



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1476 – Genetic testing for childhood syndromes

Applicant: Murdoch Children’s Research Institute

Date of MSAC consideration: MSAC 76th Meeting, 1-2 August 2019
MSAC 74th Meeting, 22-23 November 2018
MSAC 73rd Meeting, 26-27 July 2018

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefit Schedule (MBS) listing of next generation whole exome analysis (WEA) for childhood syndromes in affected individuals, with targeted cascade testing of relatives, was received from the Murdoch Children’s Research Institute by the Department of Health.

2. MSAC’s advice to the Minister – August 2019 consideration

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the proposed new MBS items for singleton testing of affected individuals with childhood syndromes, for re-analysis of previously collected data in certain circumstances, and for cascade testing for certain purposes. MSAC accepted the additional clarification of item descriptors and utilisation forecasts requested by the MSAC Executive. MSAC also supported the inclusion of an MBS item for trio testing of affected individuals with an upper limit of \$2,900 for the fee for this item, accepting that the extra cost involved is justified by an improvement in the diagnostic yield.

Consumer summary

Murdoch Children’s Research Institute applied for public funding for genetic testing for childhood syndromes.

When children with suspected genetic syndromes, due to symptoms/developmental difficulties, are tested to confirm a diagnosis, one approach is to sequence the child’s genome. This determines the exact order within the genes to identify any differences, or genetic variants. Then, if a variant of unknown significance (a variation in the genetic sequence for which the risk of developing a disease is unclear) is found, the genes of the parents are sequenced. If the variant is also found in one of the parents, then this helps

Consumer summary

exclude a diagnosis if the parent has no symptoms; if this variant is found in neither parent, then this helps make a diagnosis.

MSAC's recommendation to the Commonwealth Health Minister

MSAC supported this application to test the parents at the same time as the child is tested (called trio testing). Although this costs more than testing the child at the start, it saves time overall and it is easier for the laboratory to identify any diagnostic variants. It therefore means that the likelihood of making a diagnosis is higher.

Summary of consideration and rationale for MSAC's advice – August 2019

MSAC recalled that, at its July 2018 meeting, it had considered a proposal to list WEA for monogenic childhood syndromes in affected individuals, with targeted cascade testing of relatives, on the MBS. MSAC did not support the application, but acknowledged that the application had merit, as WEA has potential to benefit children with genetic anomalies. MSAC considered that, given the range of clinical evidence and implementation issues, a stakeholder meeting involving consumers, requesters and providers would help inform its reconsideration of this application. The stakeholder meeting was held in October 2018. A key outcome was the proposal for broader testing criteria than those in the original proposal, resulting in an expansion in the volume of genetic testing compared with the original application.

MSAC further recalled that, at its November 2018 meeting, it had supported MBS listing of next-generation WEA for childhood syndromes in affected individuals, with limited reanalysis, and targeted cascade testing of relatives of patients with a genetic diagnosis. It had also advised that the utilisation estimates needed further consolidation and the proposed item descriptors needed further crafting, and had requested that these be provided to the MSAC Executive for review.

At its August 2019 meeting, MSAC supported as acceptable both the proposed utilisation estimates and the proposed item descriptors, noting that both had been revised multiple times. MSAC noted that the residual issue was a request to reconsider an MBS item for trio testing.

MSAC recalled that at its November 2018 meeting, it had excluded trio testing (where samples from the affected child and their parents are tested and sequenced concurrently rather than sequentially) from the item that allowed for singleton testing. The rationale was that the decision to request trio testing should be made by a sub-specialised clinical geneticist, in consultation with the laboratory, and that these services are typically located in public hospitals. However, the issue of trio testing had been raised during further stakeholder consultation and therefore was the focus of the August 2019 discussion of this application.

MSAC noted several advantages of trio testing:

- It has better diagnostic yield than singleton testing because it is more straightforward to determine the pathogenic significance of detected variants where three rather than one whole exome analyses is available for concurrent analysis.
- The assessment of test results is easier than those of singleton testing (the pathologist usually has approximately 50 variants to review, rather than 200).
- It saves pathologist's time.

However, MSAC noted that the cost of reagents would be greater for trio compared with singleton testing, because three samples would be sequenced instead of just one.

MSAC also noted that trio testing requires more effort from the requesting clinician to obtain samples from the three biological relatives rather than just the affected child. However, despite the additional work required, the forecast of relative uptake is 75:25 singleton:trio testing in year 1, 50:50 in year 2, 33:67 in year 3 and 25:75 in year 4 (and beyond). MSAC noted that these data were from limited laboratories and that singleton testing would continue to be used.

MSAC advised that a second item for trio testing should be listed alongside the item for singleton testing, noting that the appropriate fee was uncertain. MSAC therefore advised that if a fee could not be agreed to, then it would be better to omit trio testing in implementing its advice rather than delay the rest of the implementation by 6 months or more. MSAC noted that that a small fee increase would not significantly impact the budget implications overall and that sequencing costs are falling, so there could be an argument for a further adjustment at a later date. However, setting a reasonable fee sooner would allow trio testing to be funded earlier alongside singleton testing and would allow data to be collected on the relative uptake of the two approaches.

MSAC noted that, if singleton and parental testing is done sequentially, then there is a significant amount of set up that is required, and that this set up is not required for trio testing, and economies of scale would be expected with wider uptake of trio testing. MSAC noted that currently the fee is \$400 when looking a variant in biological parents, so for two parents that is an additional cost of \$800. Based on this figure, and noting that the fee for singleton testing was now expected to be \$2,100, MSAC advised an upper fee limit of \$2,900 for trio testing, and suggested that this fee be reviewed 2 years after listing, alongside a broader review of the utilisation of the items overall.

Item descriptor

MSAC disagreed with the proposal in the papers that would allow a pathologist to initiate trio testing in place of singleton testing, preferring that the definition of the requester for trio testing be the same as for singleton testing.

Proposed MBS Item
MBS item number: AAAAA2 Characterisation of germline variants known to cause monogenic disorders via whole exome or genome sequencing and analysis, as requested by a clinical geneticist or a consultant physician practising as a specialist paediatrician in consultation with a clinical geneticist in a patient aged ten years or younger with a strong suspicion of a monogenic condition based on the presence of any one of the two following clinical criteria: 1. dysmorphic facial appearance and one or more major structural congenital anomalies; or 2. intellectual disability or global developmental delay of at least moderate severity to be determined by a specialist paediatrician. Performed only after non-informative micro-array testing (item 73292) of the patient. Performed on a sample from the patient plus a sample from each of the biological parents. Performed no more than once per patient per lifetime.

Proposed MBS Item

Only to be performed where the referring specialist deems that singleton testing is inappropriate.

Not performed if AAAAA1 has been performed.

MBS Fee: \$2,900.00

Benefit: 75% = \$2,175.00 85% = \$2,465.00

Practice Notes X.X.XX

Intellectual disability or global developmental delay of at least moderate severity, to be determined by a specialist paediatrician according to DSM-5 criteria.

Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist on referral

Other MSAC-supported MBS items

Proposed MBS Items

MBS item number: AAAAA1

Characterisation of germline variants known to cause monogenic disorders via whole exome or genome sequencing and analysis, as requested by a consultant physician practising as a clinical geneticist or a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist, in a patient aged ten years or younger with a strong suspicion of a monogenic condition based on the presence of any one of the two following clinical criteria:

1. dysmorphic facial appearance and one or more major structural congenital anomalies; or
2. intellectual disability or global developmental delay of at least moderate severity to be determined by a specialist paediatrician.

Performed only after non-informative micro-array testing (item 73292).

Performed no more than once per patient per lifetime.

Not performed if AAAAA2 has been performed.

MBS Fee: \$2,100.00

Benefit: 75% = \$1,575.00 85% = \$1,785.00

Practice Notes X.X.XX

Intellectual disability or global developmental delay of at least moderate severity, to be determined by a specialist paediatrician according to DSM-5 criteria.

Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist on referral

MBS item number: BBBB

Re-analysis of whole exome or genome data obtained as described under item AAAAA, for characterisation of previously unreported germline gene variants related to the clinical phenotype, as requested by a consultant physician practising as a clinical geneticist or a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist, for a patient aged 15 years or younger with a strong suspicion of a monogenic condition.

Performed no more than twice per patient.

Performed at an interval of not less than 18 months following AAAAA.

