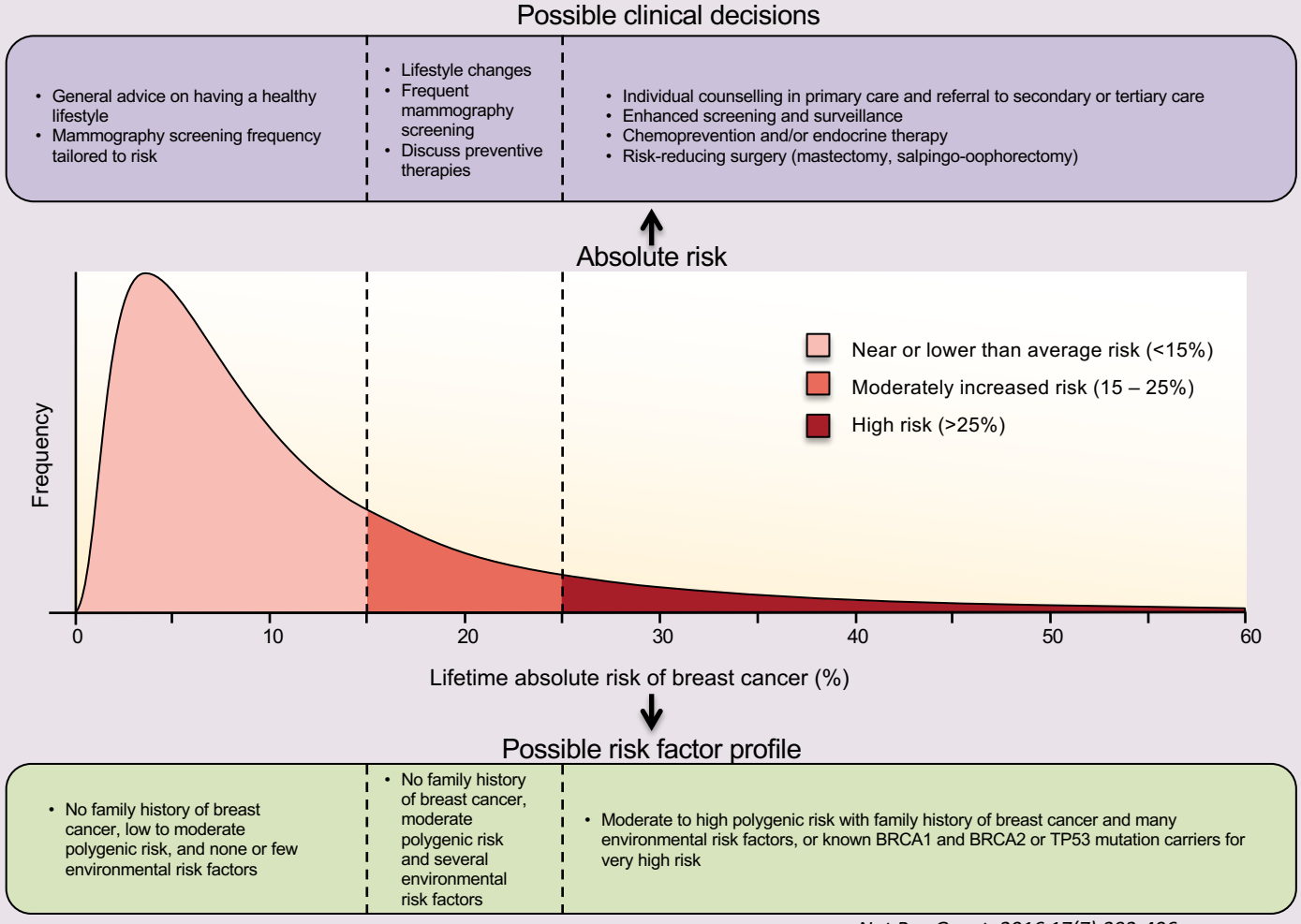
QRF: Questionnaire based Risk Factors; MD: Mammographic Density; PRS: Polygenic Risk Score.

