Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1411 – Clinical utility card for heritable mutations which increase risk in breast and/or ovarian cancer

Applicant: **Royal College of Pathologists of Australasia (RCPA)**

Date of MSAC consideration: **MSAC 65th Meeting, 26 November 2015**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

Application 1411 was a pilot fit-for-purpose assessment of **diagnostic genetic testing** for heritable mutations predisposing to breast or ovarian cancer in clinically affected individuals to estimate their relative risk of a new primary cancer, and of **predictive genetic testing** (or "cascade testing") of the family members of those affected individuals who are shown to have such a mutation. The evidence for assessment of this application was submitted in August 2015 in the form of a clinical utility card (CUC).

2. MSAC's advice to the Minister

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of genetic testing for hereditary mutations predisposing to breast and/or ovarian cancer using the clinical utility card approach supported previously, MSAC considered that the CUC provided strong evidence to support the analytical validity, clinical validity and clinical utility of the proposed genetic testing in the context of breast and/or ovarian cancer. However, MSAC had concerns regarding the adequacy of the economic analysis for decision-making and deferred public funding for testing so that the outstanding economic issues could be addressed.

MSAC noted that this application was a pilot application to test the process of applying for public funding of testing panels of genes rather than testing individual genes. MSAC supported the overall approach of the application, however greater clarity was required regarding the cost effectiveness analysis.

MSAC suggested that an economics working group be formed to determine an appropriate methodology to assist with modelling and economic analysis for this type of genetic testing for reconsideration by MSAC through the ESC.

3. Summary of consideration and rationale for MSAC's advice

MSAC considered the application for genetic testing of hereditary mutations predisposing to breast and/or ovarian cancer. This application was presented to MSAC using the CUC pro forma supported at the July 2015 MSAC meeting. The CUC allows for the assessment of the clinical utility of testing of multiple genes in the context of defined clinical presentations. This contrasts with the previously used approach whereby the cost effectiveness of testing single genes was evaluated. The assessment is therefore focused on the clinical purpose of the testing rather than technical aspects of the genetic tests. Since July 2015, further work had been undertaken to extend the CUC to include economic and financial analyses to inform an overall MSAC appraisal.

The application first considered testing of individuals affected by breast and/or ovarian cancer for genes known to predispose to these conditions. The application also included cascade testing of family members of the subset of affected individuals who are shown to have a hereditary mutation.

MSAC considered that there were different purposes to testing these two populations. The first purpose (**diagnostic genetic testing**) is applied to an individual who has been diagnosed with breast or ovarian cancer. This purpose is to identify one or more mutations known to predict the risk of a new primary cancer compared with cancer affected individuals who do not have such a mutation. The second purpose (**predictive genetic testing**) is applied to the biologically-related family members of cancer-affected individuals who are shown to have a hereditary mutation. This purpose is to determine whether that mutation, known to predict the risk of cancer, is present. Thus, there is a key difference in the genetic testing of these two populations: a wider panel of genes is proposed to be tested for the initial population of affected individuals, whilst only the identified mutation is proposed to be tested for the biological family members.

There are also key differences in the post-test consequences across these two populations. For diagnostic genetic testing of the cancer-affected individuals, the consequences of a mutation being identified are relatively simple and can be readily incorporated into the care plans of their pre-existing specialist. On the other hand, unaffected family members who are shown by predictive genetic testing to carry the mutation have more care pathways potentially available because they have yet to manifest a cancer diagnosis. The care pathways for these individuals will likely involve new specialists' consultations and counselling. In this regard, MSAC noted that limiting the requesting of MBS-funded cascade testing to "familial cancer physicians" may raise implementation issues because this is not a recognised specialty and there are only a small number of Family Cancer Clinics in Australia.

MSAC noted that the use of the CUC pro forma simplified the analysis of diagnostic genetic testing by concentrating on one or more primary genetic targets for testing ("star performers"). However, MSAC also noted that testing a panel of genes was not required for predictive genetic testing as only the specific mutation in one gene would be tested.

