Australian Government
Medical Services Advisory Committee

STAKEHOLDER MEETING MINUTES - FINAL
GENETIC TESTING FOR CHILDHOOD SYNDROMES

Friday, 19 October 2018

Attendees

Members of the Medical Services Advisory Committee (MSAC), clinical geneticists, genetic counsellors, clinicians with experience in managing children with congenital conditions, pathology providers, representatives of relevant consumer organisations, representatives from the Murdoch Children's Research Institute, and the Department of Health were in attendance.

1. Meeting open – welcome and introduction

The MSAC Chair opened the meeting at 10:30am.

The Chair thanked participants for attending and clarified that the stakeholder meeting was not an MSAC decision-making forum, but would inform the MSAC's reconsideration of the issues raised by MSAC during its July 2018 consideration of Application 1476 (next generation whole exome analysis [WEA] for childhood syndromes in affected individuals, with targeted cascade testing of relatives). MSAC's advice would then be considered by the Government.

MSAC considered that, given the current geographical inequity of access to the test options and the likelihood of similar applications for genetic testing in future, a stakeholder meeting involving consumers, requesters and providers should be convened to further discuss the issues raised by the July 2018 MSAC meeting in relation to focussing the referral pathway to WEA requests, defining the characteristics of patients who should be considered eligible for the various services proposed in the application, advising on the frequency of any repeat services, and exploring the valuation of the different consequences of providing the WEA results. The key objective of the stakeholder meeting was to obtain input from those with knowledge of this type of testing and its impacts to provide a basis for an expected MSAC reconsideration of this application and other similar future proposals.

The Chair reminded attendees that this was a confidential discussion. The outcomes of the meeting will be circulated to the attendees and subsequently published on the MSAC website, but comments will not be attributed to individuals.

Conflicts of interest

The Chair noted the conflicts of interests declared.

2. Background – recent MSAC considerations and key discussion points

At its July 2018 meeting, MSAC considered a proposal to list WEA for monogenic childhood syndromes in affected individuals, with targeted cascade testing of relatives, on the Medicare Benefits Schedule (MBS). MSAC did not support the application. MSAC acknowledged the application had merit, as WEA has huge potential to benefit children with genetic anomalies.

MSAC was concerned about several issues:

- the breadth and heterogeneity of the syndromes included
- a lack of confidence in the limited data provided for effects of changes in clinical management (including other investigations, treatments and future family planning options) and thus improvement in health outcomes overall
- the best type of technology to perform the test
- implementation issues such as equity of access, ethics of consent and specialised workforce availability
- ability to limit the test to the proposed target population (i.e. the problem of leakage).

MSAC wished to bring stakeholders together to advise on the evidence for the technology and discuss the above areas of concern. It also used the opportunity to discuss other matters that would benefit from stakeholder input:

- anecdotal benefits to patients and families/carers
- the ethical difficulty of placing a utility value on a child with a genetic condition not being born
- the difficulty in quantifying therapeutic consequences and health outcomes arising from diagnosis of genetic syndromes
- other costs to families of having a child with a genetic condition.

3. Session 1: Discussion with stakeholders – matters relating to the requesting of WEA

Treatment pathways after genetic testing referral

MSAC was concerned that patient care could be transferred from the patient's regular healthcare provider to a specialist at the institution where the testing request was initiated – likely in a large, highly specialised tertiary or quaternary institution that employed clinical geneticists and other specialists for example building cohorts of patients for research purposes. This could result in permanent relocation of the patient's clinical management. This could pose particular difficulties for regional and remote patients.

Some attendees contended that other conditions are already managed this way. Specialists do not 'take over' care – they complement it. In addition, the patients included in the application have complex conditions, and are likely to be already seen by a specialist in a tertiary institution. A request for a genetic test would thus not change who provided their clinical management. It was also noted that clinical geneticists are generally not the main treating clinicians; they are part of a multidisciplinary team.

The meeting attendees disagreed about the significance of changing clinicians after genetic testing as a potential problem. Although the concerns do not reflect current care pathways involving clinical geneticists, it was noted these pathways could change in the future.

