Technology Guidance

# Germline genetic testing

## for hereditary breast cancer and hereditary ovarian cancer

**Technology Guidance from the MOH Medical Technology Advisory Committee**

### Guidance Recommendations

The Ministry of Health's Medical Technology Advisory Committee has recommended:

- ✓ Germline genetic testing for hereditary breast cancer and hereditary ovarian cancer in individuals with relevant risk factors;
- ✓ Risk-reducing mastectomy in individuals with a pathogenic variant or likely pathogenic variant associated with hereditary breast cancer; and
- ✓ Risk-reducing bilateral salpingo-oophorectomy in individuals with a pathogenic variant or likely pathogenic variant associated with hereditary ovarian cancer.

### Funding status

Germline genetic testing, risk-reducing mastectomy, and risk-reducing bilateral salpingo-oophorectomy are recommended for subsidy from 1 December 2026. Subsidies apply only when performed in line with the clinical criteria listed in the Annex.

**Published: 5 November 2026**

## Technology evaluation

1.1. At the July 2025 meeting, the MOH Medical Technology Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of germline genetic testing for hereditary breast cancer and hereditary ovarian cancer.

1.2. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from public healthcare institutions. Published clinical and economic evidence for germline genetic testing for hereditary breast cancer and hereditary ovarian cancer was considered in line with prevailing clinical practice guidelines and local clinical practice.

1.3. The evidence was used to inform the deliberations around five core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Overall benefit of the technology for the patient and/or the system;
- Cost-effectiveness (value for money), which considers the incremental benefit and cost of the technology compared to existing alternatives;
- Estimated annual technology cost and the number of patients likely to benefit from the technology; and
- Organisational feasibility, which covers the potential impact of adopting the technology, especially barriers for diffusion.

1.4. Additional factors, including social and value judgments, may also inform the funding deliberations.

## Clinical need

2.1. Between 2018 and 2022, breast cancer was the most common cancer among females in Singapore, accounting for 29.6% of diagnoses and 17.1% of deaths, while ovarian (and related) cancers ranked sixth, accounting for 4.2% of diagnoses and 5.4% of deaths. Hereditary breast and ovarian cancers are inherited syndromes caused by pathogenic variants (PVs), primarily in *BRCA1* and *BRCA2*, as well as other genes such as *TP53* and *PTEN*, and account for 5 to 10% of breast cancer cases and 10 to 15% of ovarian cancer cases. According to the SG10K health study, about one in 150 Singaporeans carries a germline PV associated with hereditary breast or ovarian cancer, with a 50% chance of passing the variant to their offspring.

2.2. The Committee noted that germline genetic testing identifies PVs in cancer-affected individuals and informs treatment and surgical decisions. When extended to unaffected family members, it guides surveillance and risk-reduction strategies for early detection and cancer prevention, providing a more definitive basis for clinical decision-making than family history or other risk factors. The Committee acknowledged that the main comparator is no genetic testing, whereby cancer-affected individuals receive standard care for breast or ovarian cancer, and unaffected relatives undergo surveillance according to population screening guidelines.

2.3. The Committee noted that 13 genes associated with hereditary breast cancer (*ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11* and *TP53*) and nine genes associated with hereditary ovarian cancer (*BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, PALB2, RAD51C* and *RAD51D*) were included in the scope of the evaluation. The presence of PVs in these genes confers a substantially higher absolute risk of breast and/or ovarian cancers than in the general population, with risk-reducing interventions recommended in reference clinical practice guidelines and aligned with local clinical practice.

2.4. The Committee noted that management of individuals with a hereditary predisposition to breast and ovarian cancer aims to reduce their risk of developing cancer and, where risk remains, facilitate early detection and timely treatment. Risk-reducing interventions include risk-reducing surgeries and chemoprevention. Risk-reducing surgeries remove at-risk organs and include risk-reducing mastectomy (RRM) and risk-reducing bilateral salpingo-oophorectomy (RRBSO). Chemoprevention options include selective oestrogen receptor modulators (SERMs) or aromatase inhibitors (AIs) for breast cancer risk reduction, and oral contraceptives for ovarian cancer risk reduction. For individuals who have not undergone RRM, intensified breast surveillance using magnetic resonance imaging (MRI) and/or mammography, supports earlier cancer detection and enables timely intervention with the aim of improving clinical outcomes.