Proposed MBS Items
<p>If repeated, must be at an interval of not less than 18 months from previous BBBB. MBS Fee: \$500.00 Benefit: 75% = \$375.00 85% = \$425.00</p>
<p>MBS item number: CCCCC1 Detection of a single gene variant for diagnostic purposes, requested by a consultant physician practising as a clinical geneticist or a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist, for a biological sibling of a patient with a known monogenic condition where previous genetic testing performed in accordance with the conditions specified under item AAAAA or BBBB has identified the causative variant and where the results of the previous proband testing is made available to the laboratory. Not performed in association with item CCCCC2 or CCCCC3. Performed no more than once per variant per patient. MBS Fee: \$400.00 Benefit: 75% = \$300.00 85% = \$340.00</p>
<p>MBS item number: CCCCC2 Detection of a single gene variant for the purpose of reproductive decision making, requested by a consultant physician or specialist for a first-degree biological relative of a patient with a known monogenic condition where previous genetic testing performed in accordance with the conditions specified under item AAAAA or BBBB, has identified the causative variant and where the results of the previous proband testing is made available to the laboratory. Not performed in association with item CCCCC1 or CCCCC3. Performed no more than once per variant per patient. MBS Fee: \$400.00 Benefit: 75% = \$300.00 85% = \$340.00</p>
<p>MBS item number: CCCCC3 Detection of a single gene variant for segregation purposes, requested by a consultant physician practising as a clinical geneticist or a consultant physician practising as a specialist paediatrician following consultation with a clinical geneticist, for a biological parent or other biological relative with known phenotype of a patient with a suspected monogenic condition, where previous genetic testing performed in accordance with conditions specified under item AAAAA or BBBB has identified a potentially causative variant and where the results of the previous proband testing is made available to the laboratory. Not performed in association with item CCCCC1 or CCCCC2. Performed no more than once per variant per patient. MBS Fee: \$400.00 Benefit: 75% = \$300.00 85% = \$340.00</p>

Revised utilisation estimates

Updated utilisation estimates were used for the budget impact analysis presented to the July 2018 MSAC meeting. The net effect of the updated utilisation estimates was to increase the estimated costs to the MBS in the first three years and slightly decrease the costs for the subsequent two years. The increase was mainly due to revising the size of the prevalent pool which contributed to the costs of testing the “backlog” which is assumed to occur over the first three years.

The Applicant's inferred prevalence estimate of 6% for the backlog population was greater than the high end of the cited prevalence estimates:

- 0.65% AIHW (1997)
- ~3.5% ABS (2012)

or the cumulative incidence estimates of 0.62% up to 1.58% in a literature-based meta-analysis (2016). The Department suggested that it was likely that the utilisation estimates and thus the budgetary implications for this backlog population were overestimated.

Consistent with the previous budget impact analysis considered by MSAC, the annual birth numbers were increased in accordance with the growth rate of the overall population.

It was assumed that all clinically diagnosed patients would be tested and all tests conducted would be billed to the MBS (ie 100% uptake of the eligible population).

The estimate of diagnostic yield for the initial WES analysis was decreased from 57.5% to 39%. This was consistent with the expectation of MSAC and the stakeholder meeting, and reflected the wider body of evidence assessed by MSAC in July 2018 rather than the single centre Australian estimates which MSAC considered to be overestimated.

3. MSAC's advice to the Minister – November 2018 consideration

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC supported MBS listing of next-generation WEA for childhood syndromes in affected individuals, with limited reanalysis, and targeted cascade testing of relatives of patients with a genetic diagnosis. MSAC advised in each case that testing should be once in a lifetime and that there should be post-implementation monitoring, particularly looking at the diagnostic yield for laboratories and requesters, who the requesters are, and the out-of-pocket costs for patients.

MSAC also advised that the utilisation estimates needed further refinement and the proposed item descriptors needed further crafting, and requested that these be provided to the MSAC Executive for review.

Summary of consideration and rationale for MSAC's advice – November 2018

Following its decision not to support Application 1476 at its 73rd meeting, MSAC proposed that a stakeholder meeting be arranged to attempt to address a number of issues that it had identified with the application. In its re-consideration at its 74th meeting, MSAC noted the outcomes of the stakeholder meeting held in October 2018 to discuss issues in the application, and to forge a framework to guide consideration of other similar genetic testing applications in the future.

MSAC also agreed with the intended thrust of the stakeholder meeting to move requesting of these genetic tests beyond the domain of clinical geneticists, noting reliance on the Royal Australasian College of Physicians on addressing issues to do with credentialing and informed consent.

MSAC acknowledged the high clinical need for WEA, and the clear potential of WEA to benefit children by increasing diagnosis of monogenic conditions and reducing the time to obtain a diagnosis. Potential cost-offsets include avoiding a 'diagnostic odyssey' and avoiding unnecessary treatments as a result of a genetic diagnosis. However, the item descriptors require further crafting, and the projected utilisation estimates require further

review. In regards the utilisation estimates, MSAC considered that not all eligible WEA testing would necessarily be billed to the MBS, but more testing by WEA is likely to increase prevalence estimates, and these prevalence estimates need to be multiplied by the number needed to test for each genetic diagnosis.

MSAC was concerned that laboratories would use a lower-cost alternative to WEA for supported item AAAAA (see below), but accepted that laboratories have diagnostic yield targets and would thus be unlikely to use inferior technology.

MSAC advised that, for all supported items, the test requester should either be a clinical geneticist or a specialist paediatrician following consultation with a clinical geneticist, except for supported item CCCC2, as this item relates to family planning where other specialists would be more likely to request the test.

MSAC discussed the possible utilisation of trio testing in item AAAAA and its associated costs. MSAC was concerned that the fee of \$2400 would not cover the costs of trio testing for all laboratories. MSAC acknowledged that MBS items should not create a perverse incentive for trio testing where this would not be necessary. MSAC was also concerned that trio costing could result in large out-of-pocket expenses for patients' families. MSAC accepted that trio testing should be excluded from item AAAAA. The rationale for excluding trio testing in this item AAAAA is that, at this time, MSAC considered that the decision to request trio testing should be made by a sub-specialised clinical geneticist, in consultation with the laboratory. These services are typically located in public hospitals. This also avoids the potential to claim both item AAAAA and item CCCC3, which is intended when needed for segregation purposes.

MSAC considered the possibility of automated analysis to keep testing costs down, but current trials of automated analysis are for carrier testing for prospective parents for low-risk conditions, which would not be suitable for high-risk conditions.

MSAC accepted that the sequencing technology is evolving rapidly, with substantive changes estimated to be every five years. MSAC advised that testing according to item AAAAA be done once per patient in a lifetime, with a review of this decision in five years.

MSAC considered that expanding the population as proposed by the stakeholder meeting and the applicant would result in more people being tested and diagnosed, but with overall reduced diagnostic yield per test conducted, which changes the value proposition. MSAC acknowledged that avoiding the 'diagnostic odyssey' is also part of the value proposition. However, more diagnoses could result in cost offsets by avoiding later unnecessary investigations and treatments, which can be harmful for some patients. MSAC also considered that, currently, it is difficult to quantify other issues, such as likely improved and more timely access to funding via the National Disability Insurance Scheme for those who are found to have a curated germline variant diagnosing a genetically mediated condition.

MSAC noted some issues regarding equity of access, and acknowledged that the clinical referral pathway needed to move away from clinical geneticists being the only professionals requesting the test to ensure equitable access for potentially eligible patients.

MSAC noted that requesters and laboratories both contribute to improving the diagnostic yield. MSAC also noted that the economic model is relatively insensitive to diagnostic yield (ICERs increase from \$5000/QALY for a 50% diagnostic yield to \$9000/QALY for a 30% diagnostic yield).

MSAC accepted that more data would become available through appropriate data collection of post-implementation testing, especially for:

- cost savings and cost offsets as a result of more genetic diagnoses
- utilisation of trio testing
- diagnostic yield patterns for both referrers and laboratories, including by linking AAAAA testing for probands with consequent CCCC2 cascade testing of family members
- referral patterns moving away from clinical geneticists only to include paediatric specialists.

Item descriptors

MSAC advised that the following item descriptors for AAAAA, BBBB1 and BBBB2 would form a suitable basis for further consultation with re-crafted item descriptors to be reviewed by the MSAC Executive. Further policy advice was also sought regarding a time-limited MBS item for WEA of individuals who would be suitable for WEA when AAAAA is first implemented, but who would already be older than the upper age limit. This could be modelled on AAAAA but omitting the upper age limit, and would require an adequate communication plan to the defined requestor population in order to achieve its objective.