Cost to patients

Another concern was the cost of genetic testing to patients. Should the proposed MBS items be listed, and given that many specialist MBS subsidised services are associated with out of pocket expense for patients, this could affect equity of access. In a study done before the availability of WEA, the Royal College of Pathologists of Australasia evaluated the

proportion of patients who had out-of-pocket expenses for genetic testing. The cost of genetic testing varied widely between states, as did the relevant patient out-of-pocket expenses. None of the genetic tests had an MBS item number. Currently, some testing within the scope of the application is provided through public hospital laboratories at no cost to patients and for some testing there is no public hospital access and hence patients pay for the full cost of the test. It was generally believed that funding these tests via the MBS would result in decreased out-of-pocket expenses, not increased; noting the high rate of bulkbilling for MBS funded pathology testing.

In addition, the meeting discussed the concern that MBS funding would encourage lower-charging states to increase out-of-pocket costs to match other states. Attendees had anecdotal evidence that the reverse was true – that more widespread testing could result in reduced costs as a result of competition. Changes in technology that could decrease testing costs also need to be considered.

Test referral pathways

The application included a conservative model for test referral restricted to clinical geneticists following multidisciplinary review and for children with specific complex conditions, most of whom are likely to have been assessed by a clinical geneticist. However, MSAC acknowledged that this population might need to be expanded as genetic testing progresses, and similar applications are expected in the future. Thus, it was important to discuss the referral pathway(s) on a broader scale.

Referral pathways are complex and subject to different drivers. Any model must accommodate these drivers. It was noted that an equitable, safe and sustainable model is needed. It was noted that the diagnostic yield from testing is related to the quality of the referral.

The meeting discussed four options for test referral:

1. Clinical geneticists request the test, with or without multidisciplinary team input. Clinical geneticists retain responsibility for interpretation of testing and counselling patients and their families about the outcome of testing, with appropriate referral of the patient back to the referring practitioner. An advantage of such a model is that the expertise of clinical geneticists is used to its full advantage. A disadvantage of this model is that the current waiting times for accessing a clinical geneticist are already long (up to 18 months), and even more pressure would be placed on them if such a referral process was approved.
2. Paediatricians request the test but after consultation with a clinical geneticist. This model would still limit the requesting to specialists, but this would not be as restrictive as the first model. An advantage of this model is that it opens up access to the test but still retains close links into a clinical genetics service. The process of consultation between the specialist paediatricians and the clinical geneticist would enable referral of some patients ahead of testing when deemed necessary, and provide an opportunity to upskill general paediatricians with respect to appropriate testing and interpretation of testing. A disadvantage is a possible drop in diagnostic yield due to lack of direct clinical assessment by a clinical geneticist.
3. Specialist paediatricians (and other relevant specialists) can request testing without involvement of a clinical genetics service, although with the possibility of formal genetic counselling. This would open up accessibility, but could result in an even further drop in diagnostic yield, and possible leakage of testing into other patient populations. This model appeared reasonable for cascade testing.

4. Primary care clinicians – namely, general practitioners (GPs) – request the test. This would open up accessibility, but could result in an even further drop in diagnostic yield, and possible leakage of testing into other patient populations. This model was not favoured noting that all of the clinically affected children to be initially tested should have been referred to a specialist.

There was some disagreement among meeting attendees about who should be able to request such tests, although they acknowledged the advantages and disadvantages of the different options.

Remote and rural areas

Restricting test referral to clinical geneticists could disadvantage patients from rural and remote areas. The meeting noted that there are outreach clinics around the country that support access to clinical genetics services. However, the accessibility of these outreach services varies between states and territories.

The meeting noted that initial specialist assessment of these children through telehealth may not be appropriate for these complex genetic conditions. Phenotyping is an important diagnostic tool that is best done during a face-to-face consultation, especially in paediatric patients.

Safeguards that seek to balance access and quality

The meeting noted the number of existing safeguards for referral pathways that already exist, to ensure that testing is clinically appropriate and likely to benefit patients. However, the demand driven and open ended nature of MBS funding means that MBS items need to be codified in such a way that supports good access but use is confined to patients who will benefit. Hence the need for patient eligibility and provider requesting rules, that exist within a compliance framework.