## Clinical effectiveness and safety

3.1. The Committee noted that the evidence base included three health technology assessment (HTA) reports and 16 systematic reviews and meta-analyses (SRMAs). The HTA reports evaluated the accuracy of genetic testing for hereditary breast and ovarian cancers, as well as changes in management and health outcomes among individuals who tested positive, while the SRMAs assessed the impact of risk-reducing interventions on health outcomes in individuals with PVs in the *BRCA1* and *BRCA2* genes.

3.2. The Committee accepted that germline genetic testing and downstream risk-reducing interventions were generally safe. Genetic testing was associated with transient psychological morbidity that declined over time, while breast cancer surveillance did not adversely affect short-term health-related quality of life. Risk-reducing surgeries were associated with surgical complications and procedure-specific adverse effects, and SERMs increased the risk of thromboembolic events and endometrial cancer. No comparative safety evidence was identified for ovarian cancer surveillance or chemoprevention.

3.3. The Committee noted that the analytical sensitivity and specificity of germline genetic testing was 93.66 to 100% and 95.9 to 99.99% respectively with next generation sequencing compared to Sanger sequencing (reference standard). Individuals with a genetic predisposition for hereditary breast or ovarian cancer have a higher risk of breast and ovarian cancer than the general population, and that knowledge of mutation status increases uptake of risk-reducing surgeries.

3.4. The Committee considered that downstream risk-reducing interventions in individuals with a genetic predisposition for hereditary breast or ovarian cancer reduced the risk of breast and ovarian cancers and, in some groups, mortality. RRM significantly reduced breast cancer risk and, in women with a personal history of unilateral breast cancer, all-cause and breast cancer-specific mortality. RRBSO significantly reduced ovarian cancer risk and mortality irrespective of personal cancer history. Breast cancer surveillance, leading to earlier detection of breast cancer, significantly reduced breast cancer-specific mortality in women at high risk of breast cancer, including those with PVs in the *BRCA1* and *BRCA2* genes, whereas ovarian cancer surveillance showed no evidence of clinical benefit.

3.5. The Committee noted that chemoprevention with tamoxifen or AIs significantly reduced breast cancer risk in individuals with PVs in *BRCA1* and *BRCA2* and had a personal history of breast cancer; however, tamoxifen did not significantly reduce breast cancer risk in those without such a history. Oral contraceptives significantly reduced ovarian cancer incidence regardless of personal history of cancer.

3.6. The Committee recognised that evidence for risk-reducing surgeries is largely limited to individuals with PVs in the *BRCA1* and *BRCA2* genes but accepted the extrapolation of these findings to other susceptibility genes with similarly elevated cancer risks, with individualised decision-making based on gene-specific and patient risk factors.

3.7. The Committee noted that the UK National Institute of Health and Care Excellence (NICE) and Australia's Medical Services Advisory Committee (MSAC) concluded that the evidence supported the use of germline genetic testing and associated risk-reducing interventions for the early detection and prevention of breast and ovarian cancer.

## Cost effectiveness

4.1. The Committee considered cost-effectiveness evidence from HTA reports by the UK NICE and the Australia's MSAC, which found germline genetic testing for *BRCA1* and *BRCA2*, compared with no genetic testing, to be cost-effective in individuals with breast and/or ovarian cancer and their first-degree relatives. The Committee noted that cost-effectiveness findings were robust across sensitivity analyses, improved with cascade testing of relatives, and supported reimbursement recommendations by both agencies. The Committee further noted that MSAC extended its recommendation to additional breast and ovarian cancer susceptibility genes, including *CDH1*, *CHEK2*, *PALB2*, *PTEN*, *STK11* and *TP53*, on the basis that multigene panel testing did not increase testing costs or adverse effects, and that NICE recommended germline genetic testing for individuals with a carrier probability of ≥10% without an upper age limit to avoid potential inequity.