The clinical validity and clinical utility assessment in the current application focussed on *BRCA1* and *BRCA2* as the primary genetic targets for diagnostic genetic testing in affected individuals with breast and/or ovarian cancer. MSAC agreed that these test attributes had been clearly established for these primary genetic targets in these individuals. MSAC also considered other genes that could be secondary genetic targets for diagnostic genetic testing in this setting. MSAC noted that secondary genetic targets should only be included in a set of options for concurrent diagnostic genetic testing of these affected individuals if there was

sufficient evidence of clinical validity and clinical utility (albeit of a less rigorous standard than for the "star performers"). Of the other genes included in the proposed set of options for diagnostic genetic testing of individuals affected with breast and/or ovarian cancer, *STK11*, *PTEN*, *CDH1*, *PALB2*, and *TP53* all had eviQ guidelines (www.eviq.org.au) for the clinical management of individuals with a mutation in these genes, and MSAC accepted that this constituted sufficient evidence of the clinical utility of testing these secondary genetic targets (via their optional inclusion in a panel of genes for testing). However, MSAC noted that *CHK2* did not currently have consensus management guidelines, and without any such evidence of clinical utility currently available for either affected individuals or cascade testing, MSAC concluded that testing for *CHK2* mutations should not be included in the set of options for diagnostic genetic testing of individuals affected with breast and/or ovarian cancer. MSAC recognised that a laboratory may also test other genes that MSAC did not accept as "star performer" or secondary genetic targets for these individuals, and foreshadowed that such testing would fall outside the scope of public funding should MSAC support public funding on its reconsideration of the deferred application.

MSAC also noted that the prevalence of mutations in each of the identified secondary genetic targets was not provided for the targeted cancers i.e. breast and/or ovarian cancer, and that this would be a useful inclusion to confirm that inclusion of these genes would have limited consequences for overall cost-effectiveness. MSAC also noted that future CUC applications of this type should exclude testing for mutations of unknown clinical utility or prevalence.

MSAC agreed that the scope of predictive genetic testing of family members of affected individuals who have a mutation needed to be carefully defined with respect to the definition of what constitutes a "relative". Clearly the family member must be biologically related to the mutation positive index case. MSAC considered that clinical geneticists or clinical specialists (with access to accredited genetic counsellors) should be able to order predictive genetic tests. Confining test ordering to familial cancer physicians would inappropriately restrict access for relatives.

Overall, MSAC considered that the CUC provided strong evidence to support the analytical validity, clinical validity and clinical utility of the proposed genetic testing in the context of breast and/or ovarian cancer.

MSAC considered the cost effectiveness of genetic testing for hereditary mutations in breast and/or ovarian cancer and concluded that there was considerable uncertainty regarding the economic modelling, particularly for the model relating to family members. The committee noted that this is the first application of its kind and therefore suggested that a working group be formed to help develop an economic model that would better inform decision-making. MSAC also noted that such a model could serve as a tool for future applications for other conditions where a similar mix of diagnostic and predictive genetic testing is proposed.

MSAC considered that the cost-consequence analyses presenting the incremental cost per extra cancer avoided was informative in helping judge the internal validity of each model before then translating the outcome measure to QALYs gained. MSAC suggested that this cost-consequences approach could usefully be extended to capture other consequences included in the model. Similarly, MSAC suggested that relevant Markov traces be presented to help assess key variables against time for each model, such as the incremental cost per extra QALY gained, incremental QALYs gained, incremental life-years gained, incremental cancers avoided; and for each arm of each model, life-years gained with and without testing, and cancers occurring with and without testing.

MSAC noted that predictive genetic testing of family members might be offset against the costs of any enhanced surveillance which these family members would undergo if genetic testing was unavailable. Family members who did not have the family's mutation might then revert to the population risk of cancer and require only population-based cancer surveillance. MSAC noted the complexity regarding the downstream options for family members who are shown to have the family's mutation. The Markov model that formed the basis of the economic analysis estimated a transitional probability of downstream care where 40% of female carriers of a *BRCA1* or *BRCA2* mutation would opt for bilateral salpingo-oopherectomy (BSO) plus bilateral mastectomy, 40% would opt for BSO only, and 20% would opt for surveillance only. It was unclear whether these transitional probabilities were reflective of current care. MSAC also noted that high-risk unaffected individuals offered *BRCA* testing did not reported significantly worse psychological or quality of life consequences (Manchanda R et al. Journal of the National Cancer Institute 2014 Nov 30;107(1):dju379).

MSAC considered the results of the cost-utility analyses and noted that they were high with an incremental cost effectiveness ratio per QALY of $151,837 and $85,598 for affected individuals and family members, respectively. MSAC considered that these ICER/QALY estimates may not be representative of the cost utility of publicly funding this test, noting that they do not match others quoted in the literature (eg Griffith GL et al. British Journal of Cancer 2004;90:1697-703; Breheny N et al. Genomics, Society and Policy 2005;1:67-79; and Manchanda R et al. Journal of the National Cancer Institute 2014 Nov 30;107(1):dju380). An extended search for other relevant economic analyses might yield further insights which could be examined for the model prepared for this application, such as other important consequences of this type of genetic testing or adjusting for the varying relative risk of cancer by age.