The meeting again noted the waiting time to see a clinical geneticist. If the model is too restrictive, access is denied to many patients who would benefit from genetic testing. This type of genetic testing benefits infants the most; an 18-month wait for genetic testing could nullify many of the positive health outcomes associated with genetic testing. The meeting discussed that it may be best to start with a less restrictive entry to the pathway, then put more checkpoints later in the pathway to avoid unnecessarily excluding patients.

Outcome: meeting-proposed model for test referral

The proposed testing model in Application 1476 is likely too tight to provide equity of access. It was acknowledged that a model for all requested genetic testing of affected individuals is needed, not a disease-by-disease model. A narrow model is safe, but restrictive. A wider model opens up access, but leaves room for leakage and a drop in diagnostic yield.

Thus, to compromise, two pathways were agreed to:

1. a paediatrician could request the test, based on a set of codified criteria (which were discussed later in the meeting), following consultation with a clinical geneticist.
2. a GP/paediatrician could refer a patient to a clinical geneticist who could request the test, in consultation with a multidisciplinary team if necessary.

The meeting agreed that, for this more open model to be effective, all non-genetic clinicians will need to be upskilled in genetics, particularly in obtaining fully informed consent. For complex cases, requesting clinicians should seek consultation from a clinical geneticist as a part of standard care, as correct interpretation of genetic test results is critical.

The meeting raised concerns about leakage and blow-out of requests. However, complex patients are already likely to be seen in a tertiary centre. Only a small number of people would qualify for the test, and the strict requesting criteria will limit blow-out. MSAC noted that the experience from other MBS funded genetic tests is that clinicians generally limit requests to tests they believe are necessary; there is no financial driver for requesters to inappropriately request these tests.

Consent for test requests

The National Pathology Accreditation Advisory Council (NPAAC) requirements for requesting sequencing tests include written patient consent, particularly in relation to what results are reported to minimise the unnecessary reporting of incidental findings, especially as this can have consequences for the family as well as the patient. Currently, the requesting clinician is responsible for obtaining consent, and may use any of the numerous existing forms.

It was suggested that the MBS listing include information about the need for informed consent and documentation of this using standardised forms. All requests should be accompanied by a copy of the completed consent form, and clinicians who request tests can be audited as for other MBS items.

It was noted that the Australian Genomics Health Alliance (AGHA) is in the process of developing a nationally consistent and credentialed consent form to be used for all genetic testing, which would be preferred for MBS purposes. However, it is unknown whether this will be supported by all requester groups and all states and territories.

Credentialing for consent

The meeting strongly supported the idea that requesting clinicians should also complete consent credentialing before they can request, and therefore obtain consent for, a genetic test. This could be a relatively short, online test. It was suggested that the Royal Australasian College of Physicians could manage such credentialing, perhaps with inputs from organisations such as the AGHA. However, progression of this objective is outside of the MBS listing process.

Incidental findings

In the genomic context, incidental findings are unexpected genetic test results unrelated to the purpose of the request for testing. The pathology sector will need to consider how to handle incidental findings. This is currently not standardised. Some laboratories only report incidental findings that might be a part of the phenotype; others only report incidental findings upon request.

The risks of incidental findings vary. Patient safety should be protected; thus, it was agreed that a specialist (clinical geneticist) should be consulted in cases of incidental findings. This is already standard practice.

For the current Application 1476, it was not proposed that incidental findings should necessarily be reported as part of the WEA results.

4. Session 2: Discussion with stakeholders – matters relating to the eligible populations, the frequency and types of testing

Affected patient population for testing

The meeting discussed the clinical eligibility criteria that would need to be met for requesting WEA testing of monogenic childhood syndromes. The application proposed the testing criteria as being two or more of the following clinical features:

- intellectual disability
- single or multiple congenital anomalies
- dysmorphic facial features.

The meeting agreed that testing criteria should be simple, objective, auditable and easily included in an MBS item descriptor.

