

Medicare-funded cancer genetic tests: a note of caution

Clinicians need appropriate education and support in keeping pace with the genomics revolution

Media headlines stating that genetic testing for patients with a high risk of breast and ovarian cancer are now free are somewhat misleading. Clinical genetic testing for heritable, germline mutations (pathogenic variants) in two major genes (*BRCA1* and *BRCA2*) that are associated with a high risk of breast and ovarian cancer came into Australian practice in the mid-1990s, and were offered free of charge (but not under Medicare) to appropriate patients in public clinics. Until now, testing, which has proven clinical utility,¹ has mostly been offered through a network of family cancer clinics and genetics services that provide expert genetic counselling and testing of these genes in the context of familial breast and ovarian cancer.

Testing is appropriate when there is at least a 10% chance of identifying a gene mutation responsible for the personal or family history of cancer. When the chance of detecting a mutation is less than 10%, self-funded *BRCA1* and *BRCA2* testing has been available in public or private genetic services. To help decide whether testing is appropriate, there are several algorithms to calculate the mutation probability (Box 1).

The change referred to in the media is that these tests are now being mainstreamed and they can be ordered for selected patients, with a new Medicare benefit, by non-genetic specialists in either public or private practice. While the proven benefits to selected families underscore the importance of broadening the availability of appropriate genetic testing, it is also essential that any clinician who orders breast cancer genetic testing understands the complexities and implications generated.

In general, the process of genetic testing in a family begins by testing an individual with cancer (usually with a high risk family history) and searching their *BRCA1* and *BRCA2* genes for a causative mutation. If a mutation is found, then other adult at-risk genetic relatives (male or female) can be offered predictive genetic testing for this family-specific mutation. Relatives who have inherited the family mutation are confirmed to be at higher risk of cancer (and will benefit from tailored screening and prevention), whereas relatives who have not will usually remain at the background risk for breast and ovarian cancer (depending on the cancer history on the other side of the family).

When a mutation is not found using the initial mutation search in an affected family member, this negative result is not truly negative, but rather is uninformative. No predictive test can be done for family members if that is the case. There are many families with a strong family history for which there must be some genetic cause, and yet it cannot be found. Limitations in knowledge and technology need to be understood, and individuals from these families remain at potentially high risk. Such uninformative results require careful counselling so that

families (and their clinicians) are not falsely reassured by the “no mutation found” result.

Only 5% of female breast cancers, 15% of invasive epithelial ovarian cancers and up to 14% of male breast cancers are related to *BRCA1* or *BRCA2* mutations, thus, most patients with breast cancer do not need, nor will they benefit from, a genetic test. *eviQ* — a Cancer Institute NSW repository of evidence-based cancer treatment protocols and information — has published nationally agreed protocols for genetic testing.² These outline criteria that aim to achieve a maximum pick-up rate of mutations while avoiding unnecessary expense to the health system.

New funding model for genetic testing: Medicare

Since 1 November 2017, any specialist or consultant physician (in public or private practice) can order genetic testing for breast and ovarian cancer under certain criteria, covered by the Medicare Benefits Schedule (MBS) (Box 2).

Item 73296

Below, there are several notes of importance in regards to ordering this test.

Calculation of eligibility for the Medicare benefit. Eligibility is based on a quantitative algorithm giving the person being tested an over 10% chance of having a pathogenic mutation identified if testing is done. Requestors need to be familiar with the freely available algorithms (Box 1).

Interpretation of genetic variants. Small differences in DNA sequence account for the variation we see between individuals, including differences in hair, eye and skin colour; height; body shape; and susceptibility to disease. If a laboratory identifies a variant in a gene, it needs to determine if it is a harmless change (benign: a polymorphism) or harmful (disease causing: a mutation). However, the human genome is complex and classification of variants is not always straightforward.

Although there is a proposed standardised reporting system⁶ (with five classes of variants based on the degree of likelihood of pathogenicity), in Australia there is no nationally consistent approach to reporting variants. With the new MBS item numbers, it is likely that smaller laboratories, less familiar with the interpretation of sequence variants, may offer testing.