MSAC also considered that the overall cost-effectiveness would lie somewhere between the ICER for the affected individuals and the consequent ICER for family members, but did not have a confident basis to reach a conclusion. The proposed literature search should also seek to identify ways of providing a third analysis which would appropriately combine the models developed for each of these two populations.

Further refinements to the economic analysis would be usefully incorporated into the CUC pro forma for future applications for genetic testing of this type.

Although the CUC described the essential role of extended genetic counselling in the context of predictive genetic testing, MSAC recognised that access to and resourcing of genetic counselling was an important consideration in this setting, and noted that consideration of this lay outside the scope of the current application.

In deferring the application, MSAC requested that the following issues with the economic analysis of both diagnostic genetic testing of affected individuals and predictive genetic testing of family members be addressed, in particular:

- disaggregation of each cost-utility analysis to also include a cost-consequence analysis showing how testing would improve other clinically meaningful consequences, such as cancers and life-years;
- provision of Markov traces for each model to show changes over time for important variables;
- further consideration of the care pathways for predictive genetic testing of family members, including genetic counselling, to inform the management of these relevant services;

- provision of a wider literature search for other relevant economic models, and an assessment of those found to identify whether any important insights might be available, particularly for predictive genetic testing of family members, and to better inform how the two models might also be combined;
- provision of a wider literature search for other relevant consequences of this type of genetic testing.

4. Background

The application was prepared using a Clinical Utility Card (CUC) pro forma which was developed by a working group of MSAC as a methodology for evaluating genetic testing of heritable mutations from the clinical perspective of disease management, and not a gene by gene approach. Comprehensive background on the application is provided in the CUC.

The CUC presented the key facts related to the application. This Public Summary Document should be read in conjunction with the CUC.

5. Prerequisites to implementation of any funding advice

Nil

6. Proposal for public funding

Affected individuals
"Characterisation of germline gene variants, including at minimum *BRCA1* and/or *BRCA2* genes, in a patient with breast or ovarian cancer, in whom clinical and family history criteria have been determined by a treating specialist to be strongly suggestive of heritable breast/ovarian cancer predisposition based on the following criteria:

- A patient with breast and/or ovarian cancer whose personal or family history of cancer using a mutation prediction score predicts a combined mutation carrier probability of >10% according to either BOADICEA, BRCAPRO or pathology-adjusted Manchester score (combined score of 16 or greater) OR
- A patient with one or more of the following:
    - triple negative breast cancer and aged ≤40 years
    - isolated high grade (Grades 2 & 3) invasive non-mucinous ovarian, fallopian tube or primary peritoneal cancer aged ≤70 years
    - invasive non-mucinous ovarian, fallopian tube or primary peritoneal cancer at any age and a family history of breast or ovarian cancer
    - personal and/or family history of breast and/or ovarian cancer, from a population where a common founder mutation exists."

Family members
"Request by a specialist familial cancer physician for the detection of a previously identified single gene variant, in a relative of a patient with known breast or ovarian cancer where previous genetic testing has detected a variant causative of hereditary familial cancer predisposition."

Using this application as a prototype, MSAC proposed the following simplification of the item descriptors for applications using the CUC pro forma to apply for public funding of genetic testing.

- Diagnostic genetic testing of affected individuals
  "Characterisation of germline gene variants in one or more of the following genes [*BRCA1*, *BRCA2*, *STK11*, *PTEN*, *CDH1*, *PALB2*, and *TP53*], in a patient with [breast or ovarian cancer] for whom clinical and family history criteria, as assessed by a treating specialist using a quantitative algorithm, place the patient at [>10%] risk of having a clinically actionable pathogenic mutation identified".

- Predictive genetic testing of family members
  "Request by a clinical geneticist, or a medical specialist providing professional genetic counselling services, for the detection of a clinically actionable pathogenic mutation previously identified in a gene listed in Item XXXX in a relative."

Text in square brackets (relating to the "star performer" and secondary genetic targets, the medical condition, and the threshold risk of having a clinically actionable pathogenic mutation identified in affected individuals) would need to be completed for each application to MSAC for new clinical conditions. MSAC noted that the threshold for diagnostic testing may differ by clinical condition. For each clinical condition, consideration should be given to including the specific criteria for meeting the threshold risk of having a clinically actionable pathogenic mutation. This information should be incorporated in the item descriptor for diagnostic genetic testing of affected individuals. MSAC considered it was particularly important to define the threshold for testing where practices were likely to vary between specialists. The threshold for testing was likely to be particularly variable in relation to the secondary genetic targets in the panels of genes for testing.