Genet Med. 2019 Jan 15. doi: 10.1038/s41436-018-0406-9

RISK PROFILING

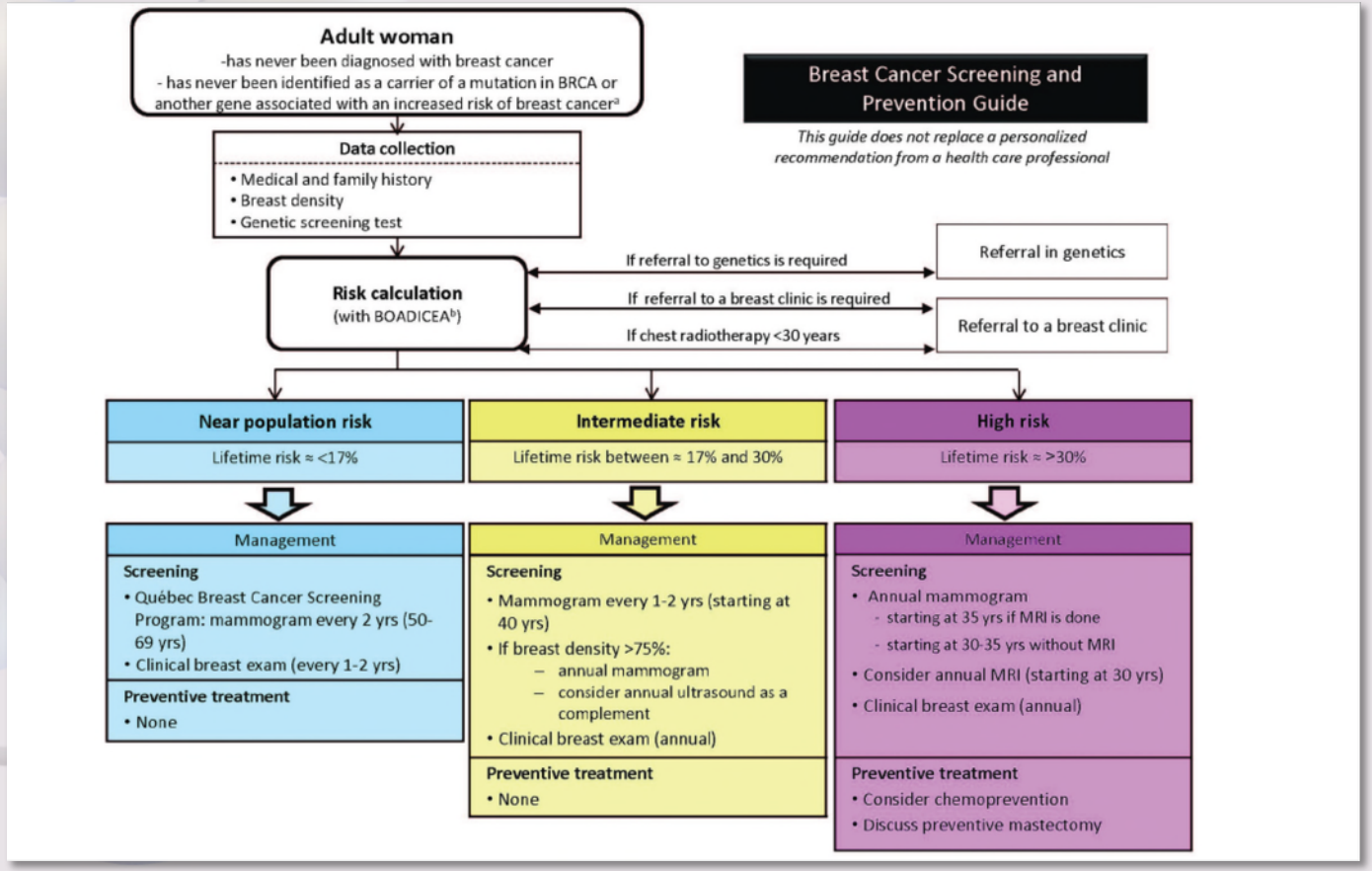


POSSIBLE HYPOTHETICAL DISTRIBUTION OF ABSOLUTE RISK FOR BREAST CANCER DECISIONS



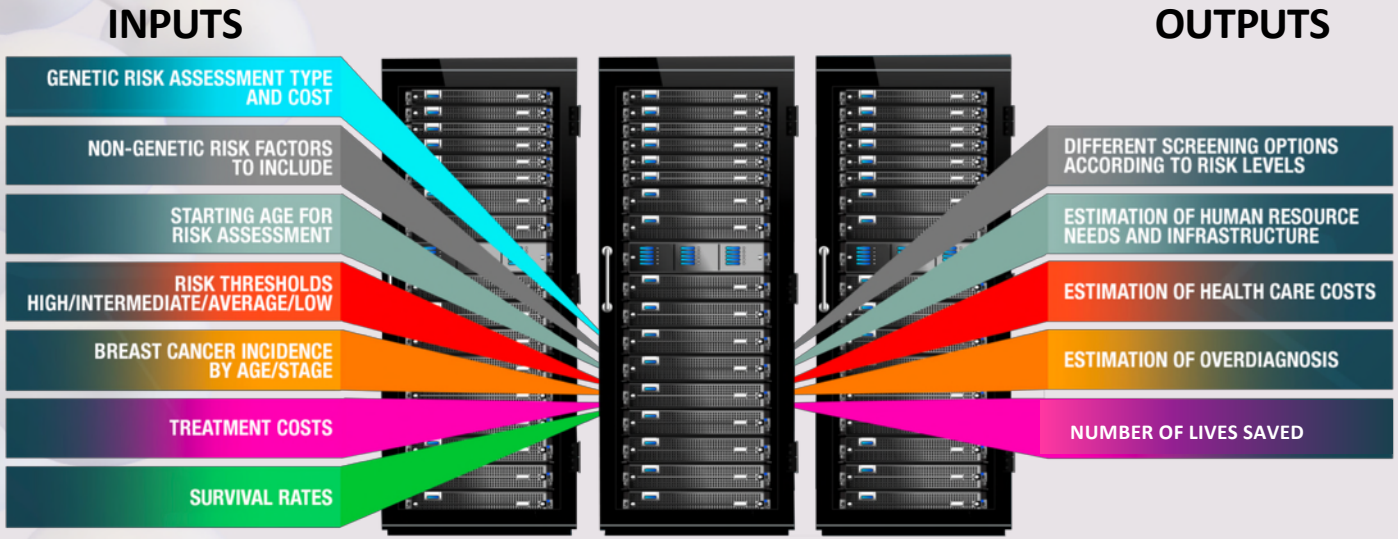
Nat Rev Genet. 2016 17(7):392-406

DECISION AID FOR BREAST CANCER RISK STRATIFICATION



Gagnon J et al. Current Oncology 2016 Dec; 23 (6): e615-e625

SOCIO ECONOMIC SIMULATION MODEL



PROJECTED IMPACT / JUDICIOUS CHOICES

NEXT STEPS
2018-2022

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

Jacques Simard
Project Leader

Anna Maria Chiarelli
Co-Project Leader

GENETIC EPIDEMIOLOGY, BIOSTATISTICS & BIOINFORMATICS

Douglas Easton

Antonis Antoniou

David Goldgar

Peter Kraft

Arnaud Droit

Bingjian Feng

HEALTH ECONOMICS

Nicole Mittmann

