Australian Government

Medical Services Advisory Committee

Public Summary Document

Application 1585 –Genetic testing for the diagnosis of early-onset or familial neuromuscular disorders

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

Date of MSAC consideration: **MSAC Executive Meeting, 8 December 2021**
MSAC Executive Meeting, 24 September 2021
MSAC 82nd Meeting, 29-30 July 2021

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 the creation of MBS items for genetic testing for the diagnosis of early-onset or familial neuromuscular disorders (NMDs) was received from the RCPA by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported creation of new Medicare Benefits Schedule (MBS) items for the genetic testing of certain patients with neuromuscular disorders (NMDs). MSAC recognised the clinical need for this testing but considered that some uncertainty remained in the estimated cost-effectiveness and financial impact, and so requested further analyses be provided to the MSAC Executive to confirm these are within an acceptable range. The MSAC Executive confirmed both were acceptable, removing the caveat around MSAC's support.

MSAC supported panel testing of affected individuals, cascade testing of biological relatives, fetal testing for known and unknown variants, reproductive partner testing and data re-analysis. MSAC advised that panel testing should use next-generation sequencing (NGS) methods with a full capture and sequencing background to ensure future data re-analysis is possible. MSAC also advised that a practice note be added to the panel testing item to ensure single gene tests for variants not detectable using NGS methods are conducted before panel testing, where a specific NMD best detected by those methods is clinically suspected.

Consumer summary

The Royal College of Pathologists of Australasia (RCPA) applied to the Medical Services Advisory Committee (MSAC) for public funding through the Medicare Benefits Schedule (MBS) for genetic testing (including a gene panel test) for the diagnosis of specific neuromuscular disorders.

Neuromuscular disorders affect nerves and/or muscles and how they function. Gene panel tests look for variants in many genes at the same time and can allow diagnosis of some neuromuscular disorders. Diagnosed patients and their clinicians would then have the option to go on with cascade testing to identify any close family members who might also be affected. They could also consider testing reproductive partners, and prenatal testing, so that those planning a baby can make informed reproductive decisions. Later re-analysis of the data from the gene panel would also be done, should new genes be found to be diagnostic for neuromuscular disorders.

MSAC recognised the clinical need for this type of genetic testing. Currently, neuromuscular disorders are diagnosed by imaging studies, muscle and/or nerve biopsies, and nerve conduction studies. MSAC considered genomic panel testing to be safer and more effective than the tests used currently. MSAC considered that funding this testing would likely significantly reduce healthcare costs to the MBS. MSAC considered that the value for money and total cost of this testing were uncertain but would likely be acceptable. MSAC asked the Department of Health to do further economic and financial analysis to confirm this before finalising the advice to support all items proposed in this application: gene panel testing, cascade testing, reproductive partner and prenatal testing, and re-analysis. The Department provided these analyses to the MSAC Executive, which advised both were acceptable, confirming MSAC's support for all items in this application.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported listing genetic testing for neuromuscular disorders on the MBS. MSAC considered the testing to be safe and effective, and likely cost-effective. However, MSAC requested more information to confirm the cost-effectiveness and total financial cost of this testing before it is listed on the MBS. The MSAC Executive confirmed both were acceptable, confirming MSAC's support for all items in this application.

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

MSAC noted that this application is for the MBS listing of genomic panel testing of patients suspected to have a NMD, for the purposes of diagnosis, providing prognostic information, enabling cascade testing of at-risk family members for what is usually a novel genetic variant, and enabling informed reproductive decision-making.

MSAC noted that there is large clinical heterogeneity both between and within NMDs, as well as genetic heterogeneity. MSAC noted that one study[1] estimated the cumulative prevalence of NMDs to be 37/100,000 people, though it considered the true prevalence is likely higher because this estimate excluded some types of NMDs.

[1] Norwood, FLM, et al., 2009. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population, *Brain*, **132**(11): 3175–3186.

MSAC noted that the National Pathology Accreditation Advisory Council (NPAAC) requirements[2] already encompass counselling requirements, and agreed with the applicant's request to remove "after appropriate genetic counselling" from the item descriptor. MSAC noted that counselling is required if the test has the potential to identify pre-symptomatic individuals. MSAC noted that specialists can offer genetic counselling, and that pathology laboratories are currently obliged to ensure that the appropriate informed consent has been obtained from the patient before testing and analysis.