7. Summary of Public Consultation Feedback/Consumer Issues

There were access and equity concerns in terms of the availability of the service and genetic counselling for rural and lower socio-economic status patients. The latter was difficult to predict at the time of assessment due to uncertainties of cost effectiveness. Consumers were supportive of accurate early detection of cancers so that families can make decisions.

8. Proposed intervention's place in clinical management

Genetic testing was proposed to be added to the management of populations selected for being of elevated risk of having an inherited mutation in particular genes, for whom a genetic diagnosis would improve overall subsequent clinical management.

9. Comparator

No genetic testing of the proposed populations.

10. Comparative safety

See CUC.

11. Comparative effectiveness

See CUC.

12. Economic evaluation

Section 6 of the CUC presented two separate Markov models, constructed using TreeAge Pro, of testing the *BRCA1* and *BRCA2* genes in breast cancer versus usual care in:

(i) clinically affected individuals who have an early breast cancer diagnosis and also fit the clinical description as described in Section 1.5 of the CUC (diagnostic genetic testing); and

(ii) family members shown to carry the family's mutation (predictive genetic testing).

An incremental cost per QALY gained and an incremental cost per breast cancer diagnosis avoided were estimated. A weighted cost per QALY based on the proportion of family members to affected individuals was also presented.

Table 1: Summary of model structure

<table>
<tr><td>Time horizon</td><td>50 years</td></tr>
<tr><td>Cohort size</td><td>100,000 for each simulation</td></tr>
<tr><td>Outcomes</td><td>Total incidence of (i) early contralateral breast cancer in affected individuals and (ii) early breast cancer in family members; QALY</td></tr>
<tr><td>Methods used to generate results</td><td><u>Affected individuals</u>
Population risk of breast cancer was derived from AIHW publications.
A higher risk (relative risk = 3.4; derived by 28.7%/8.4% 15-year risk of contralateral breast cancer) was applied to individuals who were considered to be BRCA1 or BRCA2 mutation positive.
<u>Family members</u>
Population risk of breast cancer was derived from AIHW publications.
A higher risk (relative risk = 6.4; 60%/9.3% cumulative lifetime risk of female breast cancer) was applied to individuals who were considered to be BRCA1 or BRCA2 mutation positive.</td></tr>
<tr><td>Cycle length</td><td>Annual cycles</td></tr>
<tr><td>Probabilities of preventative actions taken</td><td>
<table>
<tr><th>Preventative action</th><th>Probability</th></tr>
<tr><td>Bilateral salpingo oophorectomy only (BSO only)</td><td>40%</td></tr>
<tr><td>Affected individuals: BSO + contralateral mastectomy (CM)
Family members: BSO + bilateral mastectomy (BM)</td><td>40%</td></tr>
<tr><td>Surveillance only</td><td>20%</td></tr>
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</td></tr>
<tr><td>Discount rate</td><td>5% for costs and QALYs. The incidence of new early breast cancer was not discounted.</td></tr>
</table>

Section 6 of the CUC provided a summary of the models' variables including input costs. The CUC noted that costs applied to those undergoing contralateral or bilateral mastectomies and BSO may be overestimated. It considered that, particularly for family members undergoing these procedures, the surgeries may be conducted at the same time and be associated with a decreased cost compared with the sum of both.

<u>Results of the economic evaluation</u>

Section 6 of the CUC included a comprehensive presentation of the results of the economic evaluation.

Analysis of the incremental costs and effectiveness indicated an incremental cost of $3,129.71 to achieve an incremental QALY gain of 0.21 for affected individuals resulting in an ICER of $151,837.18 and an incremental cost of cancer avoided of $101,779.19.

Table 2: Results of the economic evaluation (incremental cost per extra QALY gained) in affected individuals

Component	Genetic testing	Usual care	Increment
Costs	$4,402.15	$1,272.43	$3,129.71
QALY	17.932	17.911	0.021
Incremental cost/extra QALY gained			**$151,837.18**

Table 3: Results of the economic evaluation (incremental cost per extra cancer avoided) in affected individuals

Component	Genetic testing	Usual care	Increment
Costs	$4,401.43	$1,270.34	$3,131.09
Cancer incidence rate	0.12064	0.15139	0.03075
Incremental cost/extra cancer avoided			**$101,779.19**

The CUC noted that QALY gains from genetic testing are small and may be clinically insignificant (0.021 over 50 years). Section 6 of the CUC noted that the low QALY gains may be due to:

1) Low mortality from early breast cancer (2.2% annually), although higher than age-related mortality.
2) Reasonably high utility value associated with early breast cancer (0.8). Assuming that an individual survives all 5 years of breast cancer at a utility of 0.8, an individual in full health would have gained an additional 1 QALY over the 5 years.
3) Diluting the benefits of the number of cancers avoided (3,075) amongst a total of 100,000 individuals resulting in a gain of 0.03075 QALY per individual.
4) Discounting would have reduced the effect of any QALY gains on a population level, as the highest incidence of breast cancer occurs when individuals are around 60 years of age, which is between 10 to 30 cycles into the model.