Michael Wolfson

ETHICS, LAW & SOCIETY

Bartha M. Knoppers

Yann Joly

MOLECULAR DIAGNOSTICS

Suzanne Kamel-Reid

Tracy Stockley

Peter Devilee

Eric Hahnen

EPIDEMIOLOGY & PUBLIC HEALTH

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Amanda Spurdle

CLINICAL ONCOLOGY, MEDICAL GENETICS & PRIMARY CARE

Jocelyne Chiquette

Laurence Eloy

Andrea Eisen

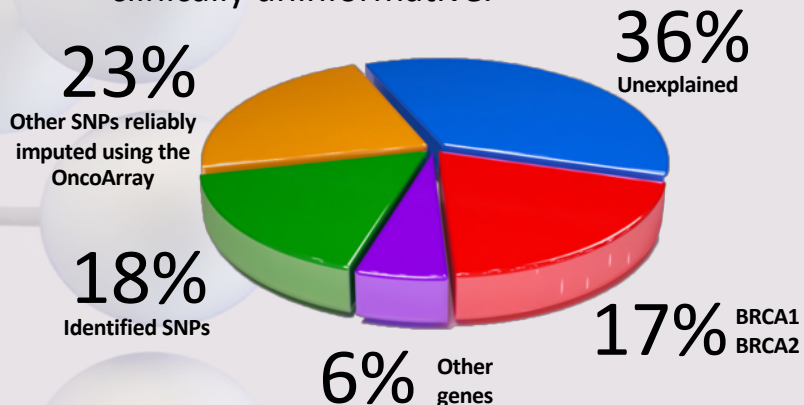
Rita Schmutzler

Gareth Evans

HIGH RISK CANCER GENETIC CLINICS

Many women receive approximate risk estimates based only on their family history.

- Multi-gene panel tests often include genes with unproven association.
- The majority of women with a family history receive negative genetic test result.
- Numerous identified variants are of uncertain significance and therefore clinically uninformative.