MSAC noted that re-analysis would not be possible if AAAA had been done using panel testing methods that restricted library preparation and sequencing to the genes of interest (selected up front), and also that there is a "once per lifetime" restriction on item AAAA. MSAC considered that re-analysis was desirable, and so advised that laboratories should be encouraged to use methods that would facilitate the reinterrogation of data for item AAAA, i.e. those with a full capture and sequencing background. MSAC considered that a conventional panel or a virtual panel on a full capture and sequencing background is appropriate, and that whole-genome sequencing (WGS) would also meet requirements of this testing but is not currently widely available in laboratories. MSAC advised that it intended re-analysis be for genes that were not included on the original virtual panel or where a variant's pathogenicity has been re-classified in the interim, where AAAA used a method that created exome or genome data. MSAC accordingly revised the item descriptor (see Table 2) and added an explanatory note for item FFFF:

> Variants may be previously unreported because the relevant gene was not included in the original virtual panel, or because the pathogenicity of the variant has been re-classified in the interim.

MSAC also advised requestors for FFFF should be the same as requestors for AAAA.

MSAC also advised that a practice note be added to the panel testing item to ensure single gene tests for variants that are not detectable using NGS methods (such as in *SMN1*, *DMPK1*, *DUX4* or *DMD*) are conducted before panel testing, where one of these NMDs is clinically suspected.

MSAC noted that a genomic panel substitutes for imaging studies, muscle and/or nerve biopsies, nerve conduction studies and sequential single gene testing to diagnose NMDs. MSAC considered there to be a clinical need for a genomic panel to replace these diagnostic options. MSAC considered genomic panels testing to have superior effectiveness and safety compared to these options.

MSAC considered the number of genes included on the panel, and advised it not necessary to specify a minimum panel size, however, the panel should, as a minimum, include the "green" genes from PanelApp UK or PanelApp Australia.

MSAC noted the diagnostic yields in the second DCAR was estimated to be 20% (based on PathWest real world data showing 19.7% in 2019 and 18.3% in 2020), and estimates were also assessed based on values of 26%, 46% and 78% diagnostic yield from the published literature evidence base, noting these values are from highly enriched cohort studies. MSAC accepted the clinical effectiveness of genomic panel testing included targeted disease management and surveillance, avoiding incorrect treatments, accurate family planning and the psychological benefit of having an accurate diagnosis. MSAC noted the clinical utility for at-risk family members, who would gain access to genetic testing to inform family planning.

[2] NPAAC Requirements for Medical testing of Human Nucleic Acids (Second Edition 2013)

MSAC noted that the proposed fees for BBBB and CCCC are above current market pricing in Australia (e.g. laboratories offer cascade testing of biological relatives, comparable to BBBB with proposed fee $450, for $250), and some fees proposed in this application are higher than for similar previously supported MBS items. However, MSAC considered that, because NMD variants are likely to be seen in a single family (i.e. 'private'), a specific test will likely need to be developed for each family's variant, and also that some currently used overseas testing is cheaper only because it is loss leading. MSAC therefore increased the fee for BBBB from $450 to $500. MSAC further noted that prenatal testing for a known variant (item CCCC) costs $1600 on a cost recovery basis, and so increased the fee for CCCC from $1000 to $1600. MSAC noted that prenatal testing for an unknown variant (item DDDD) at a public state pathology laboratory costs approximately $2,200 for a singleton and $3,000 for a trio, making the proposed fee of $1,600 too low. MSAC noted that whole exome or genome sequencing and analysis is funded on the MBS for $2100 for singleton testing (item 73358) and $2900 for trio testing (item 73359). MSAC advised a fee of $1800 would be appropriate for singleton prenatal testing for an unknown NMD variant, and $2400 where trio testing is required. MSAC supported the proposed fees for AAAA ($1200) and FFFF ($500), and agreed with ESC's advice that the fee for EEEE should be $1200. MSAC requested that the Department revise the financial analyses incorporating its updated fees, and bring the results for it to confirm the total budget impact is within an acceptable range. The Department provided these analyses to the MSAC Executive, which advised both were acceptable, confirming MSAC's support for all items in this application.

MSAC's supported fees are summarised below (Table 1).

