Australian Government
Department of Health

MEDICAL SERVICES ADVISORY COMMITTEE

CLINICAL UTILITY CARD FOR HERITABLE MUTATIONS WHICH INCREASE RISK IN [DISEASE AREA]

Eligible investigative purposes of genetic testing for this clinical utility card (CUC)

The investigative purposes of genetic testing of heritable mutations which are in scope for this CUC are:

> A. *clinically affected individuals, to make a genetic diagnosis and thus estimate their variation in (predisposition for) future risk of further disease – for these individuals, this is also called diagnostic testing;*
>
> *and, when also appropriate*
>
> B. *cascade testing of family members of those individuals who test positive for one or more relevant mutations, to make a genetic diagnosis and thus estimate each family member's variation in (predisposition for) future risk of developing the clinical disease (and, less commonly, future risk of further disease if the disease has already been diagnosed) – for these individuals, this is also called predictive testing.*

For each disease area, "star performer" gene(s) for testing are selected on the basis of having the strongest case for clinical utility, and the evidence provided in the CUC focusses on these genes. Other genes may be added to the panel of genes to be tested for the disease area on the basis of also having clinical utility, of not detracting from the clinical utility of the "star performer" genes, and of incurring negligible consequences for the incremental cost-effectiveness of the proposed genetic testing. The evidence provided in the CUC for these other genes is commensurately reduced.

For each disease area, the characteristics of the clinically affected individuals who should be selected as eligible for this genetic testing are defined. This reflects an MSAC preference for a low probability of an actionable result over a high probability of an uninterpretable or unactionable result. Cascade testing is then only contemplated for family members of those individuals who test positive for a relevant mutation, and only when this mutation is also associated with having clinical utility for the family members.

MSAC is the target audience of the CUC. However, it should also be readily interpretable to non-experts in genetics, including the Evaluation Sub-Committee, contracted assessment groups, and those who will read the resulting Public Summary Documents from MSAC.

Background

The Medical Services Advisory Committee (MSAC) has piloted arrangements to assess the utility of germline genetic testing for broad disease areas, such as cancer, cardiovascular or mental illness. This approach is to be used to inform consideration of the circumstances under which germline genetic testing for these diseases should be publicly funded. Contributions to this pilot were made by pathologists with the support of the Royal College of Pathologists of Australasia (RCPA) and from the national reference group on cancer genetics (eviQ, www.eviq.org.au). Additional support for this pilot was provided by the Australian Government Department of Health, the Monash University Assessment Group, and the Griffith University Assessment Group.

This clinical utility card (CUC) proforma is modelled on the clinical utility gene card format used by EuroGentest. When completed, a CUC provides relevant information regarding the clinical utility of genetic testing of relevant heritable mutations in particular circumstances grouped by disease area. Clinical utility refers to the ability of a genetic test to significantly affect clinical management and patient outcomes. Each CUC covers all elements relevant for assessing risks and benefits of a genetic test. However, in contrast to previous assessments of germline testing, CUC is constructed from a clinical perspective of disease management rather than a single gene by gene approach. Further, a completed CUC provides an economic evaluation of testing clinically affected individuals and the marginal cost effectiveness of also testing family members (cascade testing) where appropriate. It also assesses the budgetary implications of this testing. Its clear and concise format will facilitate MSAC consideration across a large volume of tests.

The EuroGentest website (http://www.eurogentest.org/index.php?id=668) explains that the main components of a CUC are analytical validity, clinical validity, clinical utility, and ethical, legal and social issues. A major challenge lies in balancing clinical validity, clinical utility and cost-effectiveness of testing. Some tests have excellent analytical validity, but are not viable from the clinical or economic point of view. On the other hand, some tests have poor analytical validity, but nevertheless affect patient and family management. Therefore it is important that the requirements for a test are defined in the clinical context and that the laboratory genetic test is only one of the components of an overall evaluation.

