The Changing Landscape of Hereditary Breast and Ovarian Cancer Germline Genetic Testing in Australia

Lara Petelin¹, Paul A. James^{1,2}, Alison H. Trainer^{1,2,*}

1. Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and Royal Melbourne hospital
2. Department of Medicine, University of Melbourne

Lara Petelin: PhD student, Parkville Familial Cancer Centre

Paul A. James, Clinical Geneticist, Director, Parkville Familial Cancer Centre

Alison H. Trainer, Clinical Geneticist, Clinical Lead, Parkville Familial Cancer Centre

*Corresponding author: Assoc. Prof. Alison Trainer,
Clinical Geneticist
Parkville Familial Cancer Centre
Level 1, Peter MacCallum Cancer centre
305 Gratton St
Parkville 3000
Victoria
Tel: 03 855 95322

Word count: Abstract 87 wds

Word count: Main text 1500 wds

Abstract

Federal funding for germline genetic testing in hereditary breast and ovarian cancer (HBOC) was recently introduced. Germline testing for HBOC under MBS items 73296/73297 can be requested by any specialist, whereas the previous State- and Territory-funded testing was limited to those operating within a Familial Cancer Service (FCS). The impact of this decentralisation of HBOC testing on health and economic outcomes is uncertain, primarily as it has potential to significantly disrupt

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/imj.14058](https://doi.org/10.1111/imj.14058)

the clinical framework that generated the evidence used to justify clinical implementation of the MBS schedules.

On 1st November 2017, substantive Federal funding commenced for germline genetic testing in hereditary breast and ovarian cancer (HBOC) (MBS items 73296 and 73297). The rebates primarily target the most prevalent monogenic drivers of HBOC risk, *BRCA1* and *BRCA2*, and have been welcomed by patients and clinicians.

Implementation of these schedules highlights the strength of the cost-utility argument for detecting *BRCA* mutations in high-risk women with cancer, and offering predictive testing in unaffected relatives to stratify risk and target risk reduction strategies (1).

Whilst this announcement was heralded as improving access to publicly-funded *BRCA* testing in high-risk women, the real impact is likely to be more complex. Whether the anticipated economic benefits will be achieved, or health outcomes improved in this high-risk population, is uncertain. Both the MBS schedule formulations and their implementation have potential to disrupt the previous Australian HBOC clinical framework; the very framework which generated the evidence on which the economic model justifying the schedules was developed (MSAC 1411.1).

Medicare Schedule Items 73296 and 73297

MBS schedule 73296 rebates NATA-accredited laboratories for testing HBOC genes, *BRCA1/BRCA2*, and at least one of five other genes, *PALB2*, *TP53*, *CDH1*, *PTEN* and *STK11*. The test can be requested by any specialist for a woman with a personal history of breast and/or ovarian cancer, and a >10% probability of harbouring a *BRCA* mutation. The unit fee is AUD\$1200.

Medicare item 73297 rebates testing *BRCA1/2* and one or more of the five genes in a biological relative of a woman with a pathogenic mutation identified through MBS item 73296. The unit fee is AUD\$400.

These schedules shift both funding of HBOC testing from State/Territory to the Federal level, and oversight for the test from familial cancer services (FCS) to molecular laboratories. Patients'

eligibility for publicly-funded HBOC testing is unaltered, as the specified criteria are the same as those generally applied by Australian FCSs for several years (www.eviQ.org.au).

Clinical Validity and Utility of Item 73296 Gene Panel

The clinical validity of the MBS-schedule genes is well-evidenced. All seven genes show a clear association between germline mutations and a high breast cancer (BC) risk, with *BRCA1/BRCA2* having an additional association with ovarian cancer (OC). Current main cancer risks for mutation carriers are described in Table 1(2).

