

MSAC Application

**Genetic testing for the detection of
germline variants in cancer
predisposition genes in people with
prostate cancer and their relatives**

PICO Set 2

Population

Describe the population in which the proposed health technology is intended to be used:

The population proposed for cascade testing is people who have a biological relative with prostate cancer and a germline pathogenic or likely pathogenic (P/LP) variant identified in one or more of the cancer predisposition genes encompassed by MBS item 73296. This does not include any relatives already diagnosed with prostate cancer themselves (captured in PICO set 1). Consistent with standard terminology, those affected individuals who test positive for a genetic variant are referred to as probands.

The population of biological relatives is enriched for genetic variants that run in that family. The diagnostic yield of cascade testing is therefore high and is typically estimated using Mendelian inheritance patterns. For example, for an autosomal dominant variant, on average 50% of first-degree relatives would share the same germline variant.

A family history of prostate cancer imparts a higher risk of prostate cancer

The risk of prostate cancer for a variant-positive first-degree relative at any age increases 2-fold, with first-degree family history increasing the incidence rate of prostate cancer even further in men under 65 years old compared to men aged 65 years and older (Kiciński et al., 2011; Song et al., 2025).

Germline P/LP variants impart a higher risk of developing prostate cancer

Germline P/LP variants in *BRCA1/2* and other cancer predisposition genes are associated with substantially increased risk of multiple malignancies, including prostate, breast and ovarian cancers. In prostate cancer, studies have shown that *BRCA2* carriers experience higher incidence and clinically significant disease, consistent with earlier onset and a more aggressive phenotype. A five-year prospective analysis of participants aged 40–69 years (n=3063) found a higher incidence of clinically significant prostate cancers in *BRCA2* pathogenic germline variant carriers than in non-carriers (3.1% vs 1.3%; p = 0.04) (Bancroft et al., 2026).

The increased risk of prostate cancer imparted by germline variants in cancer predisposition genes is summarised in Table 1, for the green genes included in the PanelApp Prostate Cancer (Version 1.1) panel (PanelApp Australia, 2026).

Table 1: Summary of prostate cancer risk by prostate cancer predisposition genes ('green genes' on the PanelApp Prostate cancer predisposition gene panel)

Prostate cancer predisposition gene or variant	Prostate cancer risk	Source
<i>ATM</i>	6.3-fold RR (95% CI 3.2-11.3)	(Marino et al., 2023)
<i>ATM</i> 316G (P1054R)	OR 2.13 (95% CI 1.17-3.87)	(Marino et al., 2023)
<i>BRCA1</i>	3.75-fold RR (95% CI 1.02-9.6)	(Marino et al., 2023)
	1.8- to 3.3-fold RR for diagnosis ≤65 years old	(Brandão et al., 2020)
<i>BRCA2</i>	3.18-fold RR (95% CI 1.52-6.66)	(Marino et al., 2023)
	2.5- to 8.6-fold RR for diagnosis ≤65 years old	(Brandão et al., 2020)
	4.45 (95% CI 2.99-6.661) standardised incidence ratio relative to population risk	(Nyberg et al., 2020)
<i>CHEK2</i> 1100delC	OR 3.29 (95% CI 1.85-5.85)	(Marino et al., 2023)
<i>CHEK2</i> I157T	OR 1.80 (95% CI 0.79-3.20)	(Marino et al., 2023)
<i>EPCAM</i>	Cumulative incidence of clinically significant prostate cancer by age 75 yr for <i>MSH2/EPCAM</i> carriers at 37% (95% CI: 17–57%)	(Rodgers-Fouche et al., 2026)
<i>HOXB13</i>	OR 3.28 (95% CI 2.31-4.56)	(Marino et al., 2023)
<i>MLH1</i>	3.67-fold RR (95% CI 2.32-6.67)	(Marino et al., 2023)
<i>MSH2</i>	3.67-fold RR (95% CI 2.32-6.67)	(Marino et al., 2023)
<i>MSH6</i>	3.67-fold RR (95% CI 2.32-6.67)	(Marino et al., 2023)
<i>PALB2</i>	Failed to find increased risk of prostate cancer (OR = 1.38) however OR = 8.05 for Gleason 8-10 (high grade) prostate cancer	(Wokolorczyk et al., 2021)
<i>PMS2</i>	3.67-fold RR (95% CI 2.32-6.67)	(Marino et al., 2023)
<i>TP53</i>	9.1-fold RR (95% CI 6.2–14)	(Maxwell et al., 2022)

Germline P/LP variants impart a higher risk of developing other cancers

Many of the key genes associated with prostate cancer encode proteins with functions in DNA repair, including homologous recombination repair and mismatch repair processes. When proper DNA repair is prevented, genomic instability increases and mutations accumulate over time, leading to a higher risk of prostate cancer and other cancers. For example, germline P/LP variants in prostate cancer predisposition genes are also associated with increased risk of hereditary breast and ovarian cancer syndrome (HBOC), pancreatic cancer, colon cancer, and other cancers (Table 2) (ESMO Guidelines Committee et al., 2023).

Table 2: Lifetime risk of non-prostate cancers associated with germline variants in cancer predisposition genes

Prostate cancer predisposition gene	Lifetime risk of other cancers (where increased)	Source
<i>ATM</i>	Breast 25-30%, tubo-ovarian $\leq 5\%$, pancreatic $< 5\%$	(ESMO Guidelines Committee et al., 2023).
<i>BRCA1</i>	Breast $> 60\%$, tubo-ovarian 40-60%, pancreatic $< 5\%$	(ESMO Guidelines Committee et al., 2023).
<i>BRCA2</i>	Breast $> 60\%$, tubo-ovarian 15-30%, pancreatic $< 5\%$	(ESMO Guidelines Committee et al., 2023).
<i>CHEK2</i>	Breast 25-30%, colon 15%	(ESMO Guidelines Committee et al., 2023).
<i>PALB2</i>	Breast 40-60%, tubo-ovarian 3-5%, pancreatic 2-3%	(ESMO Guidelines Committee et al., 2023).
<i>PMS2</i>	Lynch syndrome-associated cancers 25-32%	(Blount & Prakash, 2018)
<i>TP53</i>	Breast 40%, some sarcoma, brain, leukaemia, adrenocortical carcinoma, possible pancreatic cancer and colon cancer	(ESMO Guidelines Committee et al., 2023).