Following discussion, the following three sets of testing criteria were agreed to:

- at least moderate intellectual disability confirmed by the results of a credentialed psychometric test in a child aged 2 years or older; or
- at least severe developmental delay in a child aged younger than 2 years; or
- dysmorphic facial features AND one or more major structural congenital anomalies.

These criteria are broader than those in the original proposal, resulting in an expected expansion in the volume of genetic testing compared to the original application. Thus, the applicant will need to provide additional evidence to support these criteria in its reapplication and in particular provide revised utilisation estimates.

It was noted that any children missed as part of the MBS criteria could be picked up as part of current state-based funding for genetic testing – for example, children with major structural congenital anomalies but without dysmorphic facial features.

Age of affected patient population for testing

The data presented in the application covered children up to 10 years old. The meeting attendees believed that children up to 18 years old would benefit from such testing; however, the meeting attendees were advised that there is no direct evidence to support clinical benefit of testing the 10–18 year age group.

MSAC suggested supporting testing for the 0–10 year old age group, due to the evidence available. Other applications or other age groups could be considered later as more data become available.

Frequency and type of testing of affected patients

The meeting discussed the frequency of testing, and noted that this can refer to:

- how often sequencing is requested
- how often negative or equivocal results are reanalysed.

Although there are some benefits to repeating the sequencing, it was agreed that the pace of technology innovation means that a whole exome sequence would be reliable for analysis for 5 years.

It was noted that whole genome sequencing (WGS) may become the tool of the future; however, the criteria proposed here would not exclude its use in this patient population.

Reanalysis

The meeting agreed that reanalysis of the whole exome/genome sequences should be allowed in the event that the initial analysis is negative or equivocal, and proposed having no more than one funded reanalysis within the 5-year testing period at least 18 months after the initial analysis. This should be added to the proposed MBS item descriptors for reanalysis. It was noted that additional reanalyses would be possible, but not necessarily funded.

There are two aspects to reanalysis:

1. new relevant genes have been identified since the last test
2. mutations of new significance within a known gene – that is, newly curated variants.

The meeting noted that two new MBS items had been requested for reanalysis, with different fees for when reanalysis identifies new variants requiring curation (higher fee) and for when the reanalysis remains negative (lower fee). Currently, these are proposed as item numbers BBBB1 and BBBB2, respectively. To incorporate the aspect of newly curated variants within a known gene, which involves a more targeted reanalysis, the meeting proposed to change BBBB2 to '… where reanalysis is negative or reappraises a previously identified variant of unknown significance'. Consistent with the request for sequencing, these reanalysis items could be requested by a clinical geneticist or paediatrician.

The meeting raised the possibility of reanalysis becoming automated and therefore cheaper in the future. The attendees agreed that this will happen, but the timeframe was unknown. Thus, this option was not considered at this time.

Backlog testing

The meeting discussed the significance of processing the backlog of patients that would have been eligible for the proposed genetic testing except that they would be older than the age threshold of ten years at the time of initial listing. These patients were also described as the 'prevalence cohort', 'catch-up cohort", or 'grandfather group'.

If such testing is to be funded via the MBS, it was suggested that there would need to be a time limit to the MBS items. However, a time limit might create problems for testing laboratories as the end of the time period draws near.

No consensus was reached at the meeting about this issue.

Trio testing and cascade testing

The meeting discussed the benefits of testing trio exomes (testing the affected child along with one or both parents or siblings) at the same time and potentially under the same item number as single exomes; testing for trios has significantly less laboratory and clinical workload, providing more clinically useful information for the referring specialist, when testing of the affected child is positive.

The meeting discussed the possibility of incorporating trio testing into the AAAAA item descriptor for testing the affected child. Preferably, this would not change the proposed fee, especially if trio testing is more cost-effective.

The discussion then flowed into the proposed MBS item for cascade testing (CCCCC). The meeting discussed the circumstances where testing of first degree relatives of identified

probands should be made available and who should be able to request those tests. Since some of the individuals qualifying for cascade testing will be adults, clinicians able to request testing would need to be expanded to include adult specialists. A common example would be an adult sibling of an affected individual attending a fertility clinic wanting to know if they are a carrier. Younger siblings (i.e. <18 years old) of an affected individual may be able to access advice from a paediatrician.