Proposed MBS Items
<p>MBS item number: AAAAA</p> <p>Characterisation of germline variants known to cause monogenic disorders, as requested by <u>a clinical geneticist or a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist</u>, following non-informative microarray testing for copy number alteration, in a patient aged ten years or younger with a strong suspicion of a monogenic condition based on the presence of any one of the two following clinical criteria:</p> <ol style="list-style-type: none"> 1. dysmorphic facial appearance and one or more major structural congenital anomalies; or 2. intellectual disability or global developmental delay of at least moderate severity, according to DSM-5 criteria. <p>Analysis may include trio-based sequencing (patient and their biological parents).</p> <p>Performed no more than once per patient.</p> <p>MBS Fee: \$2,400.00 Benefit: 75% = \$1,800.00 85% = \$2,040.00</p> <p>Notes: <u>Trio testing is not encompassed within this item.</u></p>
<p>MBS item number: BBBB1</p> <p>Re-analysis of whole exome data obtained as described under item AAAAA, after an interval of not less than 18 months, for characterisation of previously unreported germline gene variants related to the clinical phenotype, in a patient aged fifteen years or younger with a strong suspicion of a monogenic syndrome, where re-analysis identifies new variants requiring curation, as requested by <u>a clinical geneticist or a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist.</u></p> <p>Performed no more than once per patient.</p> <p>Not to be performed in association with BBBB2.</p> <p>MBS Fee: \$650.00 Benefit: 75% = \$487.50 85% = \$552.50</p>

Proposed MBS Items

MBS item number: BBBB2

Re-analysis of whole exome data obtained as described under item AAAAA, after an interval of not less than 18 months, for characterisation of previously unreported germline gene variants related to the clinical phenotype, in a patient aged fifteen years or younger with a strong suspicion of a monogenic syndrome, where the re-analysis obtained as described under item BBBB1 provides no new information or the re-analysis is limited to one or more previously identified variants of uncertain significance, as requested by a clinical geneticist or a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist.

Performed no more than once per patient.

Not to be performed in association with BBBB1.

MBS Fee: \$350.00

Benefit: 75% = \$262.50 85% = \$297.50

MSAC was concerned about item CCCCC being a combination of tests. Although they are all 'cascade testing', the purpose of the test differs. MSAC considered that there should be three items for cascade testing:

- CCCC1 for sibling testing (which should have a narrower definition of suitable requesters consistent with item AAAAA)
- CCCC2 for reproductive decision-making (which should have a broader definition of suitable requesters consistent with MBS item descriptors for cascade testing in other contexts)
- CCCC3 for segregation studies (which should have a narrower definition of suitable requesters consistent with item AAAAA).

For proposed items CCCC1, CCCC2 and CCCC3, MSAC advised that the following item descriptors would form a suitable basis for further consultation with re-crafted item descriptors to be reviewed by the MSAC Executive:

Proposed MBS Items

MBS item number: CCCC1

Detection of a single gene variant for diagnostic purposes, in a sibling of a patient with a known monogenic condition where previous genetic testing performed in accordance with the conditions specified under item AAAAA, BBBB1, or BBBB2 has identified the causative variant and where the results of the previous proband testing is made available to the laboratory, as requested by a clinical geneticist or a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist.

Not performed in association with item CCCC2 or CCCC3.

Performed no more than once per variant per patient.

MBS Fee: \$400.00

Benefit: 75% = \$300.00 85% = \$340.00

MBS item number: CCCC2

Detection of a single gene variant, for the purpose of reproductive decision making, in a first-degree relative of a patient with a known monogenic condition where previous genetic testing performed in accordance with the conditions specified under item AAAAA, BBBB1 or BBBB2 has identified the causative variant and where the results of the previous

Proposed MBS Items

proband testing is made available to the laboratory, requested by a consultant physician or specialist.

Not performed in association with item CCCC1 or CCCC3.

Performed no more than once per variant per patient.

MBS Fee: \$400.00

Benefit: 75% = \$300.00 85% = \$340.00

MBS item number: CCCC3

Detection of a single gene variant for segregation purposes, in a parent of a patient with a suspected monogenic condition or in a sibling of a patient with a known phenotype, where previous genetic testing performed in accordance with conditions specified under item AAAAA, BBBB1 or BBBB2 has identified a potentially causative variant and where the results of the previous proband testing is made available to the laboratory, as requested by a clinical geneticist or a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist.

Not performed in association with items CCCC1 or CCCC2.

Performed no more than once per parent per variant.

MBS Fee: \$400.00

Benefit: 75% = \$300.00 85% = \$340.00

4. MSAC's advice to the Minister – July 2018 consideration

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC did not support MBS funding of WEA-based genetic testing for childhood syndromes in affected individuals or of associated reinterrogation analysis or of cascade testing.

MSAC acknowledged the high clinical need for testing to diagnose childhood syndromes and the potential benefits this could have for patients and their families. However, MSAC had several major concerns with this application regarding:

- 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
- determining the best type of technology to perform the test
- implementation issues such as equity of access, ethics of consent, specialised workforce availability, and ability to limit to the proposed target population.

MSAC considered that, given the current geographical inequity of access to the test options, a stakeholder meeting involving consumers, requesters and providers to further discuss these issues would assist to inform its reconsideration of this application.

Summary of consideration and rationale for MSAC's advice – July 2018

MSAC noted that this application is for testing for three populations:

- Population 1 – initial testing using next-generation WEA for the diagnosis of childhood syndromes (to detect probands in children 0–18 years of age)
- Population 2 – reinterrogation analysis for patients who did not have a definitive molecular diagnosis at initial WES testing (reanalysing bioinformatics, not retesting)

- Population 3 – cascade single gene testing of first-degree relatives of those affected individuals who are confirmed as having a monogenic childhood syndrome.

MSAC acknowledged that childhood genetic syndromes include a clinically and genetically heterogeneous group of disorders, many of which have a high clinical need. Patients and their families desire diagnosis to inform clinical management, prognosis and genetic counselling.

MSAC noted that this application is limited to monogenic conditions, which typically have their onset in infancy or early childhood. Individual syndromes usually have a constellation of features including dysmorphic facial appearance, single or multiple congenital anomalies, and variable degrees of intellectual disability. MSAC noted that children must exhibit at least two of these features to be eligible for WEA as proposed. MSAC noted that there is an increasing number of monogenic syndromes that do not satisfy these criteria (e.g. immune disorders).

MSAC noted that WEA is a new and rapidly evolving technology. There are more than 15,000 entries in OMIM (a full term list of all genetic conditions and phenotypes) with approximately 50 new entries being added each month. WEA is therefore potentially applicable to many other medical conditions. MSAC considered that, because WEA technology has uses beyond the proposed set of conditions, there is a high potential for use outside the intended patient group. MSAC acknowledged that current restrictions on eligibility and referral by a multidisciplinary panel probably limit this risk, but if the scope of testing is broadened, leakage could potentially be extremely large.

In this context, MSAC noted potential ethical dilemmas affecting implementation of MBS funding arising from whole exome or whole genome sequencing more broadly, including the possibility of reporting ‘off-target’ mutations and variants of unknown significance, both on initial WES testing and on re-interrogation. These would require management via informed consent and recourse to subsequent genetic counselling (with associated cost and likely need for follow-up). These analyses may identify disorders that have no prevention or treatment, non-paternity, consanguinity or incest. There are also possible forensic uses of sequencing data, and issues around data storage and privacy. Consideration should be given to prospectively limiting all WEA reporting to the set of agreed, but evolving, monogenic childhood syndromes clearly curated from the full OMIM to minimise the likelihood of incidental findings that would add to the patient and family’s concerns.

MSAC noted that four laboratories in Australia are currently authorised to perform WEA (including initial testing and bioinformatics reanalysis). MSAC noted that limited access to this technology creates equity issues. MSAC noted that testing includes multidisciplinary review of results led by a clinical geneticist attached to the testing laboratory. The Committee expected that this barrier would serve as a system constraint limiting access and equity. MSAC noted that there may be a risk that care of patients would be permanently transferred from the original referring provider and care setting to a quaternary institution that provides access to the test.

MSAC considered the identified comparators for each population to be appropriate.

MSAC noted feedback from the Royal College of Pathologists of Australasia (RCPA) suggesting that gene panels should be included in the comparator. MSAC accepted that gene panels should be included in the clinical pathway as a triage test before WES. Although whole exome sequencing (WES) fits into the clinical algorithm, it would occur downstream from these initial investigations in other centres. MSAC acknowledged advice from the applicant that, where a molecular diagnosis is found via chromosomal microarray (CMA),

there is likely to be no further utility in carrying out WEA, and that secondary confirmation of WES results is not required.

MSAC noted that the primary Australian evidence for clinical utility in Population 1 (initial testing) was derived from two studies from a single centre involving small numbers of patients (Stark 2016, 46 patients and Tan 2017, 23 patients). MSAC noted that, in the Tan study, the population was described as 2–18 years but the oldest patient was only 10 years of age. MSAC therefore queried the applicability of these results to the broader target population (0–18 years), the vast majority of whom are under 2 years of age.

MSAC noted that between 26% and 33% of patients with a molecular diagnosis will have a change in clinical management according to the three Australian reports with sample sizes ranging between 23 and 48. However there was high heterogeneity in the proportions of actionable diagnoses in the Clark 2018 meta-analysis for WES (18%; 95% CI: 13% to 24%; I^2 : 77%) compared with CMA (6%; 95% CI: 5% to 7%; I^2 : 42). Further, it was not clear whether identification of actionable diagnoses resulted in changes in management. MSAC noted there was only anecdotal evidence for this. It was less clear but critical whether any changes in management led to improved health outcomes for patients. MSAC noted that there was no evidence for this, and no discussion about any consequences of managing false positive diagnoses.