4.2. In addition, the Committee noted that a local cost analysis confirmed that increasing uptake of cascade testing and risk-reducing surgery for hereditary breast and ovarian cancers would reduce overall healthcare costs through cancer prevention and lower surveillance costs.

## Estimated annual technology cost

5.1. The Committee noted that the annual cost impact to the public healthcare system was estimated to be between SG$1 million and SG$3 million, in the first five years of subsidy listing for germline genetic testing for HBOC. The Committee noted that these estimates were most sensitive to the eligibility criteria and uptake of genetic testing.

## Organisational feasibility

6.1. The Committee noted that the implications of germline genetic testing extend beyond the cancer-affected individual and downstream risk-reducing interventions include irreversible surgeries which may have sexual and psychosocial implications. The Committee emphasised the importance of genetic and pre-procedural counselling and shared decision-making, particularly given family planning considerations and the need for individualised care.

## Recommendations

7.1. Based on available evidence, the Committee recommended subsidising germline genetic testing for hereditary breast and ovarian cancers, RRM for individuals with PVs associated with hereditary breast cancer, and RRBSO for individuals with PVs associated with hereditary ovarian cancer, in view of favourable clinical and cost-effectiveness compared to no genetic testing.

7.2. The Committee also recommended that germline genetic testing and the downstream risk-reducing surgeries be subsidised in line with additional clinical criteria (listed in the Annex) to govern appropriate use in local practice. The criteria were developed in consultation with local clinical experts and are consistent with overseas reimbursement criteria.

## Annex

### A. CLINICAL CRITERIA FOR GERMLINE GENETIC TESTING FOR HEREDITARY BREAST CANCER

#### 1) Individuals with a personal history of breast cancer with risk factors for hereditary breast cancer

For the characterisation of germline gene variants in an individual with breast cancer who fulfils any one of the following clinical criteria:

1. A pathogenic variant identified on tumour genomic testing that has clinical implications if also identified in the germline; or
2. Personal history of breast cancer with specific features:
    - ≤50 years old; or
    - Triple-negative breast cancer; or
    - Multiple primary breast cancers (synchronous or metachronous); or
    - Lobular breast cancer with personal or family history of diffuse gastric cancer; or
    - Male breast cancer; or
3. Ancestry: Ashkenazi Jewish ancestry; or
4. Family history of:
    - ≥1 close biological relative (includes first-, second-, and third-degree relatives on the same side of the family) with:
        - Breast cancer at age ≤50 years old; or
        - Male breast cancer; or
        - Ovarian cancer; or
        - Pancreatic cancer; or
        - Prostate cancer with metastasis, or high- or very-high-risk group; or
    - ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer
5. Individuals who otherwise do not meet the criteria 1 to 4 above but have a probability of ≥10% of a *BRCA1/2* pathogenic variant based on prior probability models (e.g. Manchester Score, CanRisk).

This applies to the following genes: *ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11* or *TP53*

Individuals are eligible for subsidy once per cancer diagnosis.

**2) Individual with a significant family history of breast cancer, and unknown familial genetic status**

For the characterisation of germline gene variants in an unaffected individual who fulfils the following criteria:

1. The individual has a first-degree biological relative with breast cancer who is unavailable for genetic testing; and
2. The individual has a probability ≥10% of a *BRCA1/2* pathogenic variant based on prior probability models (e.g. Manchester Score, CanRisk).

This applies to the following genes: *ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11* or *TP53*

Individuals are eligible for subsidy once per lifetime.

**3) First-degree relatives of an individual who carries a pathogenic or likely pathogenic variant in a breast cancer susceptibility gene**

For the detection of a specific germline pathogenic or likely pathogenic variant previously identified in a first-degree biological relative.

This applies to the following genes: *ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11* or *TP53*

Individuals are eligible for subsidy once per variant.