Comments on this proforma are welcome, and should be provided to:

- *Phone: +61 2 6289 7550*
- *Email: hta@health.gov.au*

SUMMARY

Proposed disease:

Proposed genes for testing:

Key analytical performance results:

Key clinical validity results:

Key clinical utility consequences:

Proposed item descriptor(s) for public funding:

Diagnostic genetic testing of affected individuals
"Characterisation of germline gene variants in one or more of the following genes [*list actionable genes from 1.3*], in a patient with [*specify the relevant disease area*] 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."

Proposed MBS fee(s):

Key economic evaluation results:

Key budgetary implications:

1. DISEASE CHARACTERISTICS

1.1. List the names of the disease(s) proposed for genetic testing within the disease area and provide the clinical rationale for this grouping

Familial

1.2. OMIM# of the disease(s)

1.3. List the names of the corresponding actionable genes which are proposed for genetic testing and, of these, identify the "star performer(s)" in this list (that is, the actionable gene(s) for which the strongest clinical utility and/or cost-effectiveness argument is likely to apply for an affected individual)

[Included genes which are not the "star performer(s)" must have both sufficient penetrance and also have some evidence that the results would have clinical utility (eg inclusion in well-regarded clinical guidelines). For each non-"star performer" gene, report its penetrance, and cite the clinical guidelines supporting its clinical utility.]

1.4. OMIM# of the genes

1.5. Target population for testing – that is, what clinical/pathological or other diagnostic criteria should be used to determine the "phenome" which should be eligible for testing? Provide the evidence and/or clinical rationale for these criteria which would ensure that the pre-test probability of a pathogenic heritable mutation or combination of mutations for the "star performer(s)" would be ≥10%.

[Although accepted as being more influenced by clinical judgement than objective facts, the threshold of 10% for a pre-test probability of pathologic heritable mutation(s) for the "star performer(s)" is influenced by MSAC's preference for a low probability of an actionable result over a high probability of an uninterpretable or unactionable result. For cancer diseases, eviQ would be a suitable initial source of information to be provided here.]

1.6. Estimated prevalence of heritable mutations of the "star performer" gene(s)

At birth:
In the target population for testing identified at 1.5:

1.7. Estimated proportion of affected individuals who fall within the target population for testing identified at 1.5

2. TEST CHARACTERISTICS OF ["STAR PERFORMER" GENE(S)]

2.1. Analytical performance

Is there an analytical reference standard used to establish the genotype: yes/no
[If yes, complete 2.1.1 below; if no, complete 2.1.2 below]

2.1.1. ***Analytical validity possible*** *(to be answered if 2.1 was marked "yes")*
Define the analytical reference standard:

Present analytical sensitivity as the proportion of positive test results if the genotype is present according to the reference standard:

Present analytical specificity as the proportion of negative test results if the genotype is not present according to the reference standard:

2.1.2. ***Analytical validity not possible*** *(to be answered if 2.1 was marked "no")*
Present analytical concordance across testing options (using proportions with their 95% CI and/or kappa statistics):

Present analytical reproducibility of each testing option (using proportions with their 95% CI and/or kappa statistics):

Present inter-rater or inter-laboratory reliability of each testing option (using kappa statistics):

Present the limit of detection of each testing option:

2.2. Clinical validity

[Clinical validity is assessed in terms of variation in risk of future events between a cohort of affected individuals who test positive for the "star performer" mutation(s) and a cohort of affected individuals who test negative for the "star performer" mutation(s).]

2.2.1. ***Definition of clinical event used to determine clinical validity of the test in an affected individual:***
[Possible events include developing a new clinical event related to the disease, or death.]

2.2.2. ***Ratio of clinical events occurring in mutation test-positive affected individuals to clinical events occurring in mutation test-negative affected individuals:***
[Depending on the event and the type of cohort study or studies available, ratios can be presented as an odds ratios (OR), relative risk (RR), or hazard ratio (HR). Also report the rate of development of the clinical event in either mutation test-positive affected individuals or mutation test-negative affected individuals.]

2.2.3. ***Mean or median duration of follow-up across the cohort study associated with this ratio:***
[Preferably, more than one ratio should be reported for more than one time point.]