There were also variations in the ICER calculated given the randomised starting age and low incidence. Nonetheless, the CUC indicated that the base case appears to sit around $150,000/QALY gain ± 10%.

For family members, the analysis indicated an incremental cost of $6,336.91 for an incremental QALY gain of 0.074 resulting in an ICER/QALY of $85,598.66 and an incremental cost per extra cancer avoided of $38,224.82.

Table 4: Results of the economic evaluation (incremental cost per extra QALY gained) in family members

Component	Genetic testing	Usual care	Increment
Costs	$8,598.25	$2,261.34	$6,336.91
QALY	17.088	17.014	0.074
Incremental cost/extra QALY gained			**$85,598.66**

Table 5: Results of the economic evaluation (incremental cost per extra cancer avoided) in family members

Component	Genetic testing	Usual care	Increment
Costs	$8,598.25	$2,261.34	$6,336.91
Cancer incidence rate	0.18808	0.35386	0.16578
Incremental cost/cancer avoided			**$38,224.82**

The QALY gain was also small for family members of affected individuals. Genetic testing appeared more cost effective in family members due to lower cost of *BRCA* test and a higher proportion of patients being *BRCA* positive, therefore more cancer cases are avoided. The greater cost in the genetic testing arm (despite the lower cost for the actual genetic test) comes from an increased number of individuals undergoing preventative surgery, and the assumption that a bilateral mastectomy would have a higher cost than a contralateral mastectomy.

The economic analysis derived overall ICERs for the whole population through a weighted average of affected individuals and family members based on two scenarios, assuming a ratio of 1 proband to 6 family members (1:6) and 1 proband to 3 family members (1:3). Two methods of weighting the ICER were also provided: weighting by the assumed number of family members per proband, and using the proportion of affected individuals and the

proportion of family members of probands compared to total number of individuals who are estimated to be tested in the first year of listing as weights.

Table 6: Weighted incremental cost per extra QALY gained

	Weighting	ICER	Weighted ICER
Assume 6 family members to 1 affected individual			
Affected individual	14.3% (1/7)	$151,837.18	$95,061.31
Family members	85.7% (6/7)	$85,598.66	
Assume 6 family members to 1 affected individual, based on number of women tested in each year in the financial estimates			
Affected individual	52.6% (1115/2119 tested in first year)	$151,837.18	$120,452.81
Family members	47.4% (1004/2119 tested in first year)	$85,598.66	
Assume 3 family members to 1 affected individual			
Affected individual	25.0% (1/4)	$151,837.18	$102,158.30
Family members	75.0% (3/4)	$85,598.66	
Assume 3 family members to 1 affected individual, based on number of women tested in each year in the financial estimates			
Affected individual	68.9% (1115/1617 tested in first year)	$151,837.18	$131,280.40
Family members	31.1% (502/1617 tested in first year)	$85,598.66	

Sensitivity analyses

Sensitivity analyses indicated that the model was most sensitive to the number of *BRCA* mutation positive individuals in the tested population as well as whether discounting was applied.

Table 7: Results of univariate sensitivity analyses for affected individuals

Univariate analyses	Incremental costs	Incremental QALY gained	Incremental cost/QALY gained
Base case	**$3,129.71**	**0.021**	**$151,837.18**
10% tested are *BRCA1* or *BRCA2* positive	$2,659.95	0.014	$191,227.61
20% tested are *BRCA1* or *BRCA2* positive	$3,568.03	0.027	$133,366.43
50% tested are *BRCA1* or *BRCA2* positive	$6,396.58	0.0697	$91,818.79
10% profit margin (lower cost) for genetic test	$3,014.23	0.0195	$154,924.46
No discounting applied	$2,664.54	0.0658	$40,522.93
Age-dependent relative risk[1]	$3,185.46	0.0142	$223,860.68
Starting age = 30	$3,172.51	0.0153	$207,790.04
Starting age = 40	$3,111.32	0.0221	$140,569.41
Starting age = 50	$3,048.39	0.0243	$125,557.83
Starting age = 30, Lifetime RR = 4.8[1]	$3,136.17	0.0216	$145,415.62
Starting age = 40, Lifetime RR = 2.7[1]	$3,147.14	0.0197	$159,804.58
Starting age = 50, Lifetime RR = 2.2[1]	$3,173.26	0.0152	$208,644.91
Cost of genetic counselling (MBS 133)	$3,112.90	0.021	$157,898.59
Annual cost for surveillance = $89.46, applied to BSO only and Surveillance only	$3,043.10	0.0198	$154,039.12
Cost of CM and BSO reduced by 50% from base case	$2,346.34	0.0223	$105,391.52
Utility for breast cancer = 0.70	$3,109.15	0.025	$124,955.38
Utility for breast cancer = 0.90	$3,126.83	0.0162	$192,848.71