## B. CLINICAL CRITERIA FOR GERMLINE GENETIC TESTING FOR HEREDITARY OVARIAN CANCER

### 1) Individuals with a personal history of ovarian cancer with risk factors for hereditary ovarian cancer

For the characterisation of germline gene variants in an individual with ovarian cancer who fulfils any one of the following clinical criteria:

1. A pathogenic variant identified on tumour genomic testing that has clinical implications if also identified in the germline; or
2. Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age; or
3. Individuals who otherwise do not meet the criteria 1 to 2 above but have a probability of ≥10% of a *BRCA1/2* pathogenic variant based on prior probability models (e.g. Manchester Score, CanRisk).

This applies to the following genes: *BRCA1, BRCA2*, *BRIP1, EPCAM, MLH1, MSH2, PALB2, RAD51C* or *RAD51D*

Individuals are eligible for subsidy once per cancer diagnosis.

### 2) Individual with a significant family history of ovarian cancer, and unknown familial genetic status

For the characterisation of germline gene variants in an unaffected individual who fulfils the following criteria:

1. The individual has a first-degree biological relative with ovarian cancer who is unavailable for genetic testing; and
2. The individual has a probability of ≥10% of a *BRCA1/2* pathogenic variant based on prior probability models (e.g. Manchester Score, CanRisk).

This applies to the following genes: *BRCA1, BRCA2*, *BRIP1, EPCAM, MLH1, MSH2, PALB2, RAD51C* or *RAD51D*

Individuals are eligible for subsidy once per lifetime.

**3) First-degree relatives of an individual who carries a pathogenic or likely pathogenic variant in an ovarian cancer susceptibility gene**

For detection of a specific germline pathogenic or likely pathogenic variant previously identified in a first-degree biological relative.

This applies to the following genes: *BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, PALB2, RAD51C* or *RAD51D*

Individuals are eligible for subsidy once per variant.

## C. CLINICAL CRITERIA FOR RISK-REDUCING MASTECTOMY

Risk-reducing mastectomy (bilateral or contralateral) may be considered for breast cancer risk reduction, with or without breast reconstruction, in an individual who fulfils the following clinical criteria:

1. The individual is 25 years and older;
2. The individual has an increased risk of breast cancer due to pathogenic or likely pathogenic variant(s) in any of the following genes: *ATM*[1], *BRCA1*, *BRCA2, CDH1, PALB2, PTEN*, *STK11* or *TP53*;
3. The individual has received genetic counselling;
4. The individual has no competing comorbidities which could severely limit her life expectancy at the time of risk-reducing mastectomy; and
5. The individual has received pre-operative counselling about psychosocial and sexual consequences of risk-reducing mastectomy. If there is a need for further counselling, the patient can be referred to a psychologist.

Risk-reducing mastectomy should only be considered after assessment of personal risk and family history of breast cancer, and recommendations of clinical practice guidelines.

[1] Risk-reducing mastectomy may be considered for carriers of the *ATM* c.7271T>G variant.

## D. CLINICAL CRITERIA FOR RISK-REDUCING BILATERAL SALPINGO-OOPHORECTOMY

Risk-reducing bilateral salpingo-oophorectomy may be considered for ovarian cancer risk reduction in an individual who fulfils the following clinical criteria:

1. The individual is 35 years and older, or earlier if there is a family history of earlier onset ovarian cancer;
2. The individual is at increased risk of ovarian cancer due to pathogenic or likely pathogenic variant(s) in any of the following genes: *BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, PALB2*, *RAD51C* or *RAD51D;*
3. The individual has completed family planning and considered their reproductive decisions;
4. The individual has received genetic counselling;
5. The individual has no competing comorbidities which could severely limit her life expectancy at the time of risk-reducing bilateral salpingo-oophorectomy; and
6. The individual has received pre-operative counselling about psychosocial and sexual consequences of risk-reducing bilateral salpingo-oophorectomy. If there is a need for further counselling, the patient can be referred to a psychologist.

Risk-reducing bilateral salpingo-oophorectomy should only be considered after assessment of personal risk and family history of ovarian cancer, and recommendations of clinical practice guidelines.

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**About the Agency**

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidelines, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

The guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

*Find out more about ACE at www.ace-hta.gov.sg/about*

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