Note: lifetime risks in the 'average risk' population are: breast cancer 11%, ovarian cancer 1.3%, pancreatic cancer 1.6%, and colon cancer 4%. Source: (ESMO Guidelines Committee et al., 2023).

Germline P/LP variants are associated with earlier and more aggressive prostate cancer

The presence of a P/LP variant in prostate cancer predisposition genes can be associated with early onset, more aggressive disease, and less favourable outcomes (Edmunds et al., 2026).

For example, *BRCA2* carriers were found to be diagnosed at a younger age (61 vs 64 years old; $p = 0.04$) and were more likely to have a more aggressive and clinically significant form of prostate cancer than *BRCA2* non-carriers (77% vs 40%; $p = 0.01$) (Page et al., 2019).

A retrospective case-case study ($n=799$) using survival analysis also found that having a *BRCA1/2* or *ATM* germline P/LP variant remained an independent predictor of lethal prostate cancer (hazard ratio = 2.13, 95% confidence interval: 1.24–3.66, $p = 0.004$) after adjusting for ethnicity, age, prostate-specific antigen (PSA), and Gleason score at the time of diagnosis (Na et al., 2017).

Specify any characteristics of patients with, or suspected of having, the medical condition, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian healthcare system in the lead up to being considered eligible for the technology:

The key characteristic of individuals proposed to be eligible for cascade testing is that they are a biological relative of a patient diagnosed with prostate cancer in whom a germline P/LP variant in *BRCA1/2* or another relevant cancer predisposition gene has been detected. Biological relatives may have had a past diagnosis of cancer but were not eligible or did not present for testing. Biological relatives will primarily be first-degree relatives (biological parents, siblings, children), although second-degree relatives (e.g. aunts/uncles, nieces/nephews, grandparents) may also be tested where appropriate.

Due to the >10% risk criterion for germline testing proposed for patients with prostate cancer (reflecting current MBS item 73296), the cascade testing population might have multiple relatives with prostate cancer and other related cancers (such as breast, ovarian or pancreatic cancer), on the same side of the family and with earlier cancer onset.

Referral

Patients diagnosed with prostate cancer and found to carry a germline P/LP variant will be encouraged by their specialist or consultant physician, general practitioner (GP), genetic counsellor, oncologist or staff from the Hereditary Cancer Registry to discuss cancer risk with their relevant biological relatives. Direct contact of relatives can be initiated by clinical services with consent of the patient, although this may be rare in practice.

The biological relative would subsequently see their GP, who can refer them to a clinical genetics service or familial cancer centre to learn more about their risk and considerations for genetic testing. Individuals can attend a public or private clinical genetics service, depending on their preference and individual circumstances.

During the initial clinical genetics service appointment, the clinician will review family history and any other relevant characteristics to estimate the individual's inherited cancer risk before offering genetic testing. Services usually also provide genetic counselling, medical advice, information on inherited cancer risk, screening and surveillance, and opportunities to participate in research.

Prior to ordering cascade testing, the ordering practitioner should ensure that written informed consent has been obtained from the individual, and that appropriate genetic counselling has been provided (as per PN.0.23). This should include informing the individual about the potential implications and outcomes of test results, the costs associated with testing, and that testing is optional and can be declined or deferred.

Provide a rationale for the specifics of the eligible population:

Individuals proposed to be eligible for cascade testing are those with a biological relative with prostate cancer in whom a germline P/LP variant has been identified in *BRCA1/2*, or another relevant cancer predisposition gene.

The requesting clinician will consider which biological relatives are available and indicated for testing, based on their likelihood to benefit from testing and potentially increased surveillance. Therefore, 'biological relatives' is the preferred description of the cascade testing population to allow for clinician discretion (e.g. testing of second-degree relatives may take place in the absence of testing a first-degree relative in a small proportion of cases, where considered appropriate).

Are there any prerequisite tests?

No

Are the prerequisite tests MBS funded?

Not applicable

Provide details to fund the prerequisite tests:

Not applicable

Intervention

Name of the proposed health technology:

Cascade testing for known germline gene variants, including copy number variation, in genes encompassed by item 73296.

Describe the key components and clinical steps involved in delivering the proposed health technology:

After a positive result (P/LP variant identified) is returned for an affected individual (PICO set 1), post-test genetic counselling should be provided by a genetic counsellor, clinical geneticist or oncologist trained in cancer genetics. This should include discussion of the clinical implications of the result, address any concerns that the proband may have about their result, and help them to identify which biological relatives may be at risk. Probands should be encouraged to inform these relatives about their increased risk of hereditary cancer, and with consent of the patient clinical services can initiate direct contact of relatives. The clinician or clinic will provide probands with a letter that explains the condition, genetics, recommended screening and management, which can help them with sharing such information with their biological relatives if appropriate.

Biological relatives who consider testing will need to see their clinician (e.g. their GP) to obtain a referral to a clinical genetics service or familial cancer centre. The relative would subsequently receive individual pre-test genetic counselling to discuss their personal cancer risk, family history, potential outcomes of testing, associated costs, and potential implications for surveillance, prevention and management. At this point, the clinician must also obtain written informed consent. It should be noted that cascade testing is optional and can be declined or deferred.

If appropriate, the relative would undergo cascade testing, targeted to the germline P/LP variant that has been identified in the proband. This genetic testing is typically performed on a blood or saliva sample through an accredited laboratory.

Post-test genetic counselling will be provided to discuss test results and provide psychosocial support. For individuals who test positive (variant detected), options for risk management should be discussed, including earlier and more intensive surveillance, risk-reducing interventions, and lifestyle modifications. Individuals who test negative would be offered surveillance as per standard of care, with consideration of relevant risk factors and family history.

Identify how the proposed technology achieves the intended patient outcomes:

Cascade testing allows for systematic identification of biological relatives who are carriers of germline P/LP variants and, as a result, guides risk-stratified prevention and improves early cancer detection. Recommended risk-management measures may include enhanced surveillance, prophylactic surgery, risk-reducing medications, and lifestyle changes.