MSAC noted that time to definitive diagnosis was not an endpoint in the Australian studies. MSAC noted evidence from a randomised control trial (NSIGHT1; Petrikin 2018), in which time to diagnosis was a secondary objective, showing that use of rapid whole genome sequencing (rWGS) in addition to standard testing reduced the median time to diagnosis to 13 days, compared to 107 days for standard testing alone. MSAC considered that the applicability of this result to use of WES in Australia was not clear.

MSAC noted that, in an Australian study of 73 patients for whom follow-up data were available, there were no significant differences in mean number of hospital admissions, median days of inpatient care, or mean number of outpatient appointments, either before and after the introduction of WES, or with or without a molecular diagnosis (Stark, 2018).

MSAC noted that the proposed main benefit of a molecular diagnosis for many patients is the cessation of further diagnostic investigations and diagnostic procedures (the ‘diagnostic odyssey’). This is the main influence of WES on quality of life (QoL) for patients and their families. MSAC noted that no QoL data were presented to quantify this influence.

In this context, MSAC noted the wide heterogeneity reported by the Clark 2018 meta-analysis of diagnostic yield in children (aged 0–18 years). The overall results for WES across 32 studies (35%; 95% CI: 31% to 39%; I^2 : 85%) were less favourable than the reported yields for the two Australian studies (57%; 95% CI: 46% to 68% for 80 patients in Stark 2016 and 52%; 95% CI: 37% to 68% for 44 patients in Tan 2017). MSAC noted that this meta-analysis also compared WES diagnostic yield with that for whole genome sequencing (WGS) and CMA. MSAC noted that, across seven studies, WGS (41%; 95% CI: 34% to 48%; I^2 : 44%) appeared to have a higher diagnostic yield than WES, and both were superior to CMA across thirteen studies (10%; 95% CI: 8% to 12%; I^2 : 81%). MSAC also noted that, when combining WES and WGS studies, the pooled yields from nineteen hospital-based studies (41%; 95% CI: 38% to 45%; I^2 : 50%), which included the two Australian studies, also mostly generated higher yields than across the eleven studies from reference laboratories (28%; 95% CI: 24% to 32%; I^2 : 81%). MSAC considered there may be publication bias and possible trends in diagnostic yield over time, but substantial unexplained heterogeneity in diagnostic yield overall.

MSAC noted that improved diagnostic certainty in a proband could serve to restore reproductive confidence for the child's parents. The study by Stark (2018) reported that fourteen couples with diagnosed children and two couples with undiagnosed children sought advice from reproductive genetic services. Early identification of couples at high or low risk would allow them to make decisions about accessing reproductive technologies and testing, including prenatal/preimplantation genetic diagnosis.

MSAC considered that, although reinterrogation analysis in Population 2 seemed to reduce the time to diagnosis, this was based on studies with small numbers, and no cost or utility information was provided for this service. MSAC noted that the clinical evidence for this population was derived from two studies (Stark 2018, Nambot 2017). MSAC noted that the diagnostic yield of WES data reanalysis for 29 infants aged 0-2 years was 4 (14%) further diagnoses (Stark 2018). The Nambot 2017 study showed a cumulative diagnostic yield across 416 patients of 128 (31%) after two reanalyses over three years. MSAC queried whether the additional benefit of reanalysis would narrow over time – as initial testing improves, the incremental diagnostic yield of reinterrogation may plateau or decrease. MSAC also queried the optimal reanalysis interval and overall number of repeats. MSAC noted advice from the applicant that the rate of incidental findings during reanalysis of the initial sequence is lower than the initial analysis itself.

MSAC noted that cascade testing in Population 3 is directed by detection of a mutation in a proband identified in Populations 1 or 2. MSAC noted clinical evidence for this population was derived from one follow-up study (Stark 2018). Of the 88 eligible first-degree relatives of infants aged 0-2 years diagnosed by WES (infants in the Stark 2016 study), 79 underwent cascade testing, of whom 12 received a molecular diagnosis (compared with 5 diagnosed by standard testing), a diagnostic yield of 15%. Of the 12 diagnosed, 3 (25%) had a change in management. However, MSAC noted the low confidence in this data due to the small numbers in this study. MSAC acknowledged that a molecular diagnosis appears to influence genetic counselling in future pregnancies.

MSAC noted feedback from Genetics and Rare Diseases Network (GARDN) and Predisposition Genetic Testing Working Group (PGTWG) expressing concern about the potential impact of increasing numbers of diagnoses on the clinical genetics workforce capacity.

MSAC considered there were a number of issues with the economic model:

- no patient-reported outcomes were included
- the utility gain from SoC diagnoses was assumed to be zero for all patients, whereas a utility gain was assigned to a proportion of patients with WES-based diagnoses
- costs of counselling and three-person review of results were not included
- disutility associated with these conditions may have been underestimated
- costs of extra treatment associated with diagnosis were not included
- the costs and timing and proportions of patients requiring reinterrogation was not clear enough to be assured that Population 1 correctly included Population 2.

MSAC summarised the following additional issues, suggesting that the model was biased in favour of the requested listings:

- the analysis was based on single-centre Australian data, with 30 of the referred cohort considered ineligible and a further nine whose families declined to give consent, leaving an initial sample size of 80 children, of whom 46 received a WES-based molecular diagnosis, of whom fifteen had a change in clinical management, eleven of whom would not have had a diagnosis with SoC

- the risk of bias was high from the non-comparative, non-blinded case series
- the imprecise results relied on were inconsistent with other sources of evidence, which had a risk of publication bias
- there was limited transferability to older children and to a non-tertiary hospital setting, noting that the test may be requested most by general paediatricians
- overall, there was low confidence in the effects of the changes in management to improve health outcomes, noting few of the diagnosed childhood syndromes have existing effective treatments.

MSAC noted that cost-effectiveness and cost-utility analyses were performed for Populations 1 and 3 combined, rather than Population 3 being assessed as an increment over Population 1 (and Population 2), with an ICER of \$7254 per quality adjusted life year (QALY) gained. MSAC noted that the key drivers of the economic model were reported to be the time horizon, the cost of standard care, the cost of WEA, the number of first-degree relatives being tested per proband, and the effect of changes in clinical management on health-related quality of life. MSAC queried the implausible insensitivity of the ICER to the major drivers of cost, change in clinical management, time to diagnosis with standard care, and incremental diagnostic yield, which suggested that model inputs may have been incorrectly specified or not included. MSAC noted that the applicant is working on a within-trial ICER including a 20-year prediction, but this was not available at the time of MSAC consideration.

MSAC considered that the conservative assumptions regarding usage could create substantial financial risk. MSAC further considered that, due to the heterogeneity of clinical and genetic conditions, including those detectable through WES but outside the intent of the application, patient numbers eligible for testing are highly uncertain. The population estimates in the application were based on data from a single centre, and it is not clear how patient numbers will change in the future. MSAC noted that there may be cost savings resulting from reduced testing in patients who receive a diagnosis with WEA, compared with standard of care, but such savings would be outweighed if usage of WES testing extended beyond the intended population.

MSAC noted the proposed fees were high and not clearly justified at \$2400 for initial testing and \$400 for cascade testing. MSAC considered that the out-of-pocket costs would still be high even with MBS listing assuming that the service would not be bulk billed. MSAC also noted that the reinterrogation analysis was proposed to include the costs for pathology and other services, but queried what the real reinterrogation analysis costs following an earlier negative test would be given automation and likely pre-loaded data. MSAC noted there was a wide variation in WEA costs between studies, but no clear drop over time (Schwarze 2018).

In its deliberations, MSAC agreed with the applicant's approach to combine the childhood syndromes rather than undertake a disease by disease approach. MSAC acknowledged the high, but non-urgent clinical need for testing to diagnose childhood syndromes, and the inequity of access to WES-based testing currently across states in Australia with varying controls on access. MSAC also acknowledged that, compared with standard of care (SoC), use of WEA improved diagnostic yield, appeared to shorten the time to diagnosis (although the amount was not quantified) and lead to changes in patient management in perhaps 5% more children in relative terms. As a consequence of these effects the patient may have access to interventions which provide better care and this may translate into patient and family relevant benefits. MSAC noted there may also be psychological harm through the identification of variations of unknown significance and the possibility of overdiagnosis and overtreatment. In addition, the main evidence relied on utility and change data in the context of wide genetic and clinical heterogeneity was derived from limited Australian data from a

small single-centre study, with limited comparisons. MSAC also expressed concern regarding implementation issues due to the high likelihood of leakage.

MSAC noted that it is not possible to know whether an effective therapy is available for an individual patient until after a diagnosis is made. MSAC noted that anecdotal benefits to patients – such as withdrawal of patients from intensive care, reproductive certainty and planning for families with one affected child – are difficult to quantify, which may account for them not being included in the submission. MSAC also acknowledged the ethical difficulty of placing a utility value on a child with a genetic condition not being born.