Uncertainty of pathogenicity. About 10% of *BRCA1* and *BRCA2* tests result in the identification of a variant of uncertain significance (VUS) that cannot be clearly classified as either benign or disease causing. The VUS rates are higher for the other five, less well studied genes included in the MBS item descriptor. Although *BRCA1*

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1 Algorithms to determine chance of finding a *BRCA1* or *BRCA2* gene mutation

Manchester Score ^{2,3}	<p>A simple, paper-based scoring system that estimates the probability of a <i>BRCA1</i> and <i>BRCA2</i> gene mutation:</p> <ul style="list-style-type: none"> • The individual being tested and all their relatives with cancer are allocated a numerical score weighted by the cancer type, cancer histopathology and age at diagnosis • The scores for the individual and the relatives on the same side of the family are added and then converted into a percentage chance of finding a mutation in that individual. For example: <ul style="list-style-type: none"> ▶ A woman with triple negative breast cancer at age 29 years (and no family history) scores +11 for being under 30 years at diagnosis, +2 for high grade pathology and +4 for triple negative histology. The total of 17 equates to an over 10% chance of finding a <i>BRCA1</i> or <i>BRCA2</i> gene mutation. Genetic testing for this woman would be covered by MBS item 73296 ▶ For a woman with grade 2, ER-positive breast cancer at age 46 years, the Manchester score gives a low chance of a mutation (+6 + 0 – 1 = +5) unless there is an accompanying strong family history of breast or ovarian cancer. In the absence of a family history, this woman would not meet the descriptor for MBS item 73296
BOADICEA Score ⁴	<p>A statistical model, with a free web-based application, for assessing the probability that an individual carries a pathogenic mutation in one of a small group of a breast cancer-related genes (including <i>BRCA1</i> and <i>BRCA2</i>) based on personal and family history of breast and ovarian cancer:</p> <ul style="list-style-type: none"> • It takes into account family cancer history, age at diagnosis, cancer pathology and family structure • It may be a more accurate predictor of mutation status than the Manchester score, but it requires a computer, additional training and takes significantly more time • It is currently limited to research use because of new regulatory issues in the United Kingdom
BRCAPRO Score ⁵	<p>A statistical model, with associated software, for assessing the probability that an individual carries a pathogenic mutation in the <i>BRCA1</i> and <i>BRCA2</i> genes based on cancer history, age at diagnosis and family history:</p> <ul style="list-style-type: none"> • It requires a computer, additional training and time

BOADICEA = Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm. MBS = Medicare Benefits Schedule. ◆

and *BRCA2* are two of the most commonly analysed human genes, after 20 years of testing, there is still argument about the classification of some variants as to pathogenicity. The identification of VUS will continue to pose considerable challenges to both the laboratory and the clinician who orders a genetic test. In the face of a VUS, the ordering clinician should be able to explain the uncertainty, but can refer the patient to a clinical genetics service for expert assistance.

Even when a variant is clearly pathogenic, genetic counselling sessions can take a long time to address both the personal and familial implications of the result. The identification of a VUS adds complexity to these sessions and may cause confusion for clinicians and

patients, particularly when a clinician has limited experience with the nuances of genetic testing. In fact, misinterpretation of *BRCA1* or *BRCA2* genetic test results has already resulted in inappropriate surgery (including bilateral mastectomy), with legal consequences.^{7,8} Genetic counsellors and genetics specialists have specific expertise in explaining the possible clinical, psychosocial and familial implications, and the uncertainties of a VUS to the patient, their family and their doctors.