Earlier detection of prostate and other cancers

Earlier and intensified surveillance in P/LP variant carriers enables earlier detection, when disease is more likely to be localised and treated with curative intent. Earlier diagnosis increases the likelihood of effective surgical management or targeted or less intensive therapies and reduces the reliance on systemic treatments that are often associated with greater toxicity. This ultimately improves patient experience, quality of life, and clinical outcomes, including survival.

In relation to prostate cancer, identification of a germline P/LP variant, particularly in *BRCA2*, may prompt a recommendation to commence routine PSA testing earlier than age 50 years (Diagnostic Evaluation, 2026). Targeted screening studies demonstrate that PSA surveillance

initiated from age 40 years in *BRCA2* carriers detects prostate cancer at a younger age and with a substantially higher proportion of clinically significant tumours compared with non-carriers, supporting risk-adapted surveillance strategies informed by genetic status rather than testing based on age alone (Bancroft et al., 2026).

Risk management guidance for *BRCA1/2* carriers also includes chest and breast awareness, recognising the increased risk of breast cancer in this population and prompting early clinical assessment of new chest changes (*Diagnostic Evaluation*, 2026; eviQ; eviQ; RACGP). These individuals may be eligible for earlier breast cancer screening (commencing from 25-30 years), or recommended enhanced imaging techniques, such as breast magnetic resonance imaging (MRI) (eviQ). A large international cohort study found that participation in an MRI surveillance program was associated with an 80% relative reduction in breast cancer mortality in *BRCA1* carriers (HR 0.20, 95% CI 0.10–0.43; $P < 0.001$), with 3.2% cumulative risk in the MRI surveillance cohort vs 14.9% in the cohort without this surveillance (Lubinski et al., 2024).

Prophylactic surgery and risk-reducing medications

Prophylactic surgery for primary prevention amongst high-risk carriers is well-established for numerous cancers. This provides biological relatives with options to reduce their cancer risk.

Based on individual risk profile and preferences, bilateral risk-reducing mastectomy may be considered, and has been shown to confer a 90% to 95% risk reduction in breast and ovarian cancer risk for *BRCA* mutation carriers (Ludwig et al., 2016). Individuals who are not planning to have bilateral risk-reducing mastectomy within 3 years may be recommended risk-reducing medication to reduce their risk of developing breast cancer (Clinical Oncology Society of Australia, 2024; eviQ). A pooled analysis of studies of evaluating outcomes of tamoxifen and raloxifene showed a 20% relative risk reduction in breast cancer risk for *BRCA1/2* carriers compared with controls (RR 0.80, 95% CI 0.72–0.88, $p = 0.04$) (Alwashmi et al., 2025).

Taking into account a patient's risk profile and preferences, risk-reducing salpingo-oophorectomy may be recommended for people with a pathogenic *BRCA1* variant between the ages of 35 and 40 years, and for those with a *BRCA2* variant between 40 and 45 years, to reduce their risk of ovarian and fallopian tube cancer (ESMO Guidelines Committee et al., 2023). Risk-reducing salpingo-oophorectomy has been shown to reduce ovarian cancer risk by over 80% and improve overall survival in *BRCA1/2* pathogenic variant carriers (Masuda et al., 2025). Risk-reducing hysterectomy is not routinely recommended; however, some women will choose to undergo hysterectomy at the time of risk-reducing salpingo-oophorectomy to reduce their risk of some gynaecological cancers (eviQ).

While case reports exist of select high-risk carriers undergoing prophylactic prostatectomy to reduce their risk of prostate cancer, this is not recommended in clinical practice (Tiwari et al., 2022).

Lifestyle changes

Knowledge of germline status may also support behaviour change and broader risk reduction through lifestyle modifications, such as smoking cessation, a reduction in alcohol consumption, increased physical activity, and weight management. In a large population-based study ($n=12,411$), men in the highest quartile of polygenic risk for prostate cancer had a lifetime risk of lethal prostate cancer of 1.6% (95% CI, 0.8–3.1%) when adhering to healthy lifestyle behaviours, compared with 5.3% (95% CI, 3.6–7.8%) among those with unhealthy behaviours, indicating marked risk differences within the same genetic risk stratum (Plym et al., 2023).

Health economic evidence

The benefit of germline genetic testing in prostate cancer patients is proposed to arise primarily through improved health outcomes for their biological relatives.

Reflecting this structure of anticipated health outcome benefits across the two populations, health economic studies have reported that adding cascade testing greatly improves cost-effectiveness compared to germline testing for only localised prostate cancer patients. An Australian study of germline *BRCA* testing for localised prostate cancer in three different populations reported a quality-adjusted life year (QALY) gain of 0.029 and an incremental cost-effectiveness ratio (ICER) of \$47,294/QALY for patients with a family history of prostate cancer plus cascade testing of their relatives (Table 3) (Teppala et al., 2025).

Table 3: Cost-utility of germline *BRCA* testing for prostate cancer patients alone, vs addition of cascade testing

Population	Affected individuals only		Affected individuals + cascade	
	Incremental QALYs	ICER (\$/QALY)	Incremental QALYs	ICER (\$/QALY)
Risk classification: high / very high	0.003	\$591,408	0.087	\$18,872
Family history of prostate cancer	0.0003	\$3.9 million	0.029	\$47,294
Ashkenazi Jewish ancestry	0.002	\$650,098	0.112	\$14,637

Source: (Teppala et al., 2025)

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

Not applicable

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

Yes

Provide details and explain:

Cascade testing is required once per variant, as per the current descriptor for MBS item 73297.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

As per the current descriptor for MBS item 73297, a specialist or consultant physician is required to request this service. Appropriate pre- and post-test genetic counselling should be provided to the patient by the specialist treating practitioner (e.g. the treating oncologist), a genetic counselling service or a clinical geneticist on referral as per the relevant practice note (PN.0.23).