POPULATION BREAST CANCER SCREENING PROGRAM

Recommendations assume all women have the same level of risk based on their age.

- Overscreening women at lower risk and underscreening women at high risk.
- Adapt existing healthcare systems for risk-based screening.

  Implementation issues to be addressed:

  - Invitation
  - Risk assessment
  - Linked to care pathway
  - Communication
  - Monitoring and evaluation
  - Costing data
  - Socio-ethical and legal issues

RESEARCH STRATEGY

OUR OVERARCHING GOALS ARE:

- 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.

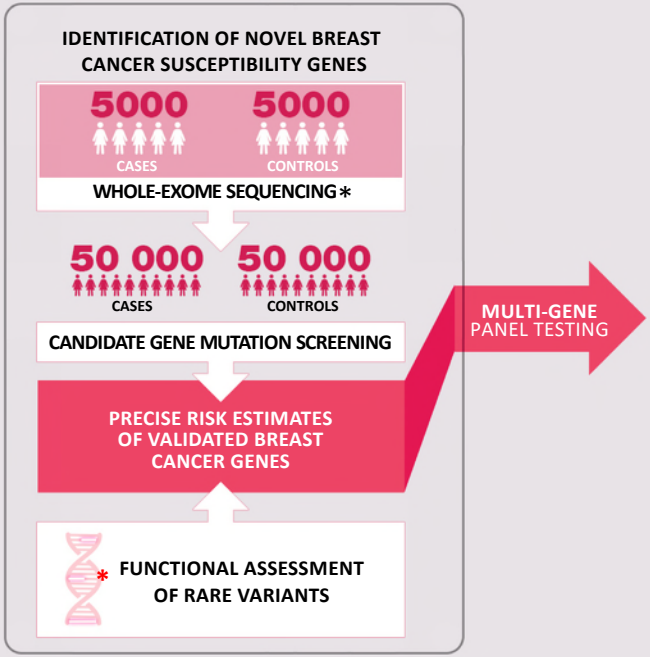
OUR PROJECT WILL PROVIDE:

***Patient-oriented*:** A more accurate risk prediction improving genetic counselling of high risk women about screening and risk reduction strategies.