[1] Based on data provided in Section 2.2.2 of CUC

The ICER was most sensitive to the proportion of women who tested positive for *BRCA1* or *BRCA2* mutations, the assumed utility for early breast cancer, the relative risk of breast cancer among those who are positive for *BRCA1* or *BRCA2* mutations, the costs assumed for CM and BSO and the removal of discounting of costs and effects in the model.

The CUC noted that, while the relative risk for those aged <40 years (RR=4.8) was greater than that applied in the base case (RR=3.4), the relative risks for those aged 40-49 and ≥50 years were 2.7 and 2.2, respectively, both less than the base case. Only a proportion of patients would begin the model aged <40 years, but most would spend the majority of time in the model in age brackets >40 years, leading to a much higher ICER.

Table 8: Results of univariate sensitivity analyses for family members

Univariate analyses	Incremental costs	Incremental QALY gained	Incremental cost/QALY gained
Base case	**$6,336.91**	**0.074**	**$85,598.66**
No discounting applied	$3,314.05	0.3718	$8,913.20
Age-dependent relative risk[1]	$4,241.85	0.2460	$17,241.45
Cost of genetic counselling (MBS 133)	$6,089.16	0.0752	$81,021.46
Annual cost for surveillance = $89.46, applied to BSO only and Surveillance only	$5,921.27	0.0793	$74,667.23
Cost of CM and BSO reduced by 50% from base case	$2,984.86	0.0794	$37,605.12
Utility for breast cancer = 0.70	$6,314.49	0.0953	$66,233.05
Utility for breast cancer = 0.90	$6,301.31	0.0555	$113,589.18

[1] Based on Based on data provided in Table 6.4.1 of CUC (Antoniou et al Am J Hum Genet 2002 72:1117-30)

The ICER derived for family members was most sensitive to the assumed utility for early breast cancer, the relative risk of breast cancer among those who are positive for *BRCA1* or *BRCA2* mutations, the costs assumed for BM and BSO and the removal of discounting of costs and effects in the model.

Section 6 of the CUC noted that the age-dependent relative risks reported in Antoniou et al (2003) were greater than the risk in the base case (RR = 6.4), which already represented a 60% life time risk of breast cancer, compared to a baseline lifetime risk in individuals with no *BRCA* mutation of 9.3%. The CUC considered that it was unclear how the age-dependent rates reported in Antoniou et al (2002) reconciled with the reported lifetime risk.

The CUC also noted two significant limitations to the model:

1) *BRCA* mutation is likely to increase the risk of breast cancer at an earlier age compared to the general population. However, because the model applies a fixed relative risk to the population incidence, the number of breast cancers in younger individuals who have a *BRCA* mutation may be underestimated, which may lead to an underestimation in the QALY gain from genetic testing as the risk of mortality at the early age may be higher.

   The CUC suggested there was insufficient data to construct a *BRCA* gene specific, age-dependent breast cancer risk curve in Australian individuals to inform the model. Even though Antoniou et al 2003 reported age-specific relative risk for breast cancer in *BRCA* mutation positive carriers (ie. family members), the baseline rate (incidence in England and Wales from 1973-1977) may not be appropriate for comparison with the current Australian population, and the relative risks reported, once applied to the AIHW Australian data, exceed the estimates from the Antoniou study.

Table 9: Actual age-specific incidence in Antoniou et al. compared to applying RR reported in Antoniou et al. to AIHW incidence rates

Age	RR reported by Antoniou et al.	Actual reported in Antoniou et al. (%)	Estimates of applying RR in Antoniou et al. to AIHW data[1] (%)
30-34	33	0.74	4.44
35-39		1.59	9.59
40-44	32	2.92	18.18
45-49		4.28	28.02
50-54	18	2.65	20.03
55-59		3.01	21.46
60-64	14	2.70	21.96
65-69		2.49	23.35

[1] Calculated as 1 – (probability of having no breast cancer) over the age period specified, given an annual risk of breast cancer estimated by multiplying the age-specific incidence of cancer in Australians reported by the AIHW with the relative risks reported in Antoniou et al.