2.2.4. ***Mean or median age across the cohort study associated with this ratio:***

[If the ratio is expected to vary by age, present any available data which enables an assessment of the association between age and clinical validity.]

2.2.5. ***Prevalence (or diagnostic yield) associated with this ratio:***

[If the prevalence is likely to vary from the study population of affected individuals and the target population for testing at 1.5, present the attributable fractions for the two populations.]

3. CLINICAL UTILITY OF ["STAR PERFORMER" GENE(S)] FOR AFFECTED INDIVIDUALS

3.1. Can a genetic diagnosis be made other than through a genetic test? yes/no

If yes, how:

Clinically	yes/no
Family history	*yes/no*
Imaging	*yes/no*
Endoscopy	*yes/no*
Biochemistry	*yes/no*
Electrophysiology	*yes/no*
Other (please describe):	

3.2. How would disease management of the affected individual be influenced by the result of the genetic test compared with not testing?

Summarize the differences in optimal treatment for mutation positive and negative affected individuals for the incident current manifestation of the disease, with each management strategy for mutation-positive affected individuals and mutation-negative affected individuals being compared with the comparator of clinical management in the absence of testing.

Incident disease	*Mutation positive*	*Mutation negative*	*Incremental benefit of the differential approach*
[Disease type]			
Surgery			
Medicines			
Other			

Provide supporting evidence for the claimed magnitudes of benefits for the selections above.

Summarize the differences between prevention strategies for mutation positive and negative affected individuals, with each management strategy for mutation-positive affected individuals and mutation-negative affected individuals being compared with the comparator of clinical management in the absence of testing.

Prevention of disease	*Mutation positive*	*Mutation negative*	*Incremental benefit of differential approach*
[Disease type]			
Surgery			
Medicinal prophylaxis			
Screening			
Other			

Provide supporting evidence for the claimed magnitudes of benefit for the selections above.

4. IMPLEMENTATION ISSUES AND RATIONALE FOR ANY CASCADE TESTING

4.1. Clinical context of testing for an individual presenting with an eligible "phenome"

Clinical setting in which testing can be ordered and the test results are interpreted for an individual presenting with an eligible "phenome": (for example, specialist physician/surgeon).

Role of pre-test genetic counselling or information for this individual: required/not required.

If required, nature of counselling or information to be provided:

If not required, brief explanation of why not:

Role of post-test genetic counselling or information for this individual, including in relation to any referral to a hereditary cancer clinic or family cancer centre to manage family members (focussing on first-degree relatives for simplicity, noting that this is not intended to necessarily limit any public funding of cascade testing to first-degree relatives):

A. *in event of a mutation-positive test result:* required/not required.

If required, nature of counselling or information to be provided:

If not required, brief explanation of why not:

B. *in event of a mutation-negative test result:* required/not required.

If required, nature of counselling or information to be provided:

If not required, brief explanation of why not:

4.2. Genetic risk assessment in family members of a proband (i.e. an affected individual who has tested positive for mutation)

4.2.1. *Definition of clinical event used to determine clinical validity of the test in a family member of a proband:*

[Possible events include diagnosis of the disease.]

4.2.2. *Ratio of clinical events occurring in mutation test-positive family members to clinical events occurring in mutation test-negative family members:*

[Depending on the event and the type of cohort study or studies available, ratios can be presented as an odds ratios (OR), relative risk (RR), or hazard ratio (HR). Also report the rate of development of the clinical event in either mutation test-positive family members or mutation test-negative family members.]

4.2.3. *Mean or median duration of follow-up across the cohort study associated with this ratio:*

[Preferably, more than one ratio should be reported for more than one time point.]

4.2.4. *Mean or median age across the cohort study associated with this ratio:*

[If the ratio is expected to vary by age, present any available data which enables an assessment of the association between age and clinical validity.]

