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

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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):

Mean cost of care (2 yrs):

Cancer stages:

Stage I
Stage II
Stage III
Stage IV
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

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.

Coldman A et al. (2014) JNCI 106(11)
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
  - British Journal of Cancer 2011 104:1656-1663

- Polygenic susceptibility to prostate and breast cancer: implications for personalised screening
  - Nature Genetics 2002 31:33-36

- 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

- Prediction of Breast Cancer Risk Based on Profiling With Common Genetic Variants
  - J Natl Cancer Inst. 2015 107(5)

- Association analysis identifies 65 new breast cancer risk loci
  - Nature 2017 551:92-94

- Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer
  - Nature Genetics 2017 49:1767-1778

- 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.

GENETIC LOCI IDENTIFIED FOR BREAST CANCER BY RISK ALLELE FREQUENCY AND RISK CONFERRED
ALELIC ARCHITECTURE OF SNPS ASSOCIATED WITH BREAST CANCER

Minor allele frequency in Europeans

Odds ratios

Pre-iCOGS
iCOGS
Oncoarray
Other studies
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.
PERSONALISED RISK STRATIFICATION FOR PREVENTION AND EARLY DETECTION OF BREAST CANCER

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

Canada  USA  Mexico  Columbia  Denmark  Finland  Norway  Sweden  Germany  Netherlands  Poland  Ireland  UK  Belgium  France  Italy  Portugal  Spain  Greece  Israel  Cyprus  Belarus  Russia  China  Korea  Hong Kong  Japan  Taiwan  Thailand  Malaysia  Singapore  Australia
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
ARTICLE

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

OPEN

Shared heritability and functional enrichment across six solid cancers

Xia Jiang et al.


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

<table>
<thead>
<tr>
<th>Category</th>
<th>Enrichment (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conserved region</td>
<td>9.78 (5.72–13.84)</td>
<td>2.28 × 10⁻⁵</td>
</tr>
<tr>
<td>TFBS</td>
<td>4.04 (2.91–5.17)</td>
<td>1.43 × 10⁻⁷</td>
</tr>
<tr>
<td>H3K9ac</td>
<td>3.41 (2.14–4.69)</td>
<td>2.04 × 10⁻⁴</td>
</tr>
<tr>
<td>H3K4me3</td>
<td>3.23 (2.47–4.00)</td>
<td>8.91 × 10⁻⁹</td>
</tr>
<tr>
<td>Super Enhancer</td>
<td>2.56 (2.23–2.89)</td>
<td>1.99 × 10⁻¹⁰</td>
</tr>
<tr>
<td>H3K27ac (PGC)</td>
<td>2.36 (1.91–2.80)</td>
<td>2.12 × 10⁻⁹</td>
</tr>
<tr>
<td>H3K27ac (Hniz2)</td>
<td>1.90 (1.65–2.15)</td>
<td>1.86 × 10⁻¹⁲</td>
</tr>
<tr>
<td>H3K4me1</td>
<td>1.84 (1.56–2.12)</td>
<td>2.57 × 10⁻⁹</td>
</tr>
<tr>
<td>Repressed region</td>
<td>0.34 (0.07–0.61)</td>
<td>1.15 × 10⁻⁶</td>
</tr>
</tbody>
</table>

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)

OncoArray:
- Europeans: 61,282/45,494
- Asians: 7,799/6,480

iCOGS:
- Europeans: 46,785/42,892
- Asians: 6,269/6,624

11 GWAS:
- Europeans: 14,910/17,588

CIMBA BRCA1:
- Europeans: 9,414/9,494

ER+ 69,501
ER- 21,468
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.
Unexplained: 36%

BRCA1: 17%

BRCA2: 6%

Other genes (CHEK2, PALB2, ATM, TP53, PTEN, STK11 and CDH1): 18%

SNPs (5x10^-8) GWAS+iCOGS+OncoArray: 23%

Other SNPs imputed using OncoArray data: 17%
ASSOCIATION BETWEEN THE 313 SNP POLYGENIC RISK SCORE (PRS) AND BREAST CANCER RISK IN WOMEN OF EUROPEAN ORIGIN

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.
The estrogen receptor–negative breast cancer PRS comprised of 53 SNPs was used for BRCA1 carriers
BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors

Andrew Lee, MSci, CASM1, Nasim Mavaddat, MBBS, PhD1, Amber N. Wilcox, MPH2, Alex P. Cunningham, MSc, PhD1, Tim Carver, PhD1, Simon Hartley, MSc, PhD1, Chantal Babb de Villiers, PhD1, Angel Izquierdo, MD5, Jacques Simard, PhD5, Marjanka K. Schmidt, PhD6, Fiona M. Walter, MD, FRCGP5, Nilanjana Chatterjee, PhD7,8, Montserrat Garcia-Closas, MPH, DrPH7, Marc Tischkowitz, MD, PhD9, Paul Pharoah, PhD7,10, Douglas F. Easton, PhD7,10 and Antonis C. Antoniou, PhD7

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 (≥ 17% and < 30%)
Blue=high risk (≥ 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

Risk categories
Pink=near population risk (< 17%)
Yellow=moderate risk (≥ 17% and < 30%)
Blue=high risk (≥ 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)

<table>
<thead>
<tr>
<th>Family history</th>
<th>Lifetime (20-80)</th>
<th>QRF Only</th>
<th>QRF and MD</th>
<th>PRS Only</th>
<th>QRF, MD and PRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown Family history</td>
<td>Average population risk (%)</td>
<td>11.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% at near population risk</td>
<td>97.0</td>
<td>90.5</td>
<td>89.2</td>
<td>84.2</td>
</tr>
<tr>
<td></td>
<td>% at moderate risk</td>
<td>3.0</td>
<td>9.5</td>
<td>10.6</td>
<td>14.2</td>
</tr>
<tr>
<td></td>
<td>% at high risk</td>
<td>0.0</td>
<td>0.0</td>
<td>0.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Mother affected at age 50</td>
<td>% at near population risk</td>
<td>35.1</td>
<td>42.3</td>
<td>52.3</td>
<td>55.1</td>
</tr>
<tr>
<td></td>
<td>% at moderate risk</td>
<td>64.4</td>
<td>53.6</td>
<td>45.6</td>
<td>38.0</td>
</tr>
<tr>
<td></td>
<td>% at high risk</td>
<td>0.5</td>
<td>4.1</td>
<td>2.1</td>
<td>6.8</td>
</tr>
</tbody>
</table>

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

- Genetic risk profile
- Family history of cancer
- Demographic data
- Mammographic density
- Lifestyle and hormonal factors
  - Reproductive history
  - BMI
  - Height
  - Alcohol
  - Oral contraceptives
Possible clinical decisions

- General advice on having a healthy lifestyle
- Mammography screening frequency tailored to risk
- Lifestyle changes
- Frequent mammography screening
- Discuss preventive therapies
- Individual counselling in primary care and referral to secondary or tertiary care
- Enhanced screening and surveillance
- Chemoprevention and/or endocrine therapy
- Risk-reducing surgery (mastectomy, salpingo-oophorectomy)

Possible risk factor profile

- No family history of breast cancer, low to moderate polygenic risk, and none or few environmental risk factors
- No family history of breast cancer, moderate polygenic risk and several environmental risk factors
- Moderate to high polygenic risk with family history of breast cancer and many environmental risk factors, or known BRCA1 and BRCA2 or TP53 mutation carriers for very high risk
DECISION AID FOR BREAST CANCER RISK STRATIFICATION

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

INPUTS
- Genetic risk assessment type and cost
- Non-genetic risk factors to include
- Starting age for risk assessment
- Risk thresholds: high/intermediate/average/low
- Breast cancer incidence by age/stage
- Treatment costs
- Survival rates

OUTPUTS
- Different screening options according to risk levels
- Estimation of human resource needs and infrastructure
- Estimation of healthcare costs
- Estimation of overdiagnosis
- Number of lives saved

PROJECTED IMPACT / JUDICIOUS CHOICES
NEXT STEPS
2018-2022
PERSONALIZED RISK ASSESSMENT FOR PREVENTION AND EARLY DETECTION OF BREAST CANCER: INTEGRATION & IMPLEMENTATION

GENETIC EPIDEMIOLOGY, BIOSTATISTICS & BIOINFORMATICS
- Jacques Simard
- Anna Maria Chiarelli
- Douglas Easton
- Antonis Antoniou
- David Goldgar
- Peter Kraft
- Arnaud Droit
- Bingjian Feng