Clinical utility is a measure of test-derived health benefit within a specific clinical context and underpins clinical guideline development. It has four dimensions: legitimacy, efficacy, effectiveness and appropriateness (3); ‘appropriateness’ being a measure of expected benefit versus expected negative consequences (4). For *BRCA1/BRCA2*, *PALB2*, *STK11*, *PTEN* and *TP53*, the benefit of identifying a mutation and offering risk-reduction management is clear irrespective of family history, accepting the limited data for effective surveillance of other *TP53*-associated cancers (5). In contrast, the ‘appropriateness’ of *CDH1* in this context is contentious. *CDH1* mutations increase lobular BC risk but are associated predominantly with a high risk of diffuse gastric cancer (DGC) (Table 1) and it is only in the familial DGC context that Australian (www.eviQ.org.au) and international testing and management guidelines exist (6). When a *CDH1* mutation is found in this context gastrectomy is recommended from a young age. DGC risks in the absence of a DGC family history are unknown, whilst the morbidity associated with young-onset gastrectomy if offered out of context would be significant.

Whilst MBS schedule 73296 leaves to specialist discretion the precise genes other than *BRCA1/BRCA2* to be tested, this implies control over the test that laboratories offer, which is also indirectly impacted by this funding.

Clinical Molecular Interface

Most Australian FCS are situated in public-sector hospitals together with diagnostic molecular laboratories. This close relationship has benefits for interpreting and contextualising test results, including adapting tests to clinical setting and expediting testing when required. It is especially advantageous when variants of uncertain significance (VUS) are identified which occurs increasingly

frequently as gene panels expand. Such VUSs are jointly reviewed by clinical and molecular teams often resulting in reclassification of a VUS as benign or pathogenic, sometimes many years after initial testing.

An indirect effect of this new funding will be the accelerated entry of private pathology providers into the genetic testing market. In setting the rebate so high, Medicare, as sole public funder, has not challenged test costs – at our institution, Peter MacCallum Cancer Centre, self-funded panel tests cost substantially less than the Medicare rebate well before November the 1st – but has provided a financial incentive for private laboratories. There is a risk that federal funds that might have acted to broaden eligibility criteria and improve access to testing will instead end as profits for private pathology providers.

Decentralising provision of HBOC testing

Demand for HBOC testing comes from cancer-affected and unaffected individuals with a family cancer history who wish to determine their future cancer risk, and access risk-appropriate mitigation strategies. Genetic testing is one element of hereditary risk assessments undertaken by FCSs, who comprise multidisciplinary teams; clinical geneticists, genetic counsellors, oncologists and other familial cancer specialists. Verifying self-reported family cancer histories is key to providing accurate risk assessments and is undertaken by the FCSs through obtaining pathology reports or cross-matching against cancer registries. The assessments determine: 1) which, if any, family member reaches the HBOC testing threshold, 2) the appropriate test, and 3) the residual cancer risk and management required when no mutation is detected.

FCSs foster intergenerational communication between relatives and provide a resource containing all national diagnostic HBOC test results. They offer a long-term follow-up and support structure to families, especially to young unaffected women making risk-reducing surgery decisions many years after their test result. This clinical framework underpins the high uptake of OC risk-reducing bilateral salpingo-oophorectomy (RRBSO) in *BRCA* mutation carriers which has risen from 80% (the figure used in the MSAC economic evaluation (MSAC 1411.1 and in (1))) to > 90% in recent years (7). The new schedules enable any specialist to request both mutation search and predictive HBOC tests, but whether other specialist clinics can provide the long-term support needed to sustain these rates is unknown. As the minimum RRBSO uptake threshold in the MSAC sensitivity analysis was still 68%,

should this rate drop significantly, the impact on health outcomes and cost-effectiveness could be marked.

An important driver of decentralisation is the increasing use of test results to determine treatment in women newly diagnosed with breast/ovarian cancer; mutation carriers are commonly offered bilateral mastectomy rather than breast-conserving surgery, the option of platinum-based systemic therapy(8) and access to *BRCA*-related clinical trials. The new funding will have its greatest clinical impact here, by decreasing the time from diagnosis to test result.

This prioritisation of treatment-focussed testing (TFT), whilst deemphasising a centralised testing framework and increased testing in commercial laboratories mirrors the U.S. HBOC testing model.