Testing of other genes covered by the item number. The item number covers testing for some other genes (in addition to *BRCA1* and *BRCA2*): *PALB2*, *STK11*, *PTEN*, *CDH1* and *TP53*. Importantly, inclusion in the item

2 New Medicare Benefits Schedule item descriptors

Item 73295	“Detection of germline <i>BRCA1</i> or <i>BRCA2</i> gene mutations, in a patient with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer, with high grade serous features or a high grade serous component, and who has responded to subsequent platinum-based chemotherapy, requested by a specialist or consultant physician, to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme are fulfilled. Maximum of one test per patient’s lifetime”
Item 73296	“Characterisation of germline gene mutations, requested by a specialist or consultant physician, including copy number variation in <i>BRCA1</i> and <i>BRCA2</i> genes and one or more of the following genes <i>STK11</i> , <i>PTEN</i> , <i>CDH1</i> , <i>PALB2</i> , or <i>TP53</i> in a patient with breast or ovarian cancer for whom clinical and family history criteria, as assessed by the specialist or consultant physician who requests the service using a quantitative algorithm, place the patient at > 10% risk of having a pathogenic mutation identified in one or more of the genes specified above”
Item 73297	“Characterisation of germline gene mutations, requested by a specialist or consultant physician, including copy number variation in <i>BRCA1</i> and <i>BRCA2</i> genes and one or more of the following genes <i>STK11</i> , <i>PTEN</i> , <i>CDH1</i> , <i>PALB2</i> , or <i>TP53</i> in a patient who is a biological relative of a patient who has had a pathogenic mutation identified in one or more of the genes specified above, and has not previously received a service under item 73296”

Source: Medicare Benefits Schedule Online (<http://www9.health.gov.au/mbs/search.cfm>). ◆

3 Genes, other than *BRCA1* and *BRCA2*, included in Medicare Benefits Schedule item 73296²

<i>STK11</i>	<ul style="list-style-type: none"> • Germline mutations in <i>STK11</i> are associated with Peutz–Jeghers syndrome (PJS),— an autosomal dominant genetic disorder characterised by benign gastrointestinal hamartomatous polyps, pigmented macules on the lips or oral mucosa, and a high risk of intestinal cancer • PJS mostly presents early in life with anaemia, rectal bleeding, abdominal pain, obstruction and/or intussusception • The diagnosis is usually made clinically without the need for a genetic test • Women with PJS have a poorly defined but increased risk of breast cancer • If an <i>STK11</i> mutation is detected in a woman with breast cancer but no other features of PJS, the relevance of the mutation is uncertain
<i>PTEN</i>	<ul style="list-style-type: none"> • Germline mutations in the <i>PTEN</i> gene cause a group of related clinical phenotypes that are collectively called <i>PTEN</i> hamartoma tumour syndrome (includes Cowden syndrome) • There is a high risk of benign and malignant tumours of the thyroid, breast and endometrium • Affected individuals usually have macrocephaly and specific skin lesions (trichilemmomas) • It may be associated with childhood autism • The diagnosis is often made clinically without the need for a genetic test • Testing this gene in a woman with breast cancer outside the context of this clinical scenario may lead to findings of uncertain significance
<i>CDH1</i>	<ul style="list-style-type: none"> • Germline mutations in <i>CDH1</i> cause hereditary diffuse gastric cancer • There is no good screening test for diffuse gastric cancer • As the lifetime risk of diffuse gastric cancer is very high, prophylactic gastrectomy is indicated at a young age • Female mutation carriers also have a high risk of lobular type breast cancer • When a <i>CDH1</i> mutation is found in a familial breast cancer context, the result may be confronting, particularly as the gastric cancer risk and ideal cancer risk management is much less certain in the absence of a family history of diffuse gastric cancer
<i>TP53</i>	<ul style="list-style-type: none"> • Li–Fraumeni syndrome (LFS) is caused by germline mutations in the <i>TP53</i> gene • In classical LFS mutation, carriers have a very high risk of various cancers, including early onset breast cancer, sarcoma, haematological malignancy, brain, adrenal and other tumours • The cancer risk begins in childhood • The range of malignancies, their early onset and (except for breast cancer) the lack of effective cancer screening raise a number of issues about the utility of testing • Some individuals, when fully informed, decline testing of <i>TP53</i>

number does not mandate testing these genes when *BRCA1* or *BRCA2* are tested.

PALB2 is a well established breast (probably not an ovarian) cancer-related gene. Except for one particular mutation (*PALB2* c.3113G>A) associated with a higher risk, in most families, germline mutations in *PALB2* are associated with only a moderate risk of breast cancer. Some variants in *PALB2* are not associated with breast cancer at all and this is often misunderstood.