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

Not applicable

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

A referral may be provided by a specialist or consultant physician.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

Yes

Provide details and explain:

Testing would only be delivered by approved practising pathologists with appropriate scope of practice in pathology laboratories with the relevant National Association of Testing Authorities (NATA) accreditation for this service.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

- ☒ Consulting rooms
- ☐ Day surgery centre
- ☐ Emergency Department
- ☐ Inpatient private hospital
- ☐ Inpatient public hospital
- ☒ Laboratory
- ☒ Outpatient clinic
- ☐ Patient's home
- ☐ Point of care testing
- ☐ Residential aged care facility
- ☐ Other (please specify)

Genetic testing is provided through public and private clinical genetics services and familial cancer centres.

Some services operate mainstream genetic testing models, in which cancer specialists can directly request genetic testing for their patients, with support from a familial cancer centre. Mainstream genetic testing has the benefit of enabling genetic testing discussions to occur at the point of cancer care, rather than requiring separate genetics appointments, and is often associated with greater uptake of testing (Jennings et al., 2026).

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes

Provide additional details on the proposed health technology to be rendered outside of Australia:

Not applicable

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e., how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian healthcare system). This includes identifying healthcare resources that are needed to be delivered at the same time as the comparator service:

No cascade testing

List any existing MBS item numbers that are relevant for the nominated comparators:

Not applicable

Provide a rationale for why this is a comparator:

Currently cascade testing for biological relatives of prostate cancer patients in whom a germline P/LP gene variant has been identified is not publicly funded. Therefore 'no cascade testing' is the appropriate comparator.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

- ☐ None (used with the comparator)
- ☐ Displaced (comparator will likely be used following the proposed technology in some patients)
- ☐ Partial (in some cases, the proposed technology will replace the use of the comparator, but not all)
- ☒ Full (subjects who receive the proposed intervention will not receive the comparator)

Outline and explain the extent to which the current comparator is expected to be substituted:

Where cascade testing is conducted, it will fully substitute the comparator of no cascade testing.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

- ☒ Health benefits

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Health benefits

- Prevention of cancer through prophylactic and risk-reducing measures
- Improved cancer surveillance leading to earlier detection of cancer
- Improvement in patient health outcomes from possible earlier diagnosis and intervention (including mortality, morbidity, quality of life)

Test-related outcomes

- Test accuracy (sensitivity, specificity, positive/negative predictive value) - these are already established for the NGS gene panels likely to be used for this test purpose.
- Diagnostic yield

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health harms

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Health harms

- P/LP variants are found yet there is incomplete penetrance and no later cancer diagnosis (over-surveillance)
- Test-related adverse events
- Consequences of false positive/negative results

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Resources

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Resources

- Costs of cascade testing and counselling
- Increased surveillance and management for biological relative carriers detected
- Cost-effectiveness (cost per diagnosis, cost per QALY)
- Total Australian Government healthcare costs

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Value of knowing

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Other relevant considerations

- Value of knowing (emotional benefits and harms to family, family planning, social benefits and harms to family)
- Ethical considerations (equity of access, considerations regarding informed consent, considerations regarding cascade testing, including notification of carrier status).

Proposed MBS items

How is the technology/service funded at present? (e.g., research funding; State-based funding; self-funded by patients; no funding or payments):

State-based funding, or self-funded by patients or referral/testing not offered

Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:

MBS item number (where used as a template for the proposed item)	73297
Category number	6
Category description	Pathology Services
Proposed item descriptor	<i>This application proposes simplifying the descriptor for MBS item 73297: the proposed rewording will encompass cascade testing in the biological relatives of prostate cancer patients as proposed in this application, while also linking more directly to affected individual testing under 73296 to futureproof for any future expansions to that testing.</i> Characterisation of known germline gene variants, including copy number variation, in genes encompassed by item 73296, requested by a specialist or consultant physician, for a patient: (a) who has a biological relative with a pathogenic or likely pathogenic variant identified in one or more of those genes; and (b) who has not previously received a service to which item 73295, 73296 or 73302 applies. Once per variant
Proposed MBS fee	Same as current MBS fee for item 73297 (As of March 2026; Fee: \$400.00 Benefit: 75% = \$300.00 85% = \$340.00)
Indicate the overall cost per patient of providing the proposed health technology	\$400.00
Please specify any anticipated out of pocket expenses	\$0.00
Provide any further details and explain	Gap fee is unlikely to be charged.

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

This population does not require any testing prior to becoming eligible for the proposed health technology, as their eligibility is pursuant to their relative being diagnosed with prostate cancer and having a germline P/LP variant detected (proposed in PICO set 1).

However, the cascade population would need to see a health practitioner, such as their GP for a referral to a clinical genetics service or familial cancer centre, and receive pre-test counselling from a genetics counsellor or other health practitioner specialising in genetics prior to completing genetic testing. From a health resourcing perspective, this would result in an increase in the total healthcare costs for the additional primary care appointments and genetics counselling services for this population.

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

Yes

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

The key difference is the additional primary care appointment to obtain a referral to the cancer genetics service and the subsequent appointment(s) at the cancer genetics service.

Under the comparator health technology scenario (no cascade testing), these individuals would not attend these appointments as they would not undertake cascade testing. If they have had another relative diagnosed with a relevant cancer type (such as breast or ovarian cancer), they may be already eligible for cascade testing in cancer predisposition genes under current item 73297.

The expansion of cascade testing to include the relatives of individuals diagnosed with prostate cancer with a germline P/LP variant in a cancer predisposition gene supports proactive risk management to minimise downstream healthcare costs related to advanced cancer stage at diagnosis.

USE OF THE HEALTH TECHNOLOGY

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

A tissue sample (blood or buccal) would need to be collected for cascade testing. This process could involve phlebotomists, nurses, pathology collection staff, and/or practice staff.

The sample would be tested at an accredited laboratory, which would involve a multidisciplinary team of pathologists, scientists, laboratory technicians and clinical genetics specialists.

Genetic counselling post-test would also be provided in conjunction with cascade testing.

Explain what other healthcare resources are used in conjunction with the comparator health technology:

No healthcare resources are used in the comparator health technology (no cascade testing). When cascade testing does not take place, a tissue sample is not collected, and genetic counselling does not take place.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

The proposed health technology requires pre- and post-test genetic counselling, data collection, sample collection and analysis whereas none of these are required where no cascade testing is undertaken (comparator).