Recent reviews of the U.S. system (9, 10) demonstrate that it does expedite genetic tests with two thirds being ordered prior to final breast surgery, but that lack of specialist knowledge limits optimal use of the test. From a clinical perspective, 50% of high-risk women were not tested as their specialist did not recommend it, suggesting their high-risk status went unrecognised. Such missed opportunities are reduced if a genetic opinion was sought (11). In contrast, 40% of women tested did not fulfil the U.S. high-risk HBOC criteria, which are less stringent than Australian (9, 10), as they were at population-risk. In addition, 24-50% of American surgeons reported - contrary to guidelines - treating women with *BRCA* VUSs no different to the women harbouring pathogenic mutations, resulting in a bilateral mastectomy rate of 51% in population-risk women with VUSs (9).

Specialists requesting a test through the private sector will lose significant clinical benefits accrued through validating cancer histories, recording family structures, and noting previous genetic testing within the family; information held within and across Australian FCSs. Uptake rates for predictive testing and risk-reduction strategies outside the FCS context are unknown, and by extension there is no evidence around the clinical and economic utility of HBOC testing under alternative clinical models.

Mainstreaming Familial Cancer Testing

An alternative TFT model being initiated in Australia FCSs is 'Genetic Mainstreaming'. This approach integrates genetic testing into oncology and surgical clinics whilst maintaining the coordination and follow-up of results by the FCS. This program involves an FCS-developed educational session for

specialists wishing to offer testing in their clinical setting, ensuring all testing adheres to best practice guidelines issued by the NHMRC(12), Human Genetics Society of Australasia(13) and National Pathology Accreditation Advisory Council(14). In this framework, patients receiving positive results or with high residual familial cancer risks are followed-up by the FCSs, allowing them to access skilled genetic counsellors along with recruitment to cancer-risk assessment and prevention research. Predictive testing for unaffected relatives remains FCS-based, utilising the family communication and long-term support developed by these services over more than 20 years.

A clinical framework that integrates specialist FCS expertise and oversight of test interpretation whilst increasing equity and speed of access to test results is in our view an optimal model for HBOC testing and continues to deserve support at both the Federal and local Government levels.

1. Tuffaha HW, Mitchell A, Ward RL, Connelly L, Butler JRG, Norris S, et al. Cost-effectiveness analysis of germ-line BRCA testing in women with breast cancer and cascade testing in family members of mutation carriers. *Genetics in medicine : official journal of the American College of Medical Genetics*. 2018.
2. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*. 2017;317(23):2402-16.
3. W. B, R. Z. Moving beyond ACCE: An expanded Framework for Genetic Test Evaluation 2007.

4. Kahn K.L., J. K., M.R. C, Flynn M-F, A. F, N. P, et al. Measuring the clinical appropriateness of a procedure; can we do it? *Med Care*. 1988;26(4):415-22.
5. Ballinger ML, Best A, Mai PL, Khincha PP, Loud JT, Peters JA, et al. Baseline Surveillance in Li-Fraumeni Syndrome Using Whole-Body Magnetic Resonance Imaging: A Meta-analysis. *JAMA Oncol*. 2017;3(12):1634-9.
6. van der Post RS, Vogelaar IP, Carneiro F, Guilford P, Huntsman D, Hoogerbrugge N, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. *Journal of medical genetics*. 2015;52(6):361-74.
7. Kearton S, Wills K, Bunting M, Blomfield P, James PA, Burke J. Cancer risk management in Tasmanian women with BRCA1 and BRCA2 mutations. *Familial cancer*. 2017.
8. Narod SA, Huzarski T, Gronwald J, Byrski T, Marczyk E, Cybulski C, et al. Predictors of survival for breast cancer patients with a BRCA1 mutation. *Breast cancer research and treatment*. 2017.
9. Kurian AW, Li Y, Hamilton AS, Ward KC, Hawley ST, Morrow M, et al. Gaps in Incorporating Germline Genetic Testing Into Treatment Decision-Making for Early-Stage Breast Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35(20):2232-9.
10. Kurian AW, Griffith KA, Hamilton AS, Ward KC, Morrow M, Katz SJ, et al. Genetic Testing and Counseling Among Patients With Newly Diagnosed Breast Cancer. *JAMA*. 2017;317(5):531-4.
11. Cohen PA, Nichols CB, Schofield L, Van Der Werf S, Pachter N. Impact of Clinical Genetics Attendance at a Gynecologic Oncology Tumor Board on Referrals for Genetic Counseling and BRCA Mutation Testing. *Int J Gynecol Cancer*. 2016;26(5):892-7.
12. NHMRC. <https://www.nhmrc.gov.au/files/nhmrc/publications/attachments/e99.pdf> accessed 15/02/2018 [
13. HGSA. <https://www.hgsa.org.au/resources/hgsa-policies-and-position-statements> accessed 15/02/2018 [
14. NPAAC. [https://www.health.gov.au/internet/main/publishing.nsf/Content/E688964F88F4FD20CA257BF0001B739D/\\$File/V0.25%20NAD%20Human%20Genetics.pdf](https://www.health.gov.au/internet/main/publishing.nsf/Content/E688964F88F4FD20CA257BF0001B739D/$File/V0.25%20NAD%20Human%20Genetics.pdf) Accessed 15/02/2018 [