MSAC further acknowledged the difficulty in quantifying therapeutic consequences and health outcomes arising from diagnosis of genetic syndromes. Because most genetic syndromes are not treated directly, the health outcomes gained are psychological wellbeing or avoidance of further tests or procedures. MSAC considered that it would be desirable for the societal value placed on the ‘value of knowing’ to be captured in the future assessments of genetic testing technologies. MSAC acknowledged that there are also other costs to families of having a child with a genetic condition, such as the expense of early listing on the National Disability Insurance Scheme, and childcare and education expenses, which affect out-of-pocket costs and potentially wider health system costs.

Overall, MSAC emphasised the importance of Population 1 (proband – for diagnosis and the ‘value of knowing’, and likely reducing the ‘diagnostic odyssey’), then Population 3 (family members – for informing family planning, but may need to limit this to first-degree relatives), over Population 2 (reinterrogation of proband data).

MSAC considered that, to ensure momentum is maintained with the evidence-based approach of this application, a meeting should be held involving stakeholders in addition to the applicant, including consumers, requesters (such as the Royal Australian College of Physicians and neurologists) and pathology providers to inform and assist MSAC’s reconsideration of an expected re-application. The stakeholder meeting should further discuss the reasons for not supporting this initial application and examine the basis to provide a broader assessment of the clinical utility value of the requested testing beyond an improvement in health outcomes, to also include the ‘value of knowing’, reducing resources provided and time taken in the ‘diagnostic odyssey’, and the value of avoiding future children with monogenic childhood syndromes through improved family planning options.

5. Background

Application 1476 was considered by MSAC at its July 2018 meeting. MSAC did not support MBS funding of WEA-based genetic testing for childhood syndromes in affected individuals or of associated reinterrogation analysis or of cascade testing and considered that a stakeholder meeting would assist to inform its reconsideration of this application.

6. Prerequisites to implementation of any funding advice

Genetic testing must be performed in laboratories that have received relevant National Association of Testing Authorities (NATA) accreditation.

7. Proposal for public funding

The proposed item descriptor(s) for public funding is summarised in Table 1.

Table 1 Proposed Medicare Benefit Scheme (MBS) item descriptors

<p>Genetics – Pathology Services Table</p> <p>MBS item number: AAAAA</p> <p>Characterisation of germline variants via whole exome analysis, from a phenotypically driven gene list where analysis is limited to variants in genes currently known to cause monogenic disorders, requested by a clinical geneticist following multidisciplinary review and non-informative microarray testing for copy number alteration, in a patient (<18 years old) with a strong suspicion of a monogenic syndrome based on the following criteria: Onset of clinical features prenatally, in infancy or childhood, and a minimum of two of the following features: Dysmorphic facial appearance, and/or Single or multiple congenital anomalies, and/or Intellectual disability.</p> <p>MBS Fee: \$2,400.00 Benefit: 75% = \$1,800.00 85% = \$2,040.00</p>
<p>Genetics – Pathology Services Table</p> <p>MBS item number: BBBB1</p> <p>Re-analysis of whole exome data obtained under item AAAAA, at an interval of not less than 18 months, for characterisation of new germline gene variants related to the clinical phenotype, in a patient (<18 years old) with a strong suspicion of a monogenic syndrome, where re-analysis identifies new variants requiring curation.</p> <p>MBS Fee: \$650.00 Benefit: 75% = \$487.50 85% = \$552.50</p>
<p>MBS item number: BBBB2</p> <p>Re-analysis of whole exome data obtained under item AAAAA, at an interval of not less than 18 months, for characterisation of new germline gene variants related to the clinical phenotype, in a patient (<18 years old) with a strong suspicion of a monogenic syndrome, where the re-analysis is negative.</p> <p>MBS Fee: \$350.00 Benefit: 75% = \$262.50 85% = \$297.50</p>
<p>Genetics – Pathology Services Table</p> <p>MBS item number: CCCCC</p> <p>Request by a specialist for the detection of a single gene variant, in a first-degree relative of a patient with a known monogenic syndrome where previous genetic testing performed under item AAAAA or BBBB1 has identified the causative variant.</p> <p>MBS Fee: \$400.00 Benefit: 75% = \$300.00 85% = \$340.00</p>

8. Summary of Public Consultation Feedback/Consumer Issues

Targeted consultation was undertaken, with three responses received from professional organisations.

Overall, the responses were supportive of genetic testing for childhood syndromes. However, one respondent did not agree with the proposed population and MBS item descriptor. They also indicated that, targeted gene panels may be more appropriate and cost effective whilst delivering better coverage of included genes, particularly if clinical assessment suggests a phenotype (e.g. "ciliopathy panel").

9. Proposed intervention's place in clinical management

The proposed intervention is genetic testing of all genes known to cause Mendelian diseases in humans. In practice, for each individual patient, a clinician with appropriate expertise may propose a selection of genes for prioritised analysis based on the patient's phenotype. If a

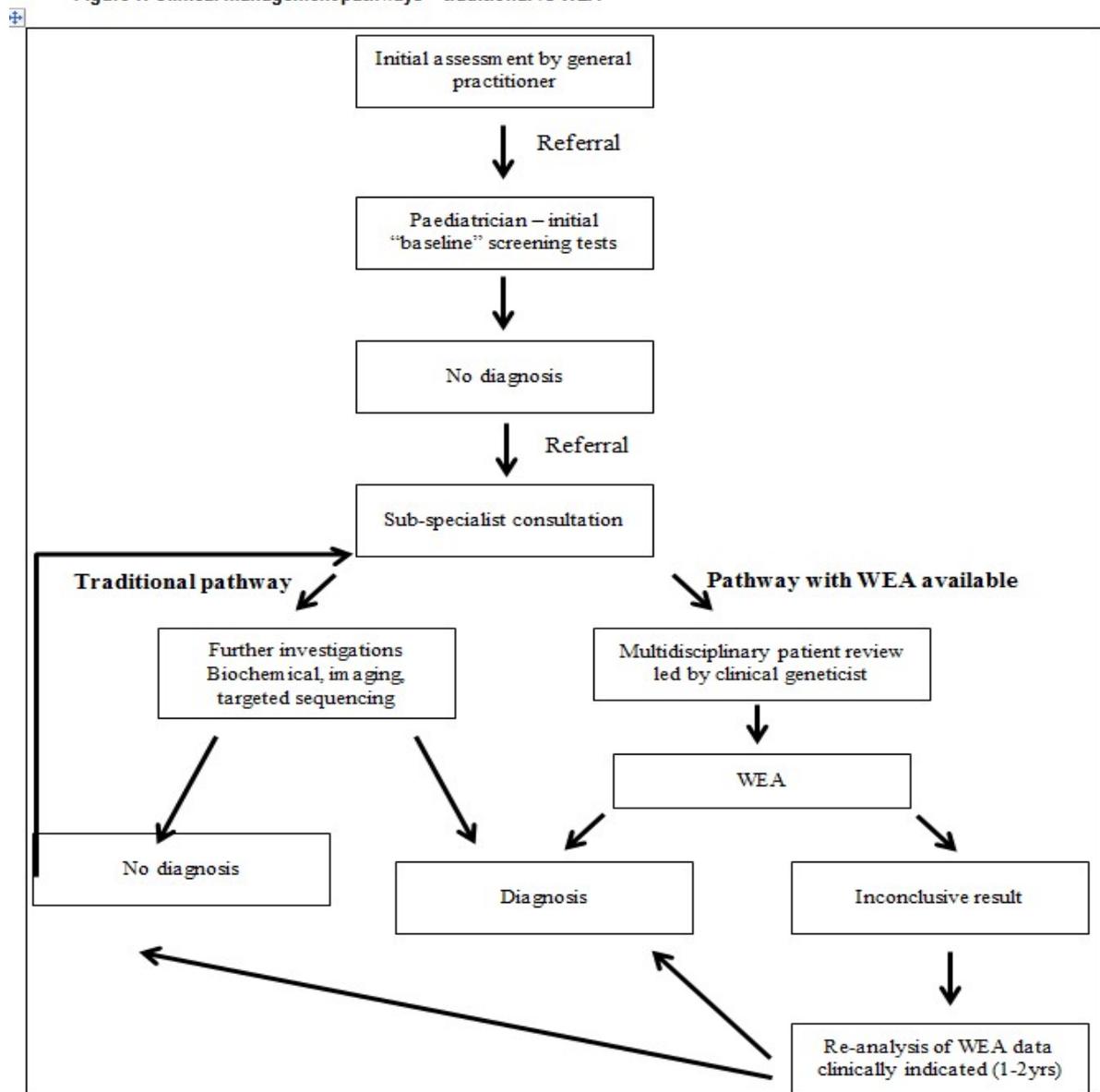
molecular diagnosis cannot be made from this initial list, investigation expands to all other genes known to cause genetic conditions (often referred to as the ‘mendeliome’), with a molecular diagnosis only made where there is sufficient evidence that a variant/s is/are linked to the individual’s phenotype.