The CUC applied a fixed relative risk which was more conservative but likely underestimated the effect of early surgical intervention which may have occurred as a result of genetic testing detecting true *BRCA* mutation positive carriers.

2) Preventative measures were assumed to be undertaken straight after any *BRCA* mutation being detected, with no option to have surgery at a later time. The CUC suggested the decision to remove breasts and/or ovaries is likely to be age-dependent because (i) it would affect the fertility of the woman and the ability to breast feed, and (ii) women who have not completed their families could choose to delay surgery. This would affect the ICER as the cost of surgeries in the current model was undiscounted. If surgeries were delayed, then the cost of surgeries would be lower due to discounting and the effect on health outcomes would be less confidently predicted.

13. Financial/budgetary impacts

Section 7 of the CUC presented a comprehensive analysis of the costs to the MBS and patients of genetic testing and associated preventive surgeries over five years.

The cost to the MBS of genetic testing and genetic counselling would increase from $2.27 million to $3.15 million over the forecast period and the total cost to the MBS of preventive surgeries would be around $8.3 million in year one and around $11.5 million in year five. The MBS cost of all items was estimated to increase from $10.9 million to $15.2 million over the period.

Table 10: Estimated number of affected individuals tested and cost of testing

	2016	2017	2018	2019	2020
Patients eligible for testing (10% of incident cases)	1,593	1,625	1,657	1,689	1,721
Uptake rate	70%	70%	80%	90%	90%
Number tested (initial)	1,115	1,138	1,326	1,520	1,549
Cost to Government of initial testing (rebate of $1,647 per test)	$1,836,124	$1,873,008	$2,182,733	$2,502,997	$2,550,419
Number of patients positive for *BRCA1* or *BRCA2* mutation (15% of tested)	167	171	199	228	232
Cost to Government of confirmatory testing (rebate of $342.13 per test)	$57,226	$58,375	$68,028	$78,010	$79,488
Total cost to Government of initial and confirmatory testing	$1,893,349	$1,931,383	$2,250,761	$2,581,006	$2,629,906
Cost to Government of genetic counselling (rebate of $224.35)	$37,526	$38,280	$44,610	$51,155	$52,124
Total cost (net co-pay) of testing and genetic counselling	$1,930,875	$1,969,662	$2,295,371	$2,632,161	$2,682,031

Table 11: Estimated number of family members tested and cost of testing

	2016	2017	2018	2019	2020
Number of affected women positive for *BRCA1* or *BRCA2* mutation	167	171	199	228	232
Number tested (average of 6 family members per proband)	1,004	1,024	1,193	1,368	1,394
Cost to Government of confirmatory testing (rebate of $342.13 per test)	$343,353	$350,250	$408,169	$468,058	$476,926
Proportion of women positive for *BRCA1* or *BRCA2* mutation	50%	50%	50%	50%	50%
Number of women positive for *BRCA1* or *BRCA2* mutation	502	512	597	684	697
Cost to Government of genetic counselling (pre-test for all family members - rebate of $224.35)	$225,155	$229,678	$267,659	$306,931	$312,746
Cost to Government of genetic counselling (post-test for all positive women - rebate of $224.35)	$112,578	$114,839	$133,829	$153,465	$156,373
Total cost to Government of genetic counselling (pre- and post-test)	$337,733	$344,517	$401,488	$460,396	$469,119
Total cost (net co-pay) of testing and genetic counselling	$681,086	$694,768	$809,657	$928,454	$946,045

Table 12: Estimated costs for testing affected individuals and family members

	2016	2017	2018	2019	2020
Cost of testing	$2,065,026	$2,106,508	$2,454,846	$2,815,035	$2,868,369
Cost of genetic counselling	$206,392	$210,538	$245,354	$281,353	$286,684
Cost of testing and genetic counselling	$2,271,418	$2,317,046	$2,700,199	$3,096,389	$3,155,053

Table 13: Estimated number of surgeries among women affected with breast cancer and determined to be positive for *BRCA1* or *BRCA2* mutations