Table 1 Fees supported by MSAC

MBS Item	Patient	Supported fee	75%	85%
MBS item AAAA	Affected individual	$1,200.00	$900.00	$1,115.30
MBS Item BBBB	Cascade	$500.00	$375.00	$425.00
MBS item CCCC	Cascade prenatal	$1,600.00	$1,200.00	$1,515.30
MBS Item DDDD1	Affected individual prenatal (singleton)	$1,800.00	$1350.00	$1,715.30
MBS Item DDDD2	Affected individual prenatal (trio)	$2,400.00	$1,800.00	$2,315.30
MBS Item EEEE	Reproductive partner	$1,200.00	$900.00	$1115.30
MBS item FFFF	Re-analysis	$500.00	$375.00	$425.00

Source: MSAC

MSAC noted that not only actionable pathogenic variants, but also likely pathogenic variants can cause NMDs and variants of unknown significance (VUS) may later be re-categorised into either of these categories, illustrating the importance of segregation studies for establishing pathogenicity of those variants. Segregation testing is especially relevant to NMDs as many variants are 'private' (i.e. unique to that family). MSAC noted that item BBBB as supported would also encompass segregation testing of relatives for variant classification, though MSAC revised the item descriptor to also include likely pathogenic variants and VUSs. At its 8 December 2021 meeting, the MSAC Executive endorsed the Department's proposed item descriptors for DDDD1 and DDDD2 fetal affected individual gene panel testing, the frequency restrictors proposed for items BBBB, CCCC, DDDD1, DDDD2, and EEEE, and proposed practice notes. The MSAC Executive also added DDDD1 and DDDD2 to prior tests for data re-analysis under FFFF (Table 2).

Table 2 MSAC's revised item descriptors

Item AAAA Characterisation of gene variant(s) by a gene panel requested by a specialist or consultant physician in a patient presenting with clinical signs and symptoms suggestive of a genetic neuromuscular disorder, other than those associated with variants that are not detected by massively parallel sequencing, and after exclusion of non-genetic causes. (See para PN.15.1 of explanatory notes to this Category) Applicable once per lifetime. Fee: $1,200.00 Benefit: 75% = $900.00; 85% = $1,112.10
Item BBBB Detection of a single identified gene variant requested by a specialist or consultant physician, in a biological relative of a patient with a ~~documented and actionable pathogenic~~ germline gene variant for a neuromuscular disorder identified by item AAAA or DDDD. Applicable once per variant. Fee: $500.00 Benefit: 75% = $375.00; 85% = $425.00
Item CCCC Prenatal detection of an actionable pathogenic familial gene variant(s) requested by a specialist or consultant physician, for a neuromuscular disorder previously identified in an index patient in the family by item AAAA, including maternal cell contamination assessment. Applicable once per pregnancy. Fee: $1,600.00 Benefit: 75% = $1,200.00; 85% =$1,512.10
Item DDDD1 Prenatal detection of unknown gene variants requested by a specialist or consultant physician, for a suspected genetic neuromuscular disorder using a gene panel, after exclusion of non-genetic causes, and including maternal cell contamination assessment. Where: a) the characterisation is performed using a sample from the fetus; and b) the characterisation is not performed in conjunction with a service to which item DDDD2 applies. Applicable once per pregnancy. Fee: $1,800.00 Benefit: 75% = $1,350.00; 85% =$1,712.10
Item DDDD2 Prenatal detection of unknown gene variants requested by a specialist or consultant physician, for a suspected genetic neuromuscular disorder using a gene panel, after exclusion of non-genetic causes, and including maternal cell contamination assessment. Where: a) the request for the characterisation states that singleton testing is inappropriate; and b) the characterisation is performed using a sample from the fetus and a sample from each of the fetus's biological parents; and c) the characterisation is not performed in conjunction with a service to which item DDDD1 applies. Applicable once per pregnancy. Fee: $2,400.00 Benefit: 75% = $1,800.00; 85% =$2,312.10
Item EEEE Single gene testing requested by a specialist or consultant physician for the characterisation of germline gene variant(s) within the same gene in which a reproductive partner has a documented pathogenic germline recessive gene variant for a neuromuscular disorder identified by item number AAAA, DDDD1 or DDDD2. Applicable once per gene. Fee: $1,200.00 Benefit: 75% = $900.00; 85% = $1,112.10

Item FFFF

Re-analysis of whole genome or exome data obtained in performing a service to which item AAAA or DDDD1 or DDDD2 applies, ~~after appropriate genetic counselling,~~ for characterisation of previously unreported ~~pathogenic~~ gene variants related to the clinical phenotype, if

a) The re-analysis is:
   i. Requested by a consultant physician practicing as a clinical geneticist; or
   ii. Requested by a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist.

Applicable only twice per lifetime

(See para PN.15.2 of explanatory notes to this Category)

Fee: $500.00 Benefit:75% = $375.00; 85% = $425.00

Practice notes:

PN.15.1

Single gene tests for variants that are not detectable using NGS methods (such as in *SMN1*, *DMPK1*, *DUX4* or *DMD*) should be conducted before panel testing, where one of these NMDs is clinically suspected.

