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Clinical Application of an Absolute Risk Model in Breast Cancer Risk Assessment

This document outlines the scientific basis and clinical benefits of incorporating absolute risk assessment, including polygenic risk scores (PRS), into breast cancer (BC) prevention strategies. It provides a structured framework to guide physicians in utilizing this model in clinical practice. Although this approach is not yet part of formal clinical guidelines, it offers a more refined method for risk stratification, enhancing the precision of preventive care.

Early Detection Reduces Mortality

Early detection remains the most critical aspect of breast cancer (BC) prevention and significantly reduces mortality rates. While modifiable factors such as obesity and unhealthy lifestyle choices contribute to cancer risk, the most effective strategy for lowering breast cancer mortality is to identify the disease in its early stages, when it is still localized. When breast cancer is detected at this stage, the five-year survival rate is about 99% [1].

Screening is Essential for Early Detection

Screening for BC is a proven strategy for early detection. Mammography is the most widely used screening tool and has been instrumental in identifying cancer at an early stage when treatment is most effective. Large-scale studies have consistently demonstrated that routine breast cancer screening significantly reduces mortality [2-4].

Screening Should Be Risk-Adjusted

Most major clinical guidelines recommend that breast cancer screening protocols be tailored to an individual's risk profile. A one-size-fits-all approach is not suitable for everyone, as women at higher absolute risk of BC will benefit from more intensive screening, including starting at an earlier age and undergoing additional imaging modalities like MRI. Conversely, those at lower absolute risk might not need to begin screening as early. Risk-adjusted screening ensures that the right individuals receive the appropriate level of screening [5].

The clinical guidelines where risk-based screening is recommended differ depending on national guidelines. A well-known approach by the National Institute for Health and Care Excellence Clinical guidelines defines the risk groups as follows [6]:

- **General population risk**

The absolute lifetime risk of developing breast cancer is similar to that of the general population, typically estimated to be less than 17%.

- **Moderate risk**

The absolute lifetime risk of developing breast cancer is moderately increased compared to the general population, typically estimated to be between 17% and 30%.

- **High risk**

The absolute lifetime risk of developing breast cancer is significantly increased compared to the general population, typically estimated to be greater than 30%.

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Risk Models Estimate Absolute Risk

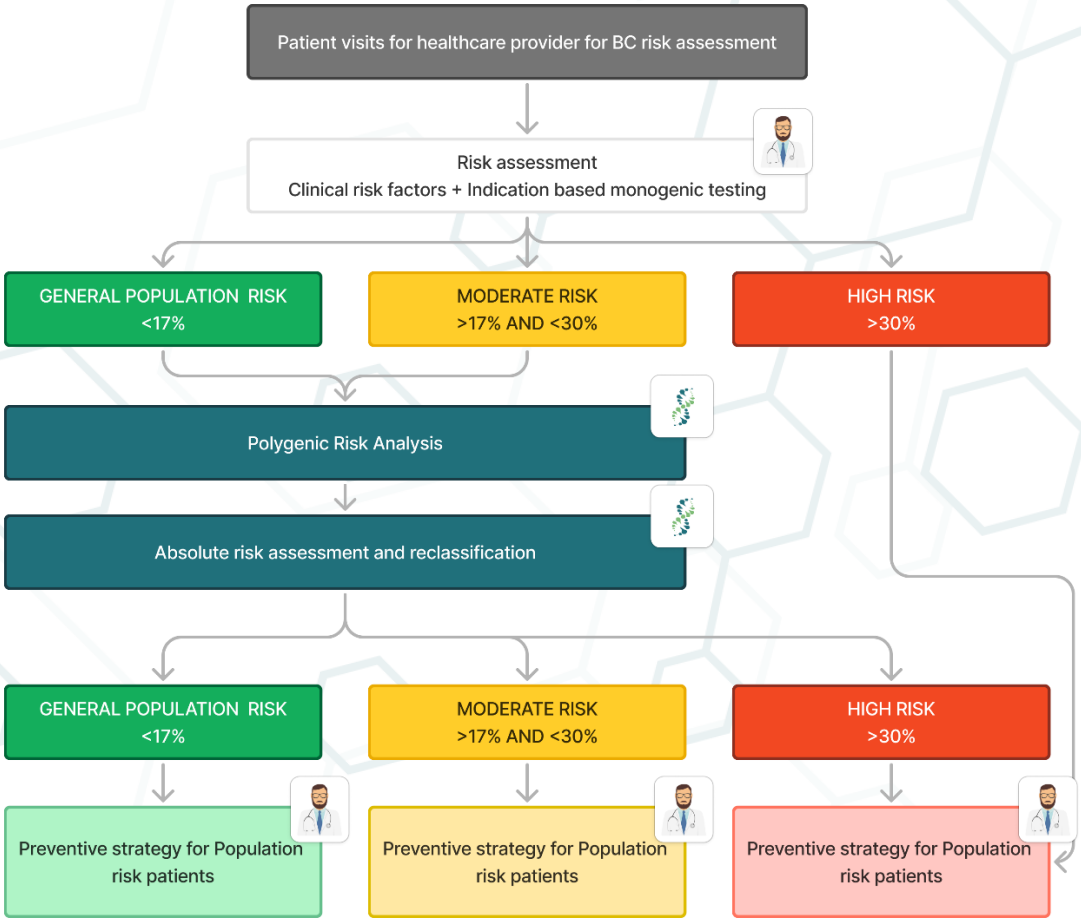
Several models are available to estimate a woman's risk of developing BC, considering established risk factors. Commonly used models include the Tyrer-Cuzick or International Breast Intervention Study (IBIS) model, which evaluates a range of factors such as age, family history of breast and ovarian cancer, age at menarche, parity, body mass index (BMI), and use of hormone replacement therapy. These models estimate an individual's absolute risk of developing BC over different time frames, such as 5 years, 10 years, or a lifetime [7].