	2016	2017	2018	2019	2020
Number of women positive for *BRCA1* or *BRCA2* mutation	167	171	199	228	232
Proportion opting for CM+BSO	40%	40%	40%	40%	40%
Number having CM+BSO	67	68	80	91	93
Cost of CM+BSO ($17,008[a])	$1,137,937	$1,160,796	$1,352,748	$1,551,232	$1,580,621
Proportion opting for BSO	40%	40%	40%	40%	40%
Number having BSO	67	68	80	91	93
Cost of BSO ($8,621[b])	$576,797	$588,383	$685,680	$786,287	$801,184
Total cost for surgery	$1,714,734	$1,749,179	$2,038,428	$2,337,519	$2,381,805

Table 14: Estimated number of surgeries among family members of the Proband determined to be positive for *BRCA1* or *BRCA2* mutations

	2016	2017	2018	2019	2020
Number of women positive for *BRCA1* or *BRCA2* mutation	502	512	597	684	697
Proportion opting for BM+BSO	40%	40%	40%	40%	40%
Number having BM+BSO	201	205	239	274	279
Cost of BM+BSO ($24,207[a])	$4,858,781	$4,956,383	$5,775,984	$6,623,471	$6,748,960
Proportion opting for BSO	40%	40%	40%	40%	40%
Number having BSO	201	205	239	274	279
Cost of BSO ($8,621[b])	$1,730,390	$1,765,150	$2,057,040	$2,358,861	$2,403,552
Total cost for surgery	$6,589,171	$6,721,533	$7,833,023	$8,982,332	$9,152,512

Table 15: Summary of total MBS costs for affected individuals and family members

	2016	2017	2018	2019	2020
Initial testing (affected individuals)	$1,836,124	$1,873,008	$2,182,733	$2,502,997	$2,550,419
Confirmatory testing (affected individuals)	$57,226	$58,375	$68,028	$78,010	$79,488
Confirmatory testing (family members)	$343,353	$350,250	$408,169	$468,058	$476,926
Genetic counselling (affected individuals)	$37,526	$38,280	$44,610	$51,155	$52,124
Genetic counselling (family pre-test)	$225,155	$229,678	$267,659	$306,931	$312,746
Genetic counselling (family members post-test)	$112,578	$114,839	$133,829	$153,465	$156,373
Preventive surgeries (affected individuals)	$1,714,734	$1,749,179	$2,038,428	$2,337,519	$2,381,805
Preventive surgeries (family members)	$6,589,171	$6,721,533	$7,833,023	$8,982,332	$9,152,512
Total cost to the MBS	$10,915,867	$11,135,142	$12,976,479	$14,880,467	$15,162,393

14. Key issues from ESC for MSAC

ESC noted that application 1411 was a pilot application which would establish an approach to assessing future applications for diagnostic genetic testing and predictive genetic testing. ESC considered that it was therefore critically important to ensure the optimal approach.

ESC viewed the economic evaluation as preliminary and advised that there were a range of methodological issues that needed to be addressed before the analysis was suitable for MSAC consideration, and before the generalizable approach could be finalised. Key issues included:

- The use of a weighted average approach to modelling the ICER for the entire eligible population (including both affected individuals and family members). ESC requested that additional modelling be undertaken based on an integrated model including both populations to derive an alternative ICER;

- Use of expert opinion as the basis of key inputs to the model (e.g. rate of use of different treatment modalities for breast cancer; number of family members tested per affected individual);
- Whether MSAC should require inputs or justification for proposed fees; and
- Potential oversimplification which excluded key benefits and behaviours (e.g. differences in surveillance across arms in the model; the risk/impact of ovarian cancer in individuals affected with breast cancer, and in the family members of probands identified with ovarian cancer).

ESC advised that the economic analysis should be revised to address the full range of issues and that it would be beneficial for ESC to review the revised analysis once completed.

ESC also considered there would be value in the CUC including a summary figure or table to illustrate the relationship between the proposed eligible populations and the population(s) and aspects of care included in the economic evaluation. This would allow MSAC to judge the potential impact on the ICERs of considering only the main effects (eg. subsequent breast cancer but not ovarian cancer in the pilot case).

ESC advised that the ICERs derived from the model were highly uncertain and likely overestimated, noting that while the modelled ICERs indicated that testing would not be cost effective in either population, the sensitivity analyses indicated potential for the ICERs and/or the weighted ICER to become cost effective when the modelling was based on age-related relative risk. For example, the use of a relative risk for the lifetime risk of breast cancer for family members instead of age-related relative risk likely underestimates the effect of surgical intervention at a younger age.

ESC advised that it did not explicitly consider the proposal to list genetic counselling services other than to support the inclusion of counselling services in the economic evaluation.

15. Other significant factors

Nil

16. Applicant's comments on MSAC's Public Summary Document

The applicant had no comments.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au