The staff, facilities, and equipment required to deliver the proposed health technology are already established in clinical practice, and in the absence of an MBS listing this is funded through existing public, private healthcare, and self-funding arrangements. Implementation is therefore expected to result in only a modest increase in healthcare resources proportionate to the additional population becoming eligible for cascade testing, as large-scale infrastructure setup and/or changes in practice are not anticipated.

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the proposed health technology:

After completing cascade testing, individuals will attend a post-test appointment to discuss their results and receive genetic counselling from a genetic counsellor or health practitioner specialising in genetics. Their subsequent clinical management would depend on the genetic test result.

For individuals with a negative result (known germline P/LP variant not identified), their cancer risk is reduced to likely population risk unless other factors apply. The negative result provides more complete information to inform shared decision-making on cancer surveillance and helps avoid unnecessary interventions. These individuals would continue to be offered surveillance as per clinical recommendations relevant to their individual circumstance, such as additional family history and personal risk factors (RACGP). A negative result can also reduce anxiety related to cancer risk (Bancroft et al., 2024).

Individuals with a positive result would have increased risk of cancer related to the P/LP variant identified. Changes in clinical management for these individuals would be recommended based on guidelines for the specific genetic variant, and may include earlier and/or increased surveillance, enhanced imaging (e.g. breast MRI), and risk-reducing medication or surgery. A positive result can also inform reproductive decision-making. If resulting changes in clinical management lead to earlier cancer detection, there may be reduced need for systemic therapy and less extensive surgery. If there is later cancer detection, treatment recommendations would remain based on standard of care.

Increased surveillance and management

Some variant-positive first-degree relatives will take up risk-reducing surgery: more often for *BRCA1/2*-positive relatives, although some carriers of P/LP variants in *ATM*, *PALB2* and *CHEK2* may also consider this. This will result in increased healthcare resources compared to the

comparator of no cascade testing (Table 4), but may also decrease healthcare resources from later cancer care avoided.

Table 4: Risk-reducing surgeries in *BRCA* positive first-degree relatives of a proband

Risk-reducing surgery	Probability of having the surgery	RR of breast cancer post-surgery	RR of ovarian cancer post-surgery
Mastectomy	0.3	0.114 +/- 0.07	(Not reported)
Salpingo-oophorectomy	0.53	0.55 +/- 0.06	0.20 +/- 0.04
Mastectomy + salpingo-oophorectomy	0.17	0.114 +/- 0.07	

Source: (Teppala et al., 2025), Table 1.

Each RR describes the likelihood of developing cancer in first-degree relatives who do vs do not undergo the surgery in question. The RR for mastectomy + salpingo-oophorectomy is for the combined risk of breast or ovarian cancer.

RR = relative risk

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the comparator health technology:

In the absence of cascade testing, individuals would receive standard of care. This would include screening and surveillance offered as per clinical recommendations relevant to their individual circumstances, based on family history and personal risk factors. These risks assessments would not be as precise without genetic testing to confirm the presence or absence of a known familial variant.

Describe and explain any differences in the healthcare resources used after the proposed health technology vs. the comparator health technology:

Compared to the world without affected individual or cascade testing, cascade testing results in a range of changes in management as recommended in clinical guidelines, with concomitant changes in healthcare resources. Patients and clinicians can be confident in either the negative or positive result, and whether the familial risk applies to them. This provides optimal information for shared decision-making about clinical management underpinned by evidence. MBS-funded cascade testing will enable surveillance to be targeted to those relatives who stand to benefit the most, rather than surveillance being based on family history alone.

No cascade testing available

If cascade testing is unavailable, the familial and individual risk estimates are less precise and based on the family history and personal risk factors. Depending on the risk assessment, healthcare resource use is more likely to be confined to surveillance and less invasive procedures, as patients and clinicians are less likely to consider risk-reducing interventions if there is uncertainty about the benefit-risk ratio. There will therefore be potential for both over- and under-surveillance and intervention.

Cascade testing available: variant-negative versus variant-positive

Variant-positive relatives will undergo more intensive surveillance and/or interventions per the clinical guidelines for management for carriers of that gene variant, whereas variant-negative relatives will undergo less intensive surveillance and no cancer risk-reducing or reproductive interventions because their risk reduces to population level risk unless other factors apply. For variant-negative relatives population-level surveillance is recommended, and these patients do

not require other support services such as ongoing familial cancer carrier review programs, fertility services or psychological supports.

Cascade testing available: variant-positive

Increased surveillance in variant-positive relatives, together with the uptake of risk-reducing interventions, is anticipated to result in higher use of healthcare resources in this segment of the cascade testing population compared with the comparator (no cascade testing). This includes more frequent screening, diagnostic imaging, pathology, specialist consultations, and planned preventive interventions such as intensified surveillance, risk-reducing medications, or elective risk-reducing surgery. Within this context, enhanced surveillance is also likely to lead to a higher number of cancer diagnoses initially, reflecting earlier detection rather than a true increase in incidence. Cancer diagnoses are associated with additional appointments and investigations at the point of diagnosis.

However, earlier detection of cancer can increase the effectiveness of treatments, and may reduce the need for systemic therapy and extensive surgery, leading to less morbidity and improved survival. This may reduce downstream healthcare resource utilisation and costs compared with the comparator, where in the absence of cascade testing, individuals may not be identified early, and so may be later diagnosed with more advanced stage cancer.