***Population-oriented*:** Real-life evidence on how to shift from primarily age-based *"one-size fits all"* screening to risk-based approaches to improve the balance of benefits to harms.

HIGH RISK CANCER GENETIC CLINICS

ACTIVITY 1



* This number will double in collaboration with the EU-funded Horizon 2020 BRIDGES project

HIGH RISK CANCER GENETIC CLINICS

ACTIVITY 1

IDENTIFICATION OF NOVEL BREAST CANCER SUSCEPTIBILITY GENES

5000 CASES 5000 CONTROLS

WHOLE-EXOME SEQUENCING*

50 000 CASES 50 000 CONTROLS

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**

*** This number will double in collaboration with the EU-funded Horizon 2020 BRIDGES project**

POPULATION BREAST CANCER SCREENING PROGRAM

RISK STRATIFICATION TOOLS

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

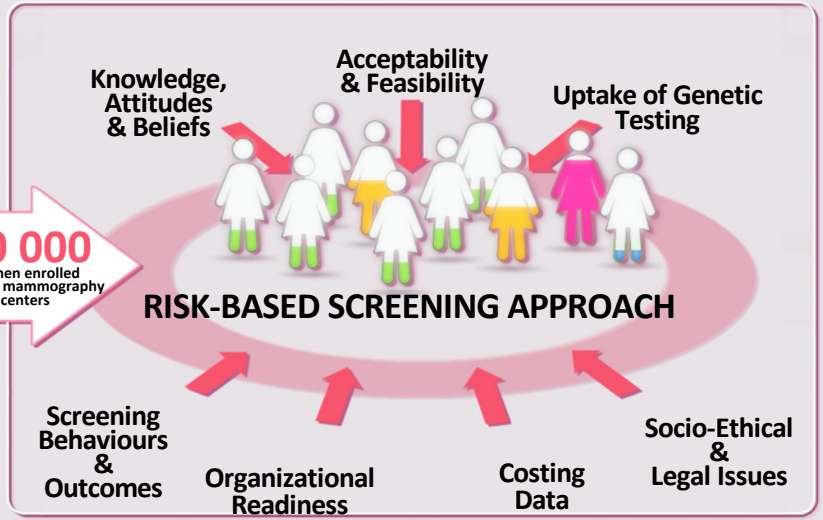
POPULATION BREAST CANCER SCREENING PROGRAM

ACTIVITY 3

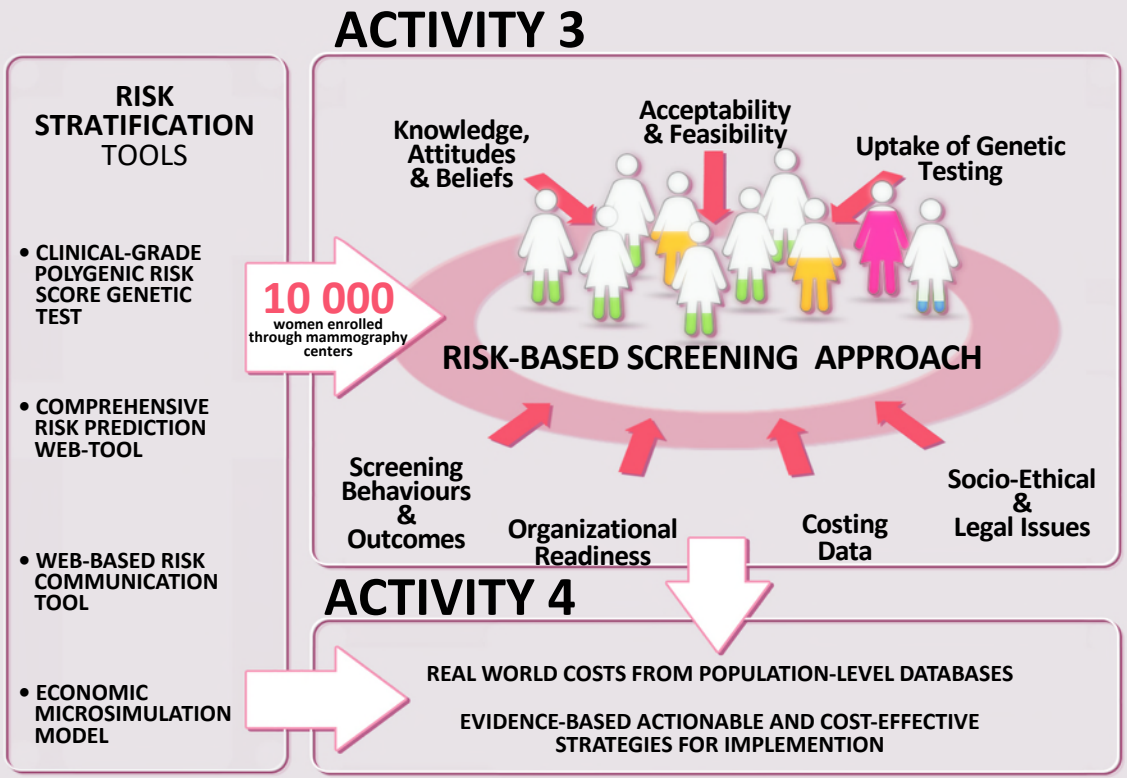
RISK STRATIFICATION TOOLS

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

10 000 women enrolled through mammography centers



POPULATION BREAST CANCER SCREENING PROGRAM



POPULATION BREAST CANCER SCREENING PROGRAM

ACTIVITY 3

RISK STRATIFICATION TOOLS

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

10 000 women enrolled through mammography centers

Knowledge, Attitudes & Beliefs

Acceptability & Feasibility

Uptake of Genetic Testing

RISK-BASED SREENING APPROACH

Screening Behaviours & 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

ORGANIZATIONS INVOLVED IN ACHIEVING THE BENEFITS

Jean Latreille
Direction de la cancérologie

Laurence Eloy
Medical Coordinator - Québec Breast Cancer Screening Program

Jocelyne Chiquette
Lead Physician, Coordination Center for the Québec Region Québec Breast Cancer Screening Program

Linda Rabeneck
Vice-President, Prevention and Cancer Control

Anna Chiarelli
Provincial Scientific Lead, Ontario Breast Screening Program

Nicole Mittmann
Chief Research Officer

Suzanne Kamel-Reid
Co-Chair, Molecular Oncology Advisory Committee

Andrea Eisen
Breast Cancer Lead

INTERNATIONAL COLLABORATIVE EFFORTS

MyPeBS Personalising Breast Screening

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.

