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Polygenic Risk Score for Breast Cancer: a Clinical Use Case

Allelica, Inc. | info@allelica.com | +1 202 949 2834

Breast Cancer PRS in a clinical pathway

OVERVIEW

This document outlines an approach for using a Polygenic Risk Score (PRS) in a breast cancer clinical pathway. Following a patient request for a breast cancer (BC) risk evaluation from her physician, an initial assessment based on traditional risk factors such as age, family history of breast cancer, and age of menarche is performed. In addition, the physician will prescribe a genetic test, which combines information on presence or absence of known but rare single-gene mutations and risk from common genome-wide variants via PRS. To enable genetic analysis, the physician collects a saliva sample. The sample is sent to a lab, DNA is extracted and sequenced, and the resulting genetic data is analysed in combination with clinical risk information. The physician receives a Patient Report within 2 weeks, which provides information on the patient's PRS, her probability of disease by age 75, and her 10 year risk of breast cancer. On the basis of this analysis, the patient's risk is classified as similar to the general Population, Moderate, or High. The physician communicates results to the patient and prescribes a prevention plan based on results.

ABSOLUTE RISK CLASSIFICATION

The risk classification for breast cancer in this use case is based on a new model which takes into account clinical risk and genetic factors. These are identified through patient consultation and genetic analysis. The integrated absolute risk classification is therefore based on a more complete set of information than classifications that do not use genetic data. Full description found on Page 6.

PRECONDITIONS

- Healthcare provider offers oncology risk assessment services.
- Healthcare provider has an internal or partner laboratory equipped with technology necessary for sample processing: DNA extraction and sequencing.
- Risk classification uses WGS or microarray genotyping data and all analyses are performed in a secure cloud computing environment or on premises.
- The addition of information on a patient's mutation carrier status requires either a previous genetic test or data from WGS or WES and refers to the identification of pathogenic mutations in known BC genes including *BRCA1, BRCA2, PALB2, CHEK2*, and *ATM*.

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MOTIVATING FACTORS

- Trigger 1: Patient is interested in understanding her breast cancer risk, for example because she has family history of disease, already knows she's a carrier, or has an active interest in personal BC prevention.
- Trigger 2: Patient has BC with no clear indication of cause through normal clinical evaluation (e.g. no family history or known mutations in BC genes). She is interested in whether polygenic risk can explain her disease.
- This test is not diagnostic and therefore not appropriate for women presenting with an indicator of acute disease.

OBJECTIVE OUTCOME

Physician uses comprehensive risk assessment to provide the patient with either (1) an actionable plan to manage her individual absolute risk of breast cancer and reduce likelihood of her contracting the disease or (2) a potential explanation for the cause of her disease.

BASIC FLOW: SCENARIO 1

DESCRIPTION	This scenario describes the situation of a patient who has no history of breast cancer
1	Patient comes to physician for BC risk assessment
2	Physician performs initial assessment for clinical risk factors, including family history, smoking, and age, and communicates the additional value of incorporating polygenic information
3	Physician prescribes polygenic and potentially single-gene assessment of the patient's DNA
4	Physician performs sampling and sends DNA to laboratory for analysis and sets 2 week follow up appointment
5	Physician receives patient result as a report and automatically to EHR
6	Patient identified as having Population risk of BC
7	Physician provides patient with information on standard national BC guidelines: mammographic screening as per national guidelines, basic wellness advice, description of how age and modifiable risk factors will alter risk over time

ALTERNATIVE FLOW A: Patient has Moderate risk

6A	Patient identified as having Moderate risk of BC
7A	Physician provides patient with Moderate Risk Action Plan: annual mammogram from 40 years of age, general wellness advice & lifestyle recommendations

ALTERNATIVE FLOW B: Patient has High risk

6B	Patient identified as having High risk of BC
7B	Physician provides patient with High Risk Action Plan: annual mammogram from age 30, recommendations for chemoprevention, behavioural changes (ex. stop smoking, reduce alcohol intake)

NOTES

Risk classification is the result of age, fixed risk elements (e.g. family history and genetics) and modifiable factors such as smoking and BMI. Absolute risk therefore changes over time and should be monitored.

The exact course of action for individuals at Population, Moderate and High is at the discretion of the physician and depends on availability of resources but should be based on current national guidelines.

Although a woman's risk may be accurately estimated, these predictions do not allow one to say precisely which woman will develop breast cancer as some women who do not develop breast cancer have higher risk estimates than those who do develop the disease.

This framework identifies women with Population, Moderate and High absolute risk of disease, and only recommends a change in clinical care pathway for women with Moderate and High risk. For example, further personalisation for women at borderline risk is possible.*

The effect of PRS on absolute risk depends on ancestry and is accounted for in the integrated model.

*Risk classification is based on National Institute for Health and Care Excellence Clinical guidelines (2021)

BASIC FLOW: SCENARIO 2

DESCRIPTION	This scenario describes the situation of a patient who presents with incident breast cancer or who is in remission and knows that she is not a single-gene mutation carrier
1	Patient comes to physician for assessment to understand cause of BC
2	Physician reviews patient's previous risk assessment test results
3	Physician prescribes polygenic assessment of the patient's DNA
4	Physician performs sampling and sends DNA to laboratory for analysis and sets 2 week follow up appointment
5	Physician receives patient result as a report and automatically to EHR
6	Patient and physician discuss results and potential effect of polygenic risk to cancer diagnosis

ABSOLUTE RISK CLASSIFICATION

The following risk classifications have been calculated based on the interaction between the following factors:

- Single-gene mutation carrier status
- Polygenic Risk Score
- Family history of breast cancer
- Lifestyle (diet, smoking status, etc.)

The thresholds for moving between risk strata are dependent on national guidelines and those quoted below are based on the National Institute for Health and Care Excellence Clinical guidelines (2021).

POPULATION RISK	The lifetime risk of BC in the general population is ~10%. Women whose risk is similar to this which in practice equates to a <17% probability of disease by age 75 and a <2% absolute risk over 10 years are placed in this category.
MODERATE RISK	The moderate risk category applies to women who have a 17 - 30% probability of developing BC by the age of 75 or >3% 10 year risk of developing BC and under the age of 50
HIGH RISK	The high risk category applies to women who have a >8% absolute risk over 10 years if under 50 or have a more than 30% probability of developing BC by the age of 75 as compared to the general population

Benefit of integrating PRS into risk models

The addition of PRS into standard risk classification models increases the number of individuals identified at high risk of disease. These individuals are both more likely to get disease and are unlikely to be identified through traditional models. This so-called 'invisible' population is identified thanks to PRS picking up risk that is not captured in standard risk assessments. For Breast Cancer, this is around 10% of cases of disease in people under the age of 45, and 20% of late onset cancer. Therefore using PRS has the significant potential to reduce the burden of BC by allowing targeted interventions on those most at risk.

CONTACT
info@allelica.com | +1 202 949 2834

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THE POLYGENIC RISK SCORE COMPANY