4.2.5. *Prevalence (or diagnostic yield) associated with this ratio:*

4.2.6. *How would disease management of the family member be influenced by the result of the genetic test compared with not testing?*

Summarize the differences between prevention strategies for mutation positive and negative family members, with each management strategy for mutation-positive individuals and mutation-negative individuals being compared with the comparator of clinical management in the absence of testing. [Where appropriate, split the following table into males and females or nominate the gender for which the clinical utility arguments are the strongest.]

*Prevention of disease**	*Mutation positive*	*Mutation negative*	*Incremental benefit of differential approach*
[Disease type]			
Surgery			
Medicinal prophylaxis			
Screening			
Other			

**Note that the above generally refers to family members unaffected by disease. If test results mean that further investigations detect signs of sub-clinical disease (for example an ECHO detecting hypertrophy of the ventricle in cardiac disease), extend the table to include any differences in clinical management of sub-clinical disease. For family members who already have a clinical diagnosis of the disease, refer to the treatment table at 3.2.*

Provide supporting evidence for the claimed magnitudes of benefits for the selections above.

Does the previous table provide sufficient justification in terms of clinical utility for cascade testing when limited to first-degree family members of a proband? yes/no

If yes, there is no need to extend the justification further, noting that this is not intended to necessarily limit any public funding of cascade testing to first-degree relatives.

If no, briefly describe the significance of any variation in prevention strategies across first- to third-degree family members.

If cascade testing is undertaken on a relevant actionable gene other than the "star performer gene(s)", indicate whether the expected benefits would be:

A. *the same as* yes/no

B. less than or yes/no

C. greater than yes/no

that observed with the "star performer gene(s)".

4.2.7. *Clinical context of testing for a family member of a proband*

Clinical setting in which family members can be approached, testing can be ordered, and the test results are interpreted: (for example, hereditary cancer clinic; family cancer centre).

Role of pre-test genetic counselling or information for the family member: required/not required.

If required, nature of counselling or information to be provided:

If not required, brief explanation of why not:

Role of post-test genetic counselling or information for the family member:

A. *in event of a mutation-positive test result:* required/not required.

If required, nature of counselling or information to be provided:

If not required, brief explanation of why not:

B. *in event of a mutation-negative test result:* required/not required.

If required, nature of counselling or information to be provided:

If not required, brief explanation of why not:

5. DESCRIPTION OF GENETIC TESTING FOR [DISEASE AREA]

5.1. Proposed description of testing for differential genetic diagnosis

Describe the mutational spectrum in terms of the frequency and nature of the aberrations (such as deletions and copy number variations) that occur within the target genes listed at 1.3 in order to justify the nature and range of the proposed testing needed both to detect any relevant mutations and also to validate their detection.

What is the range of testing which therefore needs to be done, and what is the justification for this approach to testing? What samples are involved (eg cheek swabs, blood)?

5.2. Scale of gene analysis?

What is the scale of gene analysis? Select one or more from the following five categories:

A. *monogenic testing – limited mutation testing or whole gene testing* yes/no

B. small gene panel – assaying 2 to ≤10 genes yes/no

C. medium gene panel – assaying 11 to ≤200 genes yes/no

D. *large gene panel – assaying >200 genes, but remaining sub-exome* yes/no

E. *non-targeted – whole exome sequencing or whole genome sequencing* yes/no

Provide responses to 5.3 to 5.6 below consecutively for <u>each</u> category selected above (A to E).

5.3. Analytical validation of testing

Is it possible? yes/no

If yes, elaborate on what is required. If no, briefly explain why not.

5.4. Need for any analytical confirmatory testing

If a mutation is detected, is any further testing required to confirm its presence using an orthogonal method? yes/no

If yes, identify the confirmatory assays required. If no, briefly explain why not.

5.5. Need for any other supplementary testing

Is there a need for any other supplementary testing (for example, gene expression studies, deletion screens or checking for copy number variations)? yes/no

If yes, identify all supplementary assay(s), explain why each is needed, and estimate how often supplementary testing would be needed (as a % of all those for whom the primary test would be rendered). If no, briefly explain why not.