Wisdom

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

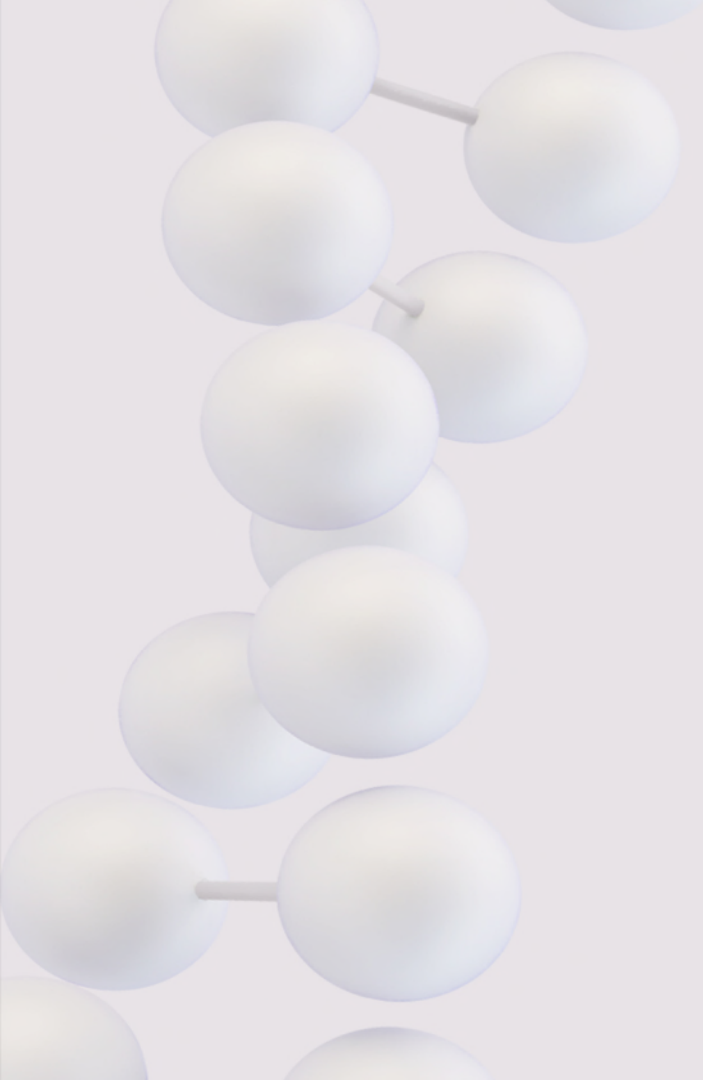
- Recruiting **100,000 women** from throughout **California, Minnesota, Iowa, North Dakota, South Dakota.**
- Will evaluate if personalized screening is as safe as annual screening, if it causes fewer harms such as unnecessary follow-up screenings, biopsies or other procedures, and whether women accept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

TAILORED BREAST SCREENING TO INDIVIDUAL RISK (START/STOP AGE, FREQUENCY, MODALITIES) WILL LEAD TO:

- Identifiable high risk women
- Early detection
- Survival
- Quality of life
- Prevention

- False positive screens
- Overdiagnosis/Overtreatment
- Invasive treatments
- Psychosocial impacts
- Clinical and economic burden

MAXIMIZE THE BENEFITS AND MINIMIZE THE HARMS



IMPLEMENTATION OF A RISK-BASED APPROACH: SOCIO-ETHICAL AND LEGAL ISSUES

Extend the roles of health professionals in managing genomic testing

- Assess feasible extension of the roles of nurses
- Assess the acceptability of extending the role of nurses

Integrate information technologies to provide clinical and informational support

- Assess the capacity of the legal framework to integrate and support telehealth technologies
- Assess the acceptability of providing telehealth counselling