The following recommendations are more likely for variant-positive biological relatives compared with those either not having testing (the comparator) or testing negative

- **PSA testing:** Based on current guidelines, individuals at moderately raised risk of prostate cancer due to family history should be offered biennial PSA testing from age 45 to 69 years old (RACGP). Individuals at high risk of prostate cancer should be offered this testing from age 40 to 69 years old. Current guidelines recommend those at population risk (including individuals who do not have a germline P/LP variant identified by cascade testing) should be offered this testing from 50 to 69 years old. This results in an additional 3-5 PSA tests per variant-positive relative. The health resources affected by an increase in PSA testing volume include primary care and pathology services, and downstream services related to abnormal PSA testing results, including urology outpatient consultations or private urology appointments, diagnostic imaging services, prostate biopsy procedures and associated pathology services, and psychosocial and supportive care services such as patient counselling.
- **Breast cancer screening:** Individuals at risk of breast cancer are recommended to commence screening as early as from age 25-30 years (eviQ), depending on the gene involved and CanRisk assessment. Genetic test results are factored into CanRisk and a positive result is likely to increase the risk assessment to the >30% risk level for eligibility for an MBS-funded MRI. There is likely to be increased utilisation of breast MRI (or contrast-enhanced mammography or ultrasound, if MRI is not possible) for the additional variant-positive individuals identified by the proposed expansion to cascade testing. Breast imaging is recommended to be completed annually in this cohort. The health resources affected by an increase in breast cancer surveillance include primary care and radiology services, and downstream services related to abnormal results, including pathology services, outpatient or private breast surgery or oncology appointments, and psychosocial and supportive care services such as patient counselling.
- **Risk-reducing medication:** Those who test positive will have a higher risk assessment than those testing negative and may be recommended to take risk-reducing medication. This is likely associated with an increase in utilisation of primary care and specialist

consultations for prescriptions or management of adverse effects, as well as increased pharmaceutical resource use due to more people being identified as eligible (without eligibility criteria proposed to change). Uptake of risk-reducing medication is relatively low, especially if there is uncertainty about the risk assessment.

- **Risk-reducing surgery:** Individuals at risk of breast, uterine and ovarian cancers may be recommended risk-reducing surgery, such as bilateral mastectomies, hysterectomy and/or salpingo-oophorectomy (eviQ). A positive genetic test result provides greater confidence in the risk assessment regarding the potential benefits of these interventions. This would correspond with an increased utilisation of specialist consultations, peri-operative resources such as imaging, pathology, and anaesthetic assessment, surgical and hospital resources (nursing and surgical workforce, operating theatre time, hospital beds, surgical consumables), and post-operative care. A health economic assessment of germline genetic testing in prostate cancer patients and their relatives suggested that of *BRCA* positive relatives, 30% would have risk-reducing mastectomy, 53% would have risk-reducing salpingo-oophorectomy, and 17% would have both (Teppala et al., 2025).
- **Psychosocial support:** Individuals may seek additional psychosocial support from their primary care practitioner, practice nurse or nurse practitioner, counsellor, or psychologist/psychiatrist, to help manage distress relating to their increased risk status. A negative result decreases distress.
- **Risk management review programs:** These are offered by Familial Cancer Clinics and Risk Management clinics for those who carry a pathogenic variant but not required for those who test negative.
- **Menopause clinic attendance:** Risk-reducing bilateral salpingo-oophorectomy for women who are premenopausal is more common in those testing positive compared with no test result. Menopause Clinic referrals for advice about mitigating the effects of a sudden menopause after surgery will thus be higher in those testing positive.
- **Fertility services:** Those testing positive may seek advice and utilise family planning options such as in vitro fertilisation and preimplantation genetic diagnosis to reduce the risk of passing the gene change on to any of their children.

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology

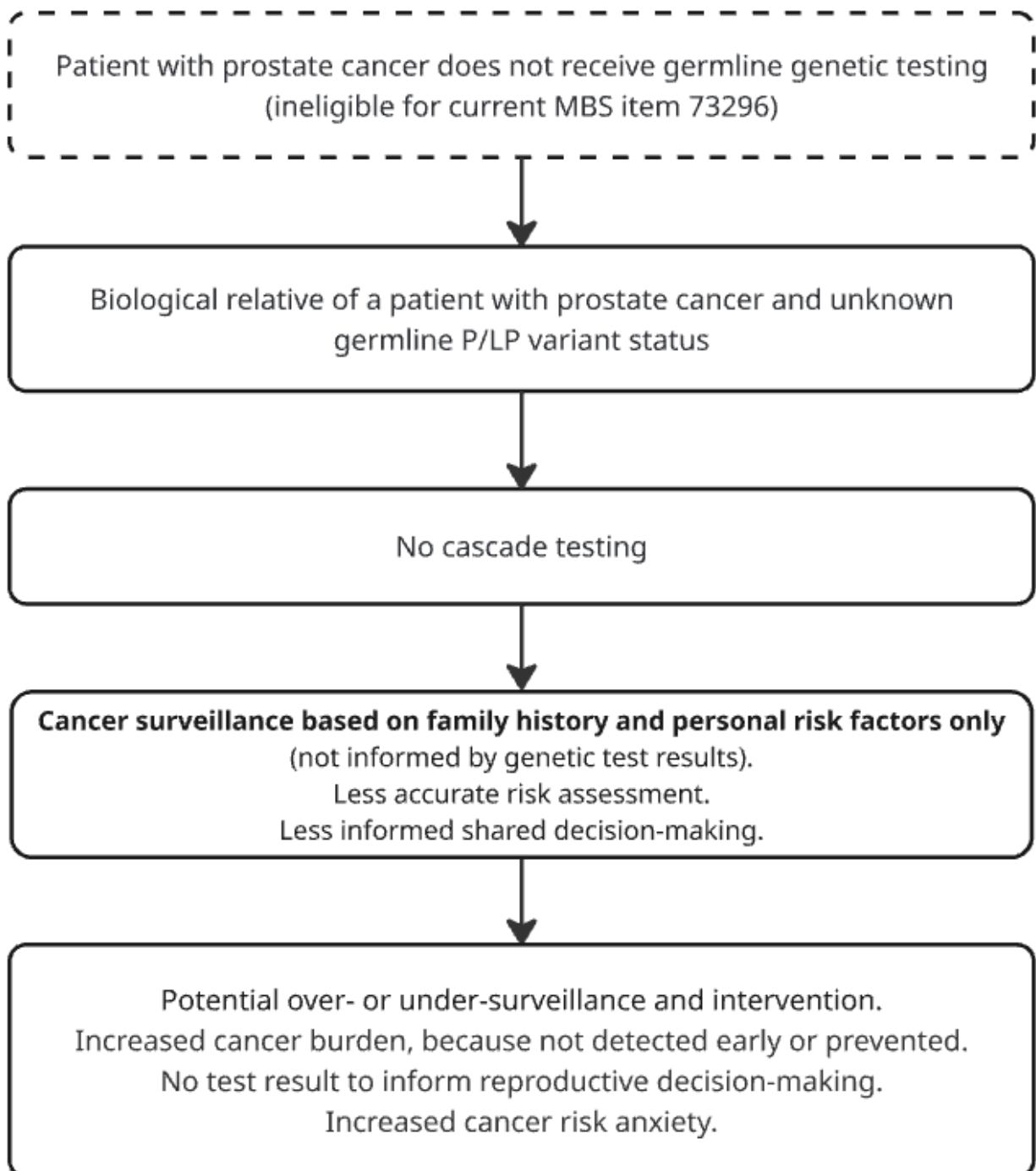


Figure 1: Current clinical management algorithm for biological relatives of a patient with prostate cancer.
P/LP = pathogenic or likely pathogenic.