5.6. Interpretive complexity

What is the interpretive complexity? Select one from the following three categories:

A. *low* yes/no

B. *intermediate* yes/no

C. high yes/no

[Considerations here include qualitative aspects (for example, level of expertise required, complexity of bioinformatics pipelines, software requirements), and quantitative aspects (for example, time component of labour required, cost of software licencing). This information should be sufficient to enable an estimate of the resources required to generate an adequate interpretation of the test results.]

6. ECONOMIC EVALUATION OF TESTING AFFECTED INDIVIDUALS AND CASCADE TESTING

[Section D of the MSAC Technical Guidelines for Investigative Services provides further technical guidance, and Section D of the Contracted Assessment Report Template for Investigative Services provides further guidance on presentational format. These can be found at: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/publications-lp-1]

6.1. Overview of the economic evaluation

6.2. Population and circumstances of use reflected in the economic evaluation

[If there is more than one disease identified at 1.1, construct the model focussing on the most prominent disease (eg disease with the likely most improved health outcomes associated with the "star performer" gene(s) identified at 1.3). Adding other diseases to the model would add complexity, which would only be justified if this would pivot the incremental cost-effectiveness ratio from being unacceptable to acceptable.]

6.3. Structure and rationale of the economic evaluation

[An integrated modelled economic evaluation should be constructed, which enables all incremental costs of the included populations to be aggregated, and all incremental health outcomes of the included populations to be aggregated, before calculating an incremental cost-effectiveness ratio (ICER). This model should be capable of generating an ICER for testing affected individuals only, generated by switching off all inputs for cascade testing of family members and considering any disutility consequences of this for affected individuals and their family members. It should then able to generate the incremental cost-effectiveness ratios (over the costs and outcomes of testing affected individuals only) of adding different groups of family members as relevant (eg first-degree siblings only, first-degree children only, first- and second-degree family members), including the population(s) for cascade testing as defined by the requested MBS item descriptor. Consideration may need to be given to cascade testing of parents and gender-specific cascade testing as may be relevant. An integrated Markov model using TreeAge Pro (2015 v 2.2) meeting these specifications for BRCA testing in the context of breast and/or ovarian cancer is available from the HTA Team in the Department of Health.]

[For both components of the model (affected individuals and family members), focus on testing for the "star performer" gene (or the most prevalent "star performer" gene if more than one is identified. Sensitivity analyses should be used to generate the incremental cost-effectiveness ratios (over the costs and outcomes of testing the "star performer" gene only) of adding any other "star performer" genes, and adding any other actionable genes identified at 1.3 (starting with the gene with the greatest predisposition consequences for

the identified disease grouping, eg that is the most prevalent and/or predicts the most risk of the disease).]

6.4. Variables in the economic evaluation

[Wherever possible, variables should be sourced from Sections 1 to 5 of the CUC. The unit cost of the proposed test should cover all genes specified in the proposed MBS item descriptor. Specify and justify the source of each additional variable.]

6.5. Results of the economic evaluation

[The model should be capable of generating ratios of the incremental cost per extra clinical event avoided (undiscounted) and the incremental cost per extra quality-adjusted life-year (QALY) gained (discounted).]

6.6. Sensitivity analyses

7. BUDGETARY IMPLICATIONS OF TESTING AFFECTED INDIVIDUALS AND CASCADE TESTING

[Section E of the MSAC Technical Guidelines for Investigative Services provides further technical guidance, and Section E of the Contracted Assessment Report Template for Investigative Services provides further guidance on presentational format. These can be found at: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/publications-lp-1]

[An epidemiological approach is likely to be most appropriate to estimate the budgetary implications.]

7.1. Justification of the selection of sources of data

[Wherever possible, variables should be sourced from Sections 1 to 5 of the CUC. Specify and justify the source of each additional variable.]

7.2. Estimation of use and costs of the proposed test

[The unit cost of the proposed test should cover all genes specified in the proposed MBS item descriptor.]

7.3. Estimation of changes in use and cost of other medical services

7.4. Estimated budgetary implications for the MBS

7.5. Identification, estimation and reduction of uncertainty