PN.15.2

Variants may be previously unreported because the relevant gene was not included in the original virtual panel, or because the pathogenicity of the variant has been re-classified in the interim.

Strikethrough indicates text removed by MSAC/MSAC Executive; green indicates text added by MSAC/MSAC Executive.
Source: MSAC and MSAC Executive

MSAC noted that the testing volumes in the second Department-contracted assessment report (DCAR) extrapolated from PathWest data to estimate the number of potential tests conducted and the total estimated cost of testing ($2,115,190 in the first year – see Table 8). However, MSAC considered the incidence estimated based on PathWest data may be too low, though the true incidence is uncertain. MSAC noted that if treatments for NMDs such as gene therapies were to be developed in the future, this could increase uptake of genetic testing. Other uncertainties include the likely uptake for prenatal testing, the number of reproductive partners choosing to be tested, the number of cascade tests and the diagnostic yield. MSAC noted the second DCAR's post-ESC analyses provided financial estimates at multiple prevalence rates (60 and 80 per 100,000), incidence rates (3.6 and 10.6 per 100,000) and diagnostic yields (18.4% from PathWest data, 20% and 26%), with estimates ranging from $1,568,340 to $4,595,532 for the first year (Table 8). MSAC also noted the applicant's statement in its pre-MSAC response that a budget impact of $2 million per year is consistent with the small number of tests expected.

MSAC noted some uncertainty remained around the expected testing volume and therefore the overall budget impact; however, these data would not be available to provide increased certainty until after this genetic testing had been implemented. MSAC also noted that it had revised the fees for many of the proposed items. Therefore, MSAC requested that the Department revise the financial analyses to incorporate its revised fees, along with, if possible, estimating a cost-effectiveness measure similar to cost per measure of diagnostic yield or variant-positive individual. MSAC advised that it expected both figures will fall within an acceptable range, but that it wished to confirm this prior to supporting listing. MSAC requested that the Department provide these analyses for the MSAC Executive to confirm. The Department provided these analyses to the MSAC Executive, which advised both were acceptable, confirming MSAC's support for all items in this application.

MSAC noted NPAAC's advice that a separate quality assurance program (QAP) would be required for each NMD on the panel test. MSAC advised that it did not expect delays due to QAPs as gene panel testing would be covered by other analyses, such as the QAP for NGS.

4. Background

This is the first application for genomic testing for neuromuscular disorders.

The first DCAR was first developed for this application using the clinical utility card (CUC) methodology as advised by PASC, incorporating the use of exemplar and facilitated diseases and genes within the NMD panels. However, several inadequacies were noted for the assessment approach used in the first DCAR, and MSAC advised at its March/April 2021 meeting that a second DCAR be commissioned using a revised streamlined assessment approach. While the second DCAR was the primary focus of MSAC's consideration at its July 2021 meeting, some material from the first DCAR is also included in this summary. ESC also requested at its June 2021 meeting that additional analyses be updated for MSAC's consideration; the assessment group for the second DCAR provided these out-of-session and they are included herein.

A related previous application is 1573, reproductive carrier screening for diseases including spinal muscular atrophy (SMA). The reproductive partner testing component of this application applies to NMDs more broadly, though for SMA will overlap with the testing already supported for application 1573.

A related previous application is 1476, genetic testing for childhood syndromes. The resulting implemented affected individual testing (e.g. MBS item 73358) is indicated by dysmorphic facial appearance and major structural congenital anomalies, or intellectual disability or global developmental delay – this patient population may slightly overlap with the clinical presentation of neuromuscular disorders in the population for this application as defined by the PICO.

5. Prerequisites to implementation of any funding advice

Genetic testing for disease should be undertaken in a National Association of Testing Authorities (NATA) accredited laboratory. The NPAAC advises that this testing is currently provided by one or perhaps two laboratories in Australia. It is complex testing that requires a competent workforce. There is no Quality Assurance program for the single panel. A separate External Quality Assurance program would need to be sourced for each disease tested for in the panel.
NPAAC further noted that there is at present a restricted number of providers, which may trigger increased workloads for those laboratories or act to curtail access to testing by the wider population.

6. Proposal for public funding

The first DCAR proposed six MBS items (summarised in Table 3, descriptors in Table 4). Items are proposed for use in population one patients (item AAAA) and fetuses (item DDDD) who are symptomatic and suspected of NMD. Items are proposed for use in the biological relatives (item BBBB) including fetuses (item CCCC) of the index patient who has been diagnosed with an actionable pathogenic gene variant for a neuromuscular disorder. Item EEEE is proposed for use for the reproductive partner of an individual with a documented and actionable pathogenic germline recessive gene variant. Finally, Item FFFF allows for re-analysis of the data obtained when performing AAAA, up to twice per lifetime for a patient who had has not previously been diagnosed with a pathogenic gene variant.