Monogenic childhood syndromes are a clinically and genetically heterogeneous group of disorders, typically with onset during infancy or early childhood. Individual syndromes usually have a constellation of features including, but not limited to, facial dysmorphism, congenital malformations, single or multi-organ functional anomalies, and variable degrees of intellectual disability.

Each genetic syndrome will have specific clinical features, depending on which organ systems are affected by the abnormal genes. The most commonly observed phenotypes are categorised as neurodevelopmental, musculoskeletal, ophthalmologic, and cardiovascular.

With the introduction of diagnostic whole exome analysis, a molecular diagnosis may be made for these patients.

Figure 1: Clinical management pathways – traditional vs WEA



10. Comparator

The genetic test targets three different patient populations. The comparators for each population are:

- Population 1 (≤ 2 years of age with suspected monogenic syndromic genetic disorders): standard of care (SoC) ‘diagnostic odyssey’
- Population 2 (test-negative patients from Population 1): no re-analysis and standard care
- Population 3 (first-degree relatives): cascade testing in families after diagnosis by standard/current methods.

11. Comparative safety

See comparative effectiveness section.

12. Comparative effectiveness

Key analytical performance results

Whole exome analysis (WEA) has a superior diagnostic yield to SoC.

Population 1: Initial testing for the diagnosis of childhood syndromes

Pooled diagnostic yield for whole genome sequencing (WGS), whole exome sequencing (WES) and chromosomal microarray (CMA) in children (aged 0–18 years) with any suspected genetic disease (Table 2) were reported in a systematic literature review and meta-analysis (Clark *et al* (2018)). WGS has a higher diagnostic yield than WES, and both were superior to CMA.

Table 2 Pooled diagnostic yield of WGS, WES and CMA

Genetic test	Diagnostic yield	95% CI	Heterogeneity (I^2)
WGS	41%	34–48%	44%
WES	35%	31–39%	85%
CMA	10%	8–12%	81%

Abbreviations: CI, confidence interval; CMA, chromosomal microarray; WES, whole exome sequencing; WGS, whole genome sequencing

Source: Clark *et al* (2018)

The diagnostic yield of WES in infants (aged 0–2 years) and children (aged 2–18 years) who are suspected of having a monogenic disorder (Table 3) were reported in two Australian prospective studies (Stark *et al* (2016) and Tan *et al* (2017)).

Table 3 Diagnostic yield of WES compared to standard diagnostic pathway in Australian paediatric populations

Study	Population	WES n/N (%)	Standard care n/N (%)	RR [95% CI]	P-value
Stark <i>et al</i> (2016)	Infants aged 0–2 years	46/80 (57.5%)	11/80 (13.75%)	4.18 [2.34, 7.47]	< 0.00001
Tan <i>et al</i> (2017)	Children aged 2–18 years	23/44 (52%)	0/44 (0%)	47.00 [2.94, 750.43]	0.006

Abbreviations: NR, not reported; WES, whole exome sequencing

Source: Stark *et al* (2016), Tan *et al* (2017), Stark *et al* (2017)

Population 2: Re-interrogation analysis for patients who did not have a definite molecular diagnosis at initial WES testing

The diagnostic yield of WES data re-analysis was 14% in a follow-up study (Stark *et al* (2018)) investigating the longer-term clinical impacts and cost-effectiveness of WES in infants aged 0–2 years with suspected monogenic disorders.

Population 3: Cascade testing of first-degree family members

The diagnostic yield of cascade testing was 15% in the follow-up study (Stark *et al* (2018)). Of the 88 eligible first-degree relatives of infants diagnosed by WES, 79 (90%) underwent cascade testing. Of those 79 relatives, twelve received a molecular diagnosis.

Key clinical validity results

Clinical validity is difficult to define in this patient group due to the multitude of conditions being tested.

Key clinical utility consequences

Overall, WEA appeared to alter clinical management, shorten the time to diagnosis and provide patient and family-relevant benefits compared with SoC. One key benefit for many patients is the cessation of further diagnostic investigations and procedures (i.e., ending the ‘diagnostic odyssey’). Improved health outcomes as a consequence of diagnosis and changes in clinical management are also important.

In a clinically ascertained cohort of 80 infants aged 0–2 years undergoing genomic testing (Stark 2016), the following anecdotal outcomes have been observed:

- *preventing further disease progression and worsening disability* in a child with thiamine transporter dysfunction syndrome who was treated because of the correct diagnosis being made, and the patient did not deteriorate further.
- *improved management of known disease complications* in a child with *RMND1*-related mitochondrial disease who was treated for life-threatening hyperkalaemia because of the correct diagnosis being made.
- *reduced number of hospital admissions* in two children who were started on the correct treatment for their condition, one with alternating hemiplegia of childhood and the other with Hz/Hc syndrome.

Given the above, the clinical events to determine clinical utility in an affected individual have been defined as: change in clinical management, time to definitive diagnosis, health resource change, and quality of life.

Population 1: Initial testing for the diagnosis of childhood syndromes

Change in management: Studies report that clinical management was changed in 18–33% of patients who received a molecular diagnosis by WEA (Table 4). Management changes included initiation of additional treatments or surveillance, cessation of treatment or surveillance, or modification to existing treatment regimens.

Table 4 Summary of change in management after molecular diagnosis by whole exome analysis

Study	Patient population	Change in management n/N (%)
Stark <i>et al</i> (2016)	Infants aged 0–2 years	15/46 (32.6%)
Tan <i>et al</i> (2017)	Children aged 2–18 years	6/23 (26%) ^a
Stark <i>et al</i> (2018)	Follow-up study with infants from Stark <i>et al</i> (2016)	16/48 (33%) ^b
Clark <i>et al</i> (2018) ^c	Children aged <18 years	WGS ^d : 27% (95% CI: 17–40%; <i>P</i> =54%) WES ^e : 18% (95% CI: 13–24%; <i>P</i> =77%)

Abbreviations: WES, whole exome sequencing; WGS, whole genome sequencing

^a One infant also had additional diagnostic investigation cancelled and the parents of another had preimplantation genetics planned.

^b Includes 44 infants who received a molecular diagnosis after initial WES and 4 infants who received a molecular diagnosis after re-analysis of WES data.

^c Meta-analysis of 36 studies including 20,068 children (WGS, WES, and CMA).

^d Meta-analysis of 26 studies including 9,014 children (WES only).

^e Meta-analysis of 7 studies including 374 children (WGS only).

Time to definitive diagnosis: Time to definitive diagnosis was not reported in the two Australian studies identified. However, the median time to report in these studies ranged from 134 to 181 days (Table 5).

Table 5 Mean duration of follow-up and average age at enrolment in Australian studies

Study	Patient population	Mean age at enrolment (range)	Median time to report or median post-report follow-up (range)
Stark <i>et al</i> (2016)	Infants aged 0–2 years	8 months (1 week–34 months)	134 days to report (83–278 days)
Tan <i>et al</i> (2017)	Children aged 2–18 years	28 months (0–121 months)	181 days to report (40–283 days)
Stark <i>et al</i> (2018)	Infants aged 0–2 years	As per Stark <i>et al</i> (2016)	473 days post-report follow-up (IQR 411–650 days)

Abbreviations: IQR, interquartile range

One randomised controlled trial (RCT) (Petrikin *et al* (2018)) focussing solely on rapid WGS (rWGS) + standard testing versus standard testing alone showed that the median time to diagnosis in the rWGS + standard testing group was 13 days (range 1–84 days), while the median time to diagnosis in the standard testing alone group was 107 days (range 21–429 days). As expected, the time to diagnosis using rapid sequencing would be significantly below that expected by standard WEA or even standard WGS.

Health resource changes: An Australian longer-term follow-up study (Stark *et al* (2018)) showed no difference in utilisation of tertiary paediatric hospital services pre- or post-result comparing those patients who received a molecular diagnosis and those who did not. Further analysis showed that among patients who received a diagnosis, WEA did not result in any significant difference in the utilisation of tertiary paediatric hospital services pre- or post-result. Whereas in patients who remained undiagnosed, WEA resulted in a significant increase in the clinical trajectory (mean difference of 142 days; 95% CI: 57.63 days to 226.37 days; $p=0.001$). Other measures of utilisation of tertiary paediatric hospital services (i.e. hospital admission, days as an inpatient, and outpatient appointments) were not significantly different in undiagnosed patients pre- or post-result.

Quality of life: No data available for this population (0-18 yrs).

Population 2: Re-interrogation analysis for patients who did not have a definite molecular diagnosis at initial WES testing

Time to diagnosis: One RCT comparing rWGS + standard testing versus standard testing alone reported median time to diagnosis as 54.73 months in the first year, which was reduced by 9 months to 46.65 months in the third year (Nambot *et al* (2017)).