Manage privacy when using BOADICEA with electronic health records

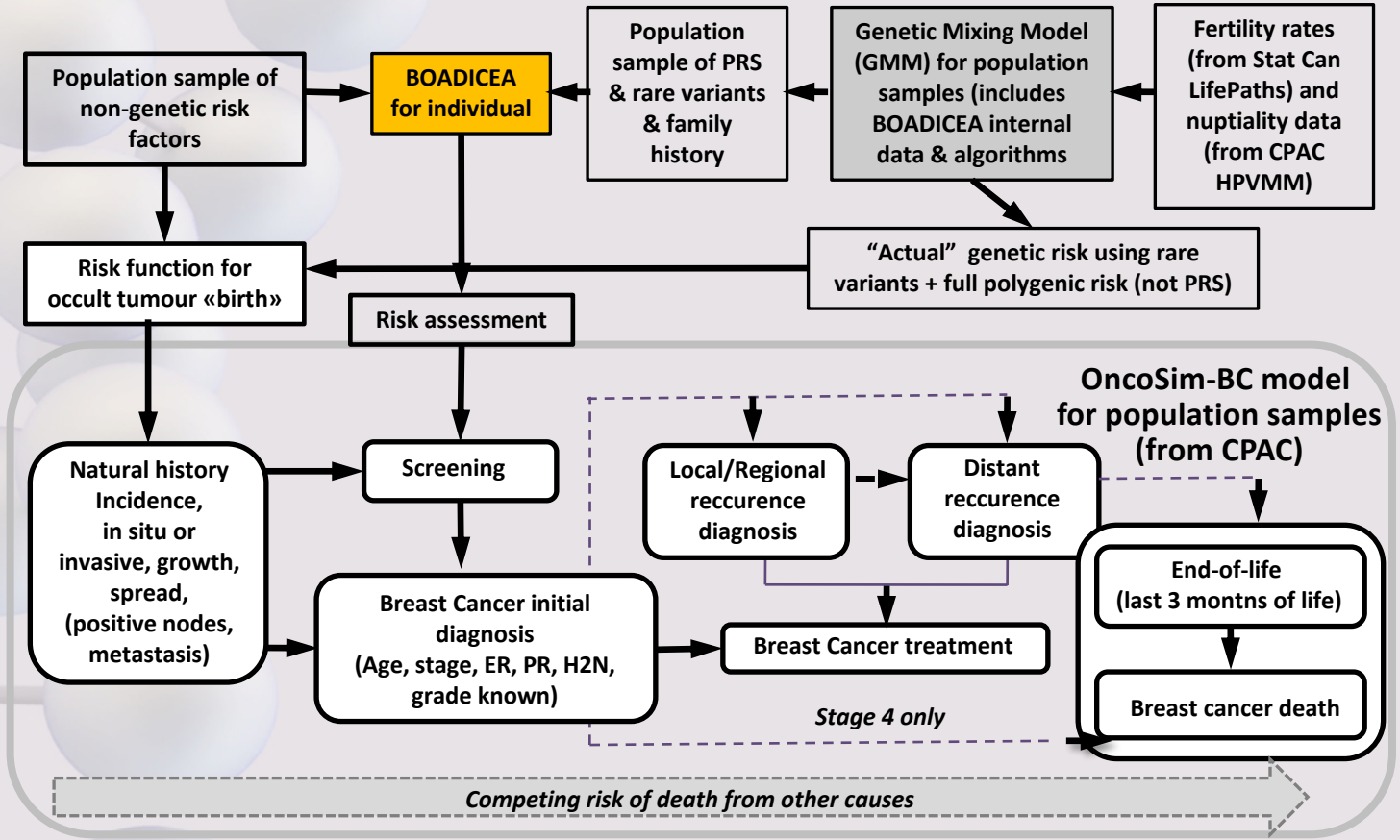
- Legal analysis of privacy management using BOADICEA with electronic health records
- Explore challenges of using BOADICEA with electronic records

Facilitate compliance with federal and provincial regulatory requirements and technology transfer options

- Map out the regulatory approval process applicable to use the BOADICEA software as a medical device in Canada
- Undertake interviews with stakeholders

Inform women on the possible risks of genetic discrimination and existing protections to mitigate them

OVERALL STRUCTURE OF POPRISKS-BC



ECONOMIC ANALYSIS

Revised and updated computer simulation models

- Combine CPAC's OncoSim-BC (Breast Cancer) with newest version of BOADICEA risk stratification algorithm (from Activity 2)
- Using Genetic Mixing Model (GMM) to estimate population joint distribution of family history and measured prevalences of rare genetic variants plus newly published polygenic risk scores (from Activity 1)

Develop real world costs for stratified BC screening

- Intensive use of ICES and CCO data
- Collect data from actual implementation of pilot risk-based screening (from Activity 3)

Assess prospective cost-effectiveness

- Both health system (i.e. direct health care costs) and social (e.g. also including labour market and income tax) perspectives