Table 1: Current lifetime gene-specific common cancer risks (source: www.eviQ.org.au and Kuchenbaecker *et al*(2))

	Life time cancer risk to age 70(80 for BRCA) (%), (95% Confidence intervals)						
	BRCA1 ⁽²⁾	BRCA2 ⁽²⁾	PALB2	TP53	STK11	PTEN	CDH1
Breast	72 (65-79)	69 (61-77)	33-55	>85	45	>30	42 (23-68)
Ovary/fallopian tube	44 (36-53)	17(11-25)			11-26		
Pancreatic		<2					
Sarcoma				60			
Brain				20-30			
Colorectal					39		
Thyroid						Increased, >10	
Endometrial						Increased, >10	
Renal						Increased, >10	
Gastric					Increased		70, (59-80) (men) 56, (44-69) (women)

Abstract

Federal funding for germline genetic testing in hereditary breast and ovarian cancer (HBOC) was recently introduced. Germline testing for HBOC under MBS items 73296/73297 can be requested by any specialist, whereas the previous State- and Territory-funded testing was limited to those operating within a Familial Cancer Service (FCS). The impact of this decentralisation of HBOC testing on health and economic outcomes is uncertain, primarily as it has potential to significantly disrupt the clinical framework that generated the evidence used to justify clinical implementation of the MBS schedules.

The Changing Landscape of Hereditary Breast and Ovarian Cancer Germline Genetic Testing in Australia

Lara Petelin¹, Paul A. James^{1,2}, Alison H. Trainer^{1,2,*}

1. Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and Royal Melbourne hospital
2. Department of Medicine, University of Melbourne

Lara Petelin: PhD student, Parkville Familial Cancer Centre

Paul A. James, Clinical Geneticist, Director, Parkville Familial Cancer Centre

Alison H. Trainer, Clinical Geneticist, Clinical Lead, Parkville Familial Cancer Centre

*Corresponding author: Assoc. Prof. Alison Trainer,
Clinical Geneticist
Parkville Familial Cancer Centre
Level 1, Peter MacCallum Cancer centre
305 Gratton St
Parkville 3000
Victoria
Tel: 03 855 95322

Word count: Abstract 87 wds

Word count: Main text 1500 wds

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Petelin, L;James, PA;Trainer, AH

Title:

Changing landscape of hereditary breast and ovarian cancer germline genetic testing in Australia

Date:

2018-10-01

Citation:

Petelin, L., James, P. A. & Trainer, A. H. (2018). Changing landscape of hereditary breast and ovarian cancer germline genetic testing in Australia. INTERNAL MEDICINE JOURNAL, 48 (10), pp.1269-+. <https://doi.org/10.1111/imj.14058>.

Persistent Link:

<http://hdl.handle.net/11343/284578>