Data for change in management, health resource changes, and quality of life were not available for this population. However, there is no reason to consider the outcomes would be sufficiently different from that observed in Population 1 (initial testing).

Population 3: Cascade testing of first-degree family members

Change in management: In an Australian study investigating the longer-term impacts of WEA in infants aged 0–2 years (Stark *et al* (2018)), three out of twelve (25%) first-degree relatives who received a molecular diagnosis had a change in management.

Restoration of reproductive confidence: In an Australian study investigating the impacts of WEA in infants aged 0–2 years, 28 couples out of 41 families tested (68.3%) were identified as being at high risk of recurrence in future pregnancies following molecular diagnosis of their child (Stark *et al* (2016)). By comparison, standard diagnostic investigations would have identified 46% (13/28) of these couples (RR 2.15; 95% CI: 1.31, 3.53; $p=0.002$). In Stark *et al* (2018), two couples with undiagnosed children and 14 couples with diagnosed children sought advice from reproductive genetic services. Importantly, 9 couples with diagnosed

children had an ongoing pregnancy compared with just one couple with a child who had remained undiagnosed.

Health resource costs: The costs associated with change in management of first-degree relatives who received a molecular diagnosis through cascade testing depends on the diagnosis itself.

13. Economic evaluation

A series of cost-utility analyses was presented reporting the cost per additional quality-adjusted life year (QALY) generated by the introduction of WEA testing. The data from Stark *et al* (2016), Stark *et al* (2017) and Stark *et al* (2018) publications were used to construct a Markov model that compared WEA with SoC in the proband population and first-degree relatives that may be affected by these results through cascade testing (i.e. siblings and parents).

Table 6 presents the base case incremental cost-effectiveness ratio (cost per QALY gained) for WEA versus SoC.

Table 6 Base case incremental cost-utility ratio – with cascade testing (discounted)

Strategy	Cost	Incremental cost	Effect (QALYs)	Incremental effect (QALYs gained)	ICER (cost per additional QALY)
SoC	\$11,175.91	-	6.330	-	-
WEA	\$12,495.24	\$1319.33	6.512	0.182	\$7254.62

Abbreviations: ICER, incremental cost-effective ratio; QALY, quality-adjusted life year; SoC, standard of care; WEA, whole exome analysis

Ranking by order of effect on the ICER, the model is most sensitive to halving the modelled time horizon, decreasing the cost of SoC by 20%, increasing the cost of WEA by 20%, increasing the number of first-degree relatives per test positive affected individual (proband) by 1.0 and decreasing the change in clinical management effect on preference-based health-related quality of life by 20%.

14. Financial/budgetary impacts

Implementing WEA early in the diagnostic pathway is expected to result in cost savings to the MBS due to the reduction in the ‘diagnostic odyssey’; however, the exact value of cost savings is difficult to quantify. Therefore, the costs to the MBS associated with the proposed listings are the upper limits expected for initial WEA for diagnosis (Population 1), re-analyses of whole exome data (Population 2), and cascade testing of first-degree family members (Population 3).

The upper limit of the total costs to the MBS for the three proposed populations projected during 2019–2023 are presented in Table 7, Table 8 and Table 9, respectively.

Table 7 Projected cost of initial WEA (Population 1), 2019–2023

	2019	2020	2021	2022	2023
Number of patients	3,406	3,454	3,503	2,753	2,803
Cost of WEA per patient	\$2,400	\$2,400	\$2,400	\$2,400	\$2,400
Total cost	\$8,173,856	\$8,290,368	\$8,408,246	\$6,607,205	\$6,727,129
MBS rebate (85%)	\$6,947,777	\$7,046,812	\$7,147,009	\$5,616,125	\$5,718,060
Patient contributions	\$1,226,078	\$1,243,555	\$1,261,237	\$991,081	\$1,009,069

Table 8 Projected cost of whole exome re-analyses (Population 2), 2019–2023

	2019	2020	2021	2022	2023
Costs associated with first re-analysis					
<i>Positive findings</i>					
Number of patients	-	-	200	203	205
Cost of re-analysis per patient	\$650	\$650	\$650	\$650	\$650
Total cost	\$-	\$-	\$129,837	\$131,687	\$133,560
MBS rebate (85%)	\$-	\$-	\$110,361	\$111,934	\$113,526
Patient contributions	\$-	\$-	\$19,475	\$19,753	\$20,034
<i>Negative findings</i>					
Number of patients	-	-	1,248	1,265	1,283
Cost of re-analysis per patient	\$350	\$350	\$350	\$350	\$350
Total cost	\$-	\$-	\$436,697	\$442,922	\$449,219
MBS rebate (85%)	\$-	\$-	\$371,192	\$376,483	\$381,836
Patient contributions	\$-	\$-	\$65,505	\$66,438	\$67,383
Costs associated with second re-analysis					
<i>Positive findings</i>					
Number of patients	-	-	-	-	172
Cost of re-analysis per patient	\$650	\$650	\$650	\$650	\$650
Total cost	\$-	\$-	\$-	\$-	\$111,919
MBS rebate (85%)	\$-	\$-	\$-	\$-	\$95,131
Patient contributions	\$-	\$-	\$-	\$-	\$16,788
<i>Negative findings</i>					
Number of patients	-	-	-	-	1,076
Cost of re-analysis per patient	\$350	\$350	\$350	\$350	\$350
Total cost	\$-	\$-	\$-	\$-	\$376,433
MBS rebate (85%)	\$-	\$-	\$-	\$-	\$319,968
Patient contributions	\$-	\$-	\$-	\$-	\$56,465
Total population (re-analyses)					
Total cost	\$-	\$-	\$566,533	\$574,609	\$1,071,131
MBS rebate (85%)	\$-	\$-	\$481,553	\$488,418	\$910,461
Patient contributions	\$-	\$-	\$84,980	\$86,191	\$160,670

Table 9 Projected cost of single variant cascade tests of first-degree family members (Population 3), 2019–2023

	2019	2020	2021	2022	2023
Number of patients	5,235	5,309	5,385	4,231	4,308
Cost of cascade testing per patient	\$400.00	\$400.00	\$400.00	\$400.00	\$400.00
Total cost	\$2,093,835	\$2,123,681	\$2,153,877	\$1,692,518	\$1,723,238
MBS rebate (85%)	\$1,779,760	\$1,805,129	\$1,830,796	\$1,438,640	\$1,464,752
Patient contributions	\$314,075	\$318,552	\$323,082	\$253,878	\$258,486

15. Key issues from ESC for MSAC

Key issues from ESC to MSAC

ESC KEY ISSUES	ESC ADVICE
Large number of disorders, emerging data	Note breadth of diseases categorised together for this HTA consideration
Australian data with 1 centre/study	Consider the applicability of Australian data that comes from only one study/centre
Strength of evidence	<p>Consider whether the evidence base is robust enough to support a clinical claim of superiority – data rests on one prospective clinical study with small sample sizes and treatment in parallel</p> <p>Consider including the cap of 2 reanalyses in the MBS item descriptor – costs will be higher if there is no cap</p>
MBS listing	<p>Consider whether MBS listing would lead to leakage (lower threshold for testing, more children being tested), which would increase costs</p> <p>Consider whether MBS listing would lead to increased capacity for testing, which would increase costs</p>
Note issues raised by PGTWG	<ul style="list-style-type: none"> • Clinical utility • Prior test = microarray triage • Analytical validity • Re-analysis • Capacity • WGS vs WES

ESC discussion

The application proposes MBS listing of testing for three populations: 1) initial testing using next generation WEA for the diagnosis of childhood syndromes (to detect probands); 2) re-interrogation analysis for patients who did not have a definite molecular diagnosis at initial WES testing; and 3) cascade testing of first-degree family members of those affected individuals who are confirmed as having a monogenic childhood syndrome. The frequency of reanalysis would be capped at 2, with a minimum 18-month interval. This involves reanalysing the bioinformatics, not re-performing the test.

ESC noted the breadth of diseases that may be covered by this application. The monogenic syndromes targeted by the proposed WEA are a clinically and genetically heterogeneous group of disorders. The OMIM – a full term list of all genetic conditions and phenotypes – includes over 24,400 entries, making it difficult to develop a definitive list. In addition, approximately 50 new entries are added to OMIM each month, highlighting that this is an emerging and evolving field. The proposed upper limit of genes for testing is all genes known to cause Mendelian diseases. In practice, clinicians may propose a selection of genes based on the patient's phenotype.

The prevalence of variants causing childhood syndromes is unknown. It is estimated that 8% of the population has a rare disorder, and 8000–10,000 rare diseases are genetic. The global

prevalence of all single gene diseases at birth is estimated at 10 per 10,000 births; however, this includes conditions such as cystic fibrosis, so is likely to be an overestimation. Within the target population, it is expected that about half will have a condition with a genetic cause. About a quarter to a half would be diagnosed by whole exome sequencing (WES).