STK11, *PTEN*, *CDH1* and *TP53* should only be tested if there are clinical indicators that they might be involved. Testing outside the clinical syndromes described in Box 3 should be approached with caution, as experience with testing of these genes and managing the medical and psychosocial consequences requires specialised training.

While ultimately all of these genes (and others, such as mismatch repair genes) may be included in a “breast/ovarian cancer panel” of genes, the testing of multiple genes may uncover unclassified variants, variants outside the usual clinical context, variants unrelated to the current cancer, or unexpected important variants for which the patient has not been well prepared.

Item 73297

This item number would, at first glance, seem to be fairly straightforward as it covers the predictive test for the family-specific mutation.

A critical prerequisite for this testing is a copy of the genetic test report from the family member in whom the mutation was identified, so the local laboratory knows which specific genetic variant to test for and can confirm if the variant is disease causing and not a VUS or a benign variant.

Laboratory requirements for predictive testing. The item descriptor allows for a predictive genetic test to be ordered by any specialist or consultant physician. However, laboratories undertaking clinical testing need to be accredited by the National Association of Testing Authorities Australia and, therefore, governed by the requirements from the National Pathology Accreditation Advisory Council. The Council considers this predictive testing to be a level 2 DNA test (with potential to lead to complex clinical issues).⁹ In other words, it is a test “... for which specialised knowledge is needed for the DNA test to be requested, and for which professional genetic counselling should precede and accompany the test,” and “specific written consent and counselling issues are associated with this grouping”.⁹ While the laboratories may not need to sight the consent form, the clinician must indicate that consent has been given on the request form. The guidelines from the Human Genetics Society of Australasia (www.hgsa.org.au/documents/item/1574) recommend the use of a consent form; however, approved consent forms vary from state to state. Liaison with family cancer clinics may be helpful for ordering clinicians.

4 Breast cancer genetic tests: key points

- Genetic testing is not necessary for most women with breast cancer, but it should be considered in those with breast cancer at a younger age and those with a relevant family history
- From 1 November 2017, several new Medicare Benefits Schedule (MBS) item numbers cover the cost of breast and ovarian cancer-related genetic testing, when the defined criteria are met
- Eligibility for the MBS rebate is based on a quantitative algorithm indicating that the patient is at > 10% risk of having a pathogenic mutation identified
- The item numbers cover testing for heritable germline mutations in seven genes:
 - ▶ the two major genes involved in breast and ovarian cancer predisposition (*BRCA1* and *BRCA2*);
 - ▶ the breast (but probably not ovarian) cancer predisposition gene *PALB2*; and
 - ▶ four genes (*STK11*, *PTEN*, *CDH1* and *TP53*) in which mutations are associated with breast cancer, but which often present with a non-breast cancer phenotype.
 Testing of these additional genes in the absence of the usual syndrome features should be approached with caution (Box 3)
- Genetic testing is complex and the identification of variants of uncertain significance (VUS) in cancer genes is a major challenge. The more genes you test, the more VUS you will find
- The clinician who orders the test must be able to interpret the results and communicate the implications of the results, including the uncertainties, to the patient and their genetic relatives
- Patients must be well informed and written consent is required before genetic testing

Item 73295

This test is relatively straightforward and not discussed here.

Conclusion

The new Medicare item numbers available for breast and ovarian cancer-related genetic testing are an important step forward in facilitating the transition to mainstream genetic testing coordinated by non-genetic health professionals. This article aims to highlight the benefits of mainstream testing, but also to alert non-genetic specialists about some important caveats regarding genetic testing (Box 4). Because genetic and genomic testing will soon be incorporated into many aspects of medical care, it is important that clinicians receive appropriate education

and support to enable safe, evidence-based practice in keeping pace with the genomics revolution. This will be optimised if ordering clinicians develop a close relationship with a local family cancer clinic or clinical genetics service, which are ideally placed, and willing, to educate and support non-genetic practitioners in the transition to mainstream genetic testing.

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