HEALTH ECONOMICS
- Nicole Mittmann
- Michael Wolfson

EPIDEMIOLOGY & PUBLIC HEALTH
- Michel Dorval
- Meghan Walker
- Jennifer Brooks
- Nora Pashayan
- Mireille Broeders
- Monte García-Closas
- Hermann Nabi

ETHICS, LAW & SOCIETY
- Bartha M. Knoppers
- Yann Joly

CLINICAL ONCOLOGY, MEDICAL GENETICS & PRIMARY CARE
- Jocelyne Chiquette
- Laurence Eloy
- Andrea Eisen
- Rita Schmutzler
- Gareth Evans

MOLECULAR DIAGNOSTICS
- Suzanne Kamel-Reid
- Tracy Stockley
- Peter Devisée
- Eric Hahnen

GENOMICS, MOLECULAR GENETICS & BIOLOGY
- Jean-Yves Masson
- Sean Tavtigian
- Irene Andrilis
- Alvaro Monteiro
- Haico van Attikum
- Amanda Spurdle

MOLECULAR DIAGNOSTICS
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.

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.
MULTI-GENE PANEL TESTING

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 1

* This number will double in collaboration with the EU-funded Horizon 2020 BRIDGES project
MULTI-GENE PANEL TESTING
IMPROVED POLYGENIC RISK SCORE
COMMON & RARE VARIANT JOINT EFFECTS
VARIANT PATHOGENICITY
ER-SPECIFIC RISK PREDICTION
NON-EUROPEAN RISK ESTIMATES
NOVEL BC SUSCEPTIBILITY GENES
PERSONALIZED RISK ASSESSMENT
IMPROVE:
• GENETIC COUNSELLING
• SHARED DECISION PROCESS ABOUT SCREENING AND RISK REDUCTION STRATEGIES
• EFFECTIVENESS OF PRIMARY PREVENTION

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

ACTIVITY 2
MORE ACCURATE RISK PREDICTION

* 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

RISK-BASED SCREENING APPROACH

Knowledge, Attitudes & Beliefs
Acceptability & Feasibility
Uptake of Genetic Testing

Screening Behaviours & Outcomes
Organizational Readiness
Costing Data
Socio-Ethical & Legal Issues
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

RISK-BASED SCREENING APPROACH

Knowledge, Attitudes & Beliefs
Acceptability & Feasibility
Uptake of Genetic Testing

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 IMPLEMENTATION
POPULATION BREAST CANCER SCREENING PROGRAM

**ACTIVITY 3**

- **Knowledge, Attitudes & Beliefs**
- **Acceptability & Feasibility**
- **Uptake of Genetic Testing**

RISK-BASED SCREENING APPROACH

- Screening Behaviours & Outcomes
- Organizational Readiness
- Costing Data
- Socio-Ethical & Legal Issues

**ACTIVITY 4**

- **Provide Real-Life Evidence**
- **Actionable Framework to Support the Transition from Age-Based to Risk-Based Screening**

- **10,000 women enrolled through mammography centers**

- **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

- **Real World Costs from Population-Level Databases**
  - Evidence-Based Actionable and Cost-Effective Strategies for Implementation
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.
Identifiable high risk women
Early detection
Survival
Quality of life
Prevention

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

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

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

- Population sample of non-genetic risk factors
- Risk function for occult tumour «birth»
- Natural history
  Incidence, in situ or invasive, growth, spread, (positive nodes, metastasis)
- Screening
- Breast Cancer initial diagnosis
  (Age, stage, ER, PR, H2N, grade known)
- Local/Regional recurrence diagnosis
- Distant recurrence diagnosis
- Breast Cancer treatment
- End-of-life
  (last 3 months of life)
- Breast cancer death
- Competing risk of death from other causes

Population sample of PRS & rare variants & family history
Genetic Mixing Model (GMM) for population samples (includes BOADICEA internal data & algorithms)
“Actual” genetic risk using rare variants + full polygenic risk (not PRS)
Fertility rates (from Stat Can LifePaths) and nuptiality data (from CPAC HPVMM)

OncoSim-BC model for population samples (from CPAC)
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