The clinical claim proposed by the applicant is that genetic testing via WEA in patients suspected of childhood syndromes is superior to standard care. The applicant argued that the overall claim is for superiority; therefore, a cost-effectiveness analysis was conducted.

ESC noted estimates for the proportions of affected individuals that would fall within the target populations. For Population 1 (initial diagnosis), estimates ranged from 40–50% (infants under 2 years referred to a paediatric hospital genetics department) to around 70% (children aged 2–18 years with a suspected monogenic disorder eligible for a prospective study).

ESC noted for Population 2 (re-interrogation analysis), an estimated 55–75% of patients would be eligible for re-interrogation. For Population 3 (cascade testing), an average of three first-degree family members per positive molecular diagnosis would be eligible for cascade testing; however, it was noted that around 10% of families decline cascade testing.

ESC agreed with the contracted assessment (CA) that WEA has a superior diagnostic yield to standard of care (SoC), although wide confidence intervals and high heterogeneity in some studies were noted. Australian prospective studies showed a higher diagnostic yield than studies from the UK and Canada, but the reason for this difference is unknown. Compared with Sanger sequencing, WES showed a false negative rate of 2%. However, the comparison was limited to genes with adequate coverage, so it was not possible to determine true analytical validity.

ESC agreed with the CA that, compared with SoC overall, WEA appeared to lead to changes in clinical management, shorten the time to diagnosis, and provide patient and family-relevant benefits. The main benefit of genetic diagnoses is cessation of further investigations and procedures. Studies showed about a third of Australian patients who were diagnosed by WES had a change in their clinical management (initiation or cessation of treatment or surveillance, or modified treatment regimen). However, there was high heterogeneity between studies. Anecdotal benefits reported in the literature include preventing further disease progression, improved management and reduced number of hospital admissions. The main benefit for Population 3 (cascade testing) was restoration of reproductive confidence. WEA identified more families at high risk of recurrence than standard diagnostic investigations. Early identification of couples at high or low risk allows them to make decisions about their reproductive choices (eg use of preimplantation genetic testing). However, ESC noted that the clinical evidence involved small numbers of patients from a single centre in Australia, so the generalisability of these results was uncertain.

ESC noted results from an RCT of rapid whole genome sequencing (rWGS) with standard testing compared to standard testing alone. Almost a third of patients had a change in management but there was no significant difference between the two groups. However, rWGS is a different technology to WES, so the applicability of these results is uncertain.

Regarding utilisation of health resources, ESC noted the Australian study showing that although WEA resulted in a significant difference in clinical trajectory, utilisation of hospital services was not different after molecular diagnosis. Although the study was limited by a small sample size, it seems WEA can improve patient management without significantly

increasing healthcare costs. Health resource costs in Population 3 (cascade testing) depend on the diagnosis (e.g. changes in treatment, use of reproductive genetic services, termination).

ESC noted that the impact on quality of life of a positive diagnosis or negative findings after WEA was not reported in the studies identified.

ESC noted the following feedback from the Predisposition Genetic Testing Working Group (PGTWG) on other significant factors:

- Clinical utility is difficult to quantify for multiple diseases. Utility should be ranked in terms of what changes health outcomes for patients; that is, over enabling more informed family planning decisions, reducing the ‘diagnostic odyssey’ or providing peace of mind.
- More detail is required on the microarray triage before WES.
- In many cases, a molecular diagnosis made by WES will need to be confirmed by a second testing method.
- Reanalysis should be limited to the set of childhood syndromes to minimise the likelihood of incidental findings that would add to the patient’s/family’s concerns.
- There are possible capacity constraints on WES testing in Australia. There are only four clinical diagnostic laboratories currently providing National Association of Testing Authorities (NATA)-accredited services for WES.
- Whole genome sequencing (WGS) is superior to WES in terms of diagnostic yield.

ESC noted that WGS is more expensive than WES and that there is debate about whether WGS is superior to WES. ESC also noted that WES testing is an emerging technology and only done by a few laboratories. If funding is limited to WES then testing would be limited to only those centres.

The economic evaluation focused on data from three Australian studies, based on a single study by Stark in 2016.

ESC noted that, although WES appears to be cost-effective when compared to SoC, there are some uncertainties about the quality of the evidence. The Stark 2016 study was biased by some clinicians not performing all the SoC genetic tests due to financial constraints. Assumptions were therefore made about what would happen if all tests were done.

The economic evaluation assumed diagnostic yield of 55% for WES and 27.5% for SoC. The meta-analysis of diagnostic sensitivity demonstrated moderate to severe heterogeneity between studies.

ESC noted that the key translation issues in the model were:

- applicability – the key study involved patients aged 0–2 years, and there is no information on the applicability of this subgroup to the proposed MBS population (0–18 years); subgroup analysis could have been done
- transformation – utility scores could not be verified, but the incremental gain is small
- other translation – time to definitive diagnosis is a key driver of the economic model but was not reported in Australian studies; it was assumed to be 5 months for WEA (based on expert opinion) and 22 months for SoC

- time horizon – 10 years is not justified; the median time to report and median follow-up total around 19 months, and longer-term costs and utility changes were not considered so are uncertain.

Costs are the main driver of the economic model. Most of the cost occurs in the initial testing phase and then becomes a maintenance cost. The period of testing, or time to diagnosis, therefore has a major influence on the model. The model includes the cost of reanalysis every 18 months, assuming that every person with a negative test would have reanalysis. It also assumes that this frequency of testing continues indefinitely, although the application proposes that reanalyses are capped at 2. Estimates of cumulative cost are therefore uncertain.

ESC queried whether reanalysis after 18 months would be done for all children with a negative result, or whether the clinical panel would decide which children are eligible for reanalysis. This was not clear in the application. ESC also discussed whether the false negative rate for WES of 2% quoted by the clinical discussant would lead to reanalysis for reasons other than new genes or variants and agreed that it would be a possibility. However, there will always be false negatives, and technologies change over time so there will always be reasons to retest.

Given the uncertainty in the model, ESC queried whether a within-trial ICER may be more appropriate. Sensitivity analysis by the discussant showed that the ICER increases if WES time to diagnosis is increased or SoC time to diagnosis is reduced, and there is a moderate change if the time horizon is limited to 2 years. ESC noted that the ICERs seemed reasonable, but noted the uncertainties in the model.

ESC noted that the sensitivity analysis in the evaluation was based on the reproductive benefits to parents however that there is very little information about this analysis.

ESC noted that the incremental benefit of WEA in terms of quality-adjusted life years (QALYs) gained is small and accumulates over time and it is mainly driven by retesting of children who originally tested negative.

ESC noted the total cost to the MBS over 5 years is \$42,675,292. Financial and budgetary impacts will be greater if:

- the proportion of suspected syndromic genetic disorders and congenital abnormalities increases
- MBS listing leads to increased supply/capacity of WEA providers
- MBS listing leads to a lower threshold for testing and more children being tested (leakage).

ESC noted that there was no justification given for the \$2400 fee in the MBS descriptor and that re-interrogation evidence seems to be weak and queried the value of two re-interrogation items with different fees. It was clarified that after a positive result (\$650 fee) there would be no further re-interrogation. Re-interrogation after a negative result (\$350 fee) could continue indefinitely every 18 months if it is not capped. It was therefore suggested that the cap of 2 reanalyses should be written into the relevant MBS item descriptor.

ESC agreed with the Department's changes to the proposed MBS item descriptor to change wording to "requested by a specialist or consultant physician" and considered the revised item descriptor to be reasonable.

ESCs noted from the consumer perspective that the proposed test appears to be safe and the importance of insuring the test is accurate as incorrect results may be detrimental. From this perspective, there is also some uncertainty about the comparator, considering that a molecular diagnosis would be made by a specialised clinician and could lead to other tests to confirm the diagnosis. It was noted that there may be some access/equity issues due to the nature of the test and a need for access to specialist clinicians and genetic counselling.

16. Other significant factors

Nil

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

The applicants are pleased with the recommendation by MSAC supporting MBS listing of genomic testing for childhood syndromes and intellectual disability, including the time limited expansion of this testing to patients older than 10 years of age. Support for testing in these populations is a very important step forward for patients and their families.

We support MSAC's advice that further consultation is required to re-craft item descriptors, and offer our assistance in this process. The current item descriptor AAAAA should indicate "genome-wide" characterisation of germline variants, and the applicants also suggest the removal of the explicit exclusion of trio testing as part of item AAAAA. The restriction to singleton WEA will limit the ability of the testing laboratories to improve processes to provide timely services under a supply constrained environment. There are significant time savings associated with analysis of trio sequencing with curation times halved for trio analysis compared with singleton analysis. Trio testing also has the added advantage of minimising reporting of variants of unknown significance which can also add to the burden on families and clinical genetics services. Where trio testing is carried out there is also no longer a requirement to perform item CCCC3. Laboratories should be able to determine the most appropriate processes for their work flows and trios may be an option they will employ even with restricted funding.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)