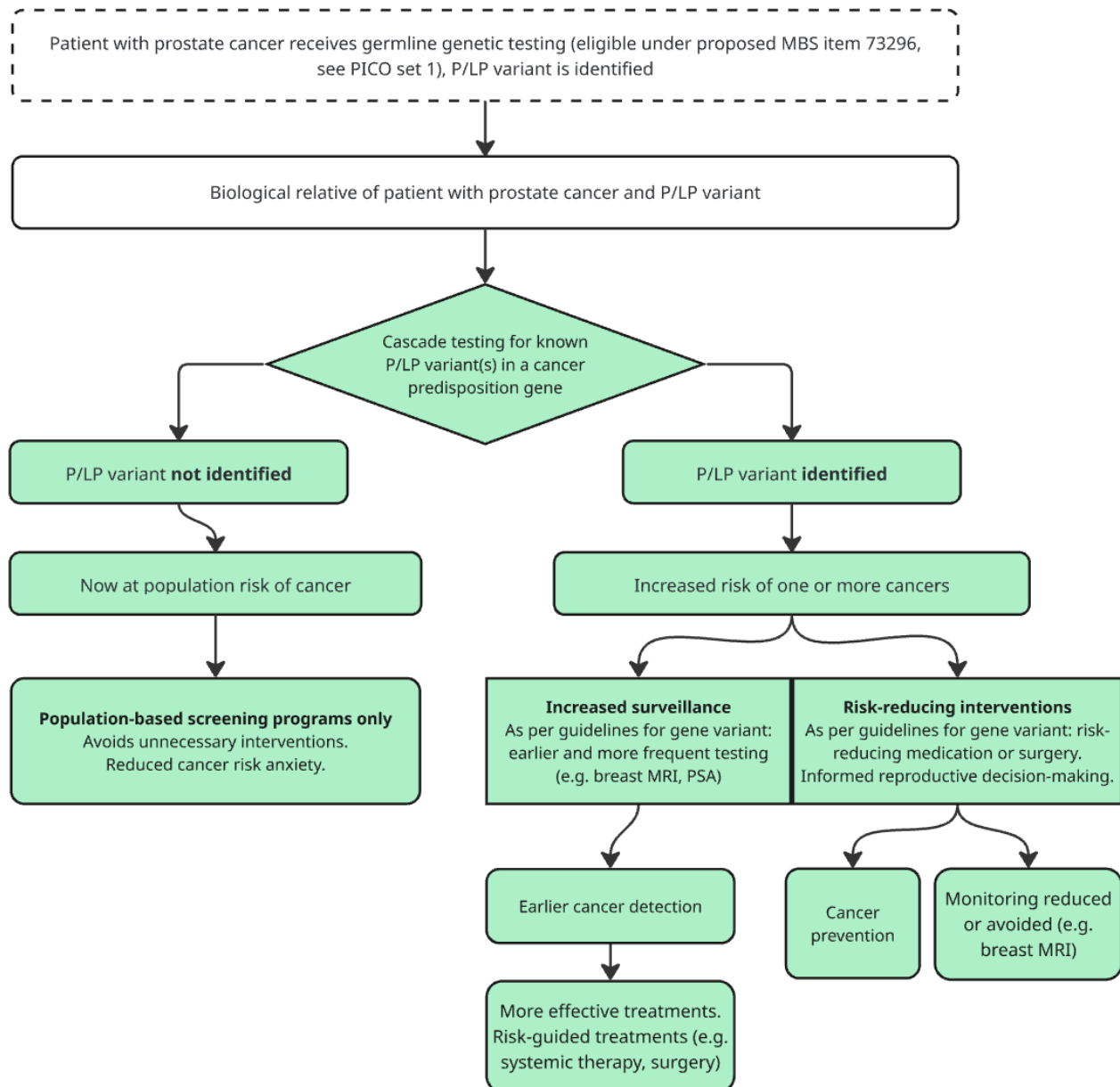


Figure 2: Proposed clinical management algorithm for biological relatives of a patient with prostate cancer and a known P/LP variant in a cancer predisposition gene.

Parts that differ between comparator and intervention are shown in green.

MRI = magnetic resonance imaging; P/LP = pathogenic or likely pathogenic; PSA = prostate-specific antigen.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

- ☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:

The proposed cascade testing is likely to have non-inferior safety and superior effectiveness in the biological relatives of patients with prostate cancer, compared to no cascade testing.

Safety is likely to be non-inferior because cascade testing introduces minimal additional physical or clinical risk beyond standard care. Germline genetic testing typically requires the collection of a biological sample, most commonly a minimally invasive or non-invasive sample such as blood or a buccal swab. These collection methods are routinely used in clinical practice and are associated with minimal risk to individuals. Psychological risks are associated with all genetic testing, and as per standard practice will be mitigated through genetic counselling.

Effectiveness is likely to be superior. The proposed cascade testing of biological relatives will enable increased surveillance of relatives found to have a germline P/LP variant. Identifying variant-positive family members also enables consideration of earlier and enhanced surveillance and risk-reducing interventions, along with informed reproductive decision-making. Individuals carrying P/LP variants in high-penetrance genes such as *BRCA1/2* may be candidates for enhanced breast surveillance with MRI, prompted to be aware of physical changes in the chest area, or recommended PSA testing at an earlier age (eviQ; eviQ; RACGP). They may also be eligible for risk-reducing medications, risk-reducing bilateral mastectomy and risk-reducing salpingo-oophorectomy, to lower their risks of breast and ovarian cancer (eviQ). Results may then influence clinical management, including treatment selection, eligibility for targeted therapies, and the intensity of ongoing monitoring.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

Biological relatives found to have a germline cancer predisposition variant are likely to experience improved health outcomes due to prevention of cancer through prophylactic surgery or risk reducing medications and earlier detection of cancer through increased surveillance. Cancers detected earlier may be more responsive to treatment leading to improved health outcomes. A health economic assessment of germline *BRCA* testing identified a QALY gain of 0.0003 from germline testing in prostate cancer patients alone, but a much greater health outcome improvement of 0.029 QALYs when cascade testing of their biological relatives was also included (Teppala et al., 2025).