The meeting clarified that the proposal in the application was to serve three different clinical populations and purposes:

- first-degree family members being tested for reproductive decision-making/family planning purposes, including for carrier status, where a causative variant has been confirmed in the proband (the usual purpose for cascade testing)
- testing for additional genetic diagnoses in siblings less severely affected or even unaffected, where a causative variant has been confirmed in the proband
- testing to segregate (i.e. additional testing of family members as necessary for the purpose of confirming or not the genetic diagnosis of the child who is the recipient of the service under AAAAA item number).

It was noted that this type of testing is not done by WEA; it is done by single-gene testing determined by the genetic diagnosis of the proband and the previously confirmed causative variant.

The meeting did not seek to redraft MBS item descriptor(s) to capture the intent of testing for these three populations.

Further exploration is required to ascertain whether the third population needs to be retained in the event that trio testing can be absorbed into proposed MBS item AAAAA.

The meeting discussed the value of having clinical geneticists and genetic counsellors being involved in the management of such individuals, so that families could be fully informed about the implications of the results. It was suggested that testing for the first of these purposes could be requested by any specialist; the other two would need to be requested by clinicians falling within the definition of requesters in the proposed MBS items AAAAA, BBBB1 and BBBB2. Attendees noted that the term ‘genetic counsellor’ is very broad, as any appropriately qualified clinician can provide genetic counselling. It was suggested that guidance about who can provide genetic counselling would refer to ‘appropriately qualified healthcare professional’ rather than genetic counselling/counsellor.

5. Session 4: Discussion with stakeholders – other matters

Clinical utility or value of genetic testing

The meeting discussed the clinical utility of genetic testing, which has been documented in the literature. It was noted that, to be supported by MSAC for MBS funding, the value of a service is usually calculated in terms of consequential health improvements, such as quality of life (QoL) improved or quality-adjusted life years (QALYs) gained.

The meeting discussed several related advantages of patients receiving a positive genetic test result:

- accessing interventions, changing clinical management or altering the disease progression
- accessing support, such as peer groups, and carer funding, such as the National Disability Insurance Scheme and Centrelink
- providing certainty for family members, which can have mental health and emotional impacts, such as relieving burden of guilt
- managing interventions and expectations in the future
- avoiding unnecessary contraindications or harmful interventions in the future
- avoiding later, ongoing testing – the 'diagnostic odyssey' – which would save resources on unnecessary future testing
- eliminating certain conditions from families
- allowing entry to clinical trials that require a positive genetic test result.

However, it was noted that clinical value needs to reflect the entire tested population, not just those who test positive. Negative consequences of receiving a negative or inconclusive result and prolonged waiting for a result should be expected to counter balance some of the positive outcomes.

Attendees noted that long-term data for broader concept of clinical value are not available, but the Australian Genomics Study is currently collecting data about willingness to pay to estimate a monetary value on testing and of knowing.

Ethics of not having a child due to a positive genetic test result and of having a child due to a negative test result

Attendees noted the well-documented positive outcomes for parents when their decision to have a child was influenced by a genetic test result, whether it was a positive or negative result. Studies have attempted to capture the clinical utility of this knowledge, but it is currently not calculated. It was noted that consumers advocate for developing a clinical utility for knowing and relieving guilt.

Other comments

The Chair invited each attendee to make any further comment. Attendees stressed the importance of timeliness for patients and their families. These children have disabilities, and are thus disadvantaged. Any support for children with complex monogenic conditions is necessary and welcomed. It is important for the Australian Government to move into the genetic testing space, to support public health and to provide equity of access across Australia.

6. Other business

The Chair thanked the attendees for their very useful contributions. MSAC will consider the issues discussed, to inform the expected reconsideration of Application 1476 and to set a precedent for similar applications in the future in a rapidly evolving field.

Next steps are that:

- revised MBS item descriptors will be drafted to reflect the stakeholder discussions
- the applicant will gather further data to support the reconsideration, as necessary
- the meeting report will be circulated for stakeholder comment
- the finalised meeting report will be tabled at an MSAC meeting.

7. Meeting close

The Chair closed the meeting at 3:40pm.