Table 3 Cost of the proposed MBS items

MBS Item	Patient	Fee	75%	85%
MBS item AAAA	Affected individual	$1,200.00	$900.00	$1,115.30
MBS Item BBBB	Cascade	$450.00	$337.50	$382.50
MBS item CCCC	Cascade prenatal	$1,000.00	$750.00	$915.30
MBS Item DDDD	Affected individual prenatal	$1,600.00	$1,200.00	$1,515.30
MBS Item EEEE	Reproductive partner	$1,200.00	$900.00	$1115.30
MBS item FFFF	Re-analysis	$500.00	$375.00	$425.00

Source: Second DCAR Table 1, based on First DCAR Table 48, with Item EEEE fee updated by ESC (June 2021) to reflect MSAC's advice in Mar/Apr 2021 on the appropriate fee for single gene testing for reproductive partners in applications 1599 and 1600. The 85% benefits reflect the greatest permissible gap of $84.70, as of 1 November 2020.

Table 4 MBS item descriptors proposed for MSAC's consideration

Category 6– Pathology Services Group P7 Genetics
Item AAAA Characterisation of gene variant(s) by a gene panel requested by a specialist or consultant physician, after appropriate genetic counselling in a patient presenting with clinical signs and symptoms suggestive of a genetic neuromuscular disorder, other than those associated with variants that are not detected by massively parallel sequencing, and after exclusion of non-genetic causes. Applicable once per lifetime Fee: $1,200.00 Benefit: 75% = $900.00; 85% = $1,115.30
Item BBBB Detection of a single identified gene variant requested by a specialist or consultant physician, after appropriate genetic counselling, in a biological relative of a patient with a documented and actionable pathogenic germline gene variant for a neuromuscular disorder identified by item AAAA or DDDD. Fee: $450.00 Benefit: 75% = $337.50; 85% = $382.50
Item CCCC Prenatal detection of an actionable pathogenic familial gene variant(s) requested by a specialist or consultant physician, after appropriate genetic counselling, for a neuromuscular disorder previously identified in an **index** patient in the family by item AAAA, including maternal cell contamination assessment. Fee: $1,000.00 Benefit: 75% = $750.00; 85% = $915.30
Item DDDD Prenatal detection of unknown gene variant(s) requested by a specialist or consultant physician, after appropriate genetic counselling, for a suspected genetic neuromuscular disorder using a gene panel, after exclusion of non-genetic causes, and including maternal cell contamination assessment. Fee: $1,600.00 Benefit: 75% = $1,200.00; 85% = $1,515.30
Item EEEE Single gene testing requested by a specialist or consultant physician for the characterisation of germline gene variant(s) within the same gene in which a reproductive partner has a documented pathogenic germline recessive gene variant for a neuromuscular disorder identified by item number AAAA or DDDD. Fee: ~~$450.00~~ $1,200.00 Benefit: 75% = ~~$337.50~~ $900.00; 85% = ~~$382.50~~ $1,115.30

Item FFFF

Re-analysis of whole exome data obtained in performing a service to which item AAAA applies, after appropriate genetic counselling, for characterisation of previously unreported pathogenic gene variants related to the clinical phenotype, if

a) The re-analysis is:
   i. Requested by a consultant physician practicing as a clinical geneticist; or
   ii. Requested by a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist.

Applicable only twice per lifetime

Fee: $500.00 Benefit:75% = $375.00; 85% = $425.00

From the item descriptors in the ratified PICO: blue text indicates changes made by the first DCAR, red text indicates changes made by the second DCAR, and orange text indicates changes made by ESC (revise the fee for EEEE based on MSAC precedent, and correct the 85% benefits to reflect the greatest permissible gap of $84.70, as of 1 November 2020).
Source: Based on Second DCAR Table 1.

The first DCAR commented that a potential issue with the MBS item descriptors as they are currently written is that the items do not require that the requesting specialist or consultant physician has any speciality in genetics or has consulted with a clinical geneticist prior to requesting the test, as occurs for similar MBS items (see Item 73359).
The second DCAR noted that clarification is needed of what is captured within the scope for affected individual testing Item AAAA in terms of acceptable test methodologies (NGS panel versus whole exome sequencing (WES) versus whole genome sequencing (WGS)). In the pre-MSAC