Variant-negative biological relatives have their risk reduce to likely population level (unless other factors apply) – they do not require the same surveillance as variant-positive relatives, may avoid unnecessary interventions, and experience reduced anxiety.

There is also value of knowing for biological relatives who receive cascade testing, including emotional benefits and harms to family, family planning, social benefits and harms to family. Whether a relative tests positive or negative in cascade testing, their subsequent reproductive decision-making will benefit from being better informed. Variant-positive relatives will be able to use reproductive technologies (e.g. IVF) if desired.

Identify how the proposed technology achieves the intended patient outcomes:

Cascade testing will allow variant-positive relatives to undergo increased surveillance and screening, leading to earlier detection of cancer, and allowing earlier treatment when treatments are more effective. Cascade testing also enables variant-positive relatives to undertake preventative measures, such as risk-reducing medications and surgery, as detailed above.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management? Yes

A change in health outcome? Yes

Other benefits?

Yes

Please provide a rationale, and information on other benefits if relevant:

Cascade testing will allow variant-positive relatives to undergo increased surveillance and screening, leading to earlier detection of cancer, and allowing earlier treatment when treatments are more effective. Cascade testing also enables variant-positive relatives to undertake preventative measures, such as risk-reducing medications and surgery, as detailed above.

There will also be value of knowing from both positive and negative germline testing results.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?



More costly



Same cost



Less costly

Provide a brief rationale for the claim:

Cascade testing is more costly than no cascade testing.

If your application is in relation to a specific radiopharmaceutical(s) or a set of radiopharmaceuticals, identify whether your clinical claim is dependent on the evidence base of the radiopharmaceutical(s) for which MBS funding is being requested. If your clinical claim is dependent on the evidence base of another radiopharmaceutical product(s), a claim of clinical noninferiority between the radiopharmaceutical products is also required.

Not applicable

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
Cost-utility analysis	The cost-utility of targeted germline BRCA testing in localized prostate cancer followed by cascade testing first-degree relatives with pathogenic variants	This Australian study evaluated the cost-utility of germline <i>BRCA</i> testing in prostate cancer patients and their relatives. Testing patients with family history of prostate cancer yielded an ICER of \$3.9million/QALY, however adding cascade testing of first-degree relatives reduced the ICER to \$47,294/QALY.	Teppala et al (2025) https://doi.org/10.1016/j.gim.2025.101463	May 2025
Prospective study	Targeted Prostate Cancer Screening in Carriers of <i>BRCA1</i> or <i>BRCA2</i> Pathogenic Germline Variants Detects Clinically Relevant Disease: 5-year Results from the IMPACT Study	In the 5-yr outcomes from this international study (n=2929), <i>BRCA2</i> pathogenic germline variant carriers had higher incidence of clinically significant prostate cancer, diagnosis at a younger age and more high-risk disease than non-carriers. Annual PSA screening resulted in early diagnosis of high-risk prostate cancer in <i>BRCA1</i> pathogenic germline variant carriers.	Bancroft et al (2026) https://doi.org/10.1016/j.eururo.2026.01.031	February 2026
Review	Germline mutations in prostate cancer: a systematic review of the evidence for personalized medicine	This review article summarises evidence for risk of prostate cancers by germline variant and evidence that prostate cancer patients with germline variants in <i>BRCA1/2</i> and <i>ATM</i> are more likely to develop aggressive prostate cancer and die due to cancer at an earlier age.	Marino et al (2023) https://doi.org/10.1038/s41391-022-00609-3	November 2023

Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
Prospective, multinational study (incl Australia)	The psychosocial impact of prostate cancer screening for <i>BRCA1</i> and <i>BRCA2</i> carriers	In this study on longitudinal psychosocial impact of targeted prostate cancer screening, <i>BRCA1</i> (n=207) and <i>BRCA2</i> (n=265) carriers had higher prostate cancer worry than non-carriers (n=288) from families with known germline pathogenic variants. Overall, there was no evidence of clinically concerning levels distress, or poor health-related quality of life.	Bancroft et al (2024) https://doi.org/10.1111/bju.16432	June 2024
Prospective, multinational study (incl Australia)	A prospective prostate cancer screening programme for men with pathogenic variants in mismatch repair genes (IMPACT): initial results from an international prospective study.	In this longitudinal study of targeted prostate cancer screening, <i>MSH2</i> (305) and <i>MSH6</i> (135) carriers had higher rates of prostate cancer detected than non-carriers. The incidence among <i>MSH2</i> carriers was 4.3% (13 of 305; 95% CI 2.3-7.2), <i>MSH2</i> non-carrier controls was 0.5% (one of 210; 0.0-2.6), <i>MSH6</i> carriers was 3.0% (four of 135; 0.8-7.4), and none were detected among the <i>MLH1</i> carriers, <i>MLH1</i> non-carrier controls, and <i>MSH6</i> non-carrier controls.	Bancroft et al (2021) 10.1016/S1470-2045(21)00522-2	October 2021
Clinical practice guideline	Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline	These clinical guidelines provide recommendations for risk reduction and screening in HBOC, focussing on unaffected carriers of pathogenic variants. They include lifetime risks for a range of cancer types by germline variant status in cancer predisposition genes including <i>ATM</i> , <i>BRCA1</i> , <i>BRCA2</i> , <i>CHEK2</i> , <i>PALB2</i> , <i>TP53</i> .	European Society for Medical Oncology (ESMO) Guidelines Committee et al., 2023 https://doi.org/10.1016/j.annonc.2022.10.004	January 2023

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

None identified.

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