Polygenic Risk Scores (PRS) Improve Risk Prediction

The goal of breast cancer risk assessment is to achieve the highest level of accuracy by incorporating as many clinically relevant risk factors as possible. Traditional risk models are valuable tools that consider factors such as age, family history, reproductive history, and lifestyle. However, recent studies have highlighted the value of integrating Polygenic Risk Scores (PRS) into these models. PRS evaluates the cumulative effect of numerous genetic variants associated with BC risk. By combining traditional risk factors with genetic data, the predictive performance of risk models is significantly enhanced [8-9].

Potential Workflow for BC Risk Assessment Using an Absolute Risk Model

The following workflow outlines a clinical pathway for incorporating an absolute risk model, including PRS analysis, into BC risk assessment. This approach offers a strategy for improving risk stratification and tailoring preventive measures based on an individual's absolute lifetime risk of developing BC.



1. Patient consultation: The process begins when a patient seeks breast cancer risk evaluation from their physician.
2. Initial assessment: The physician conducts a traditional risk assessment based on factors such as age, family history of BC, reproductive history, and other clinical parameters. For some patients, particularly those with a strong family history or other risk indicators, the physician may consider ordering a monogenic NGS test, following current guidelines for high-penetrance mutations.
3. Consideration of PRS: For patients who are classified as having average or moderate risk after the initial assessment, the physician may suggest incorporating PRS into the risk model. The inclusion of PRS could improve the precision of the risk estimate, particularly in identifying risks that are not captured by traditional risk factors alone. The decision to include PRS should be made in collaboration with the patient.
4. Sample collection and analysis: If a decision is made to include PRS, a sample is collected and sent to the laboratory for analysis. The report, which typically takes around two weeks, will include an updated absolute risk assessment combining both traditional and the polygenic risk factors.
5. Revised risk classification: Upon receiving the patient report, the physician reviews the updated risk assessment and reclassifies the patient's risk based on all available data.
6. Patient communication and preventive strategy: The physician communicates the results to the patient and discusses individualized preventive strategies based on the final risk category.

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Disclaimer

This document is intended for informational purposes only and provides guidance on the potential integration of an absolute risk model, including polygenic risk scores (PRS), into breast cancer risk assessment. It does not replace clinical judgment or established medical guidelines. Physicians are encouraged to evaluate the applicability of the outlined workflow based on individual patient circumstances and current clinical standards. The described approach has not been universally validated in clinical guidelines and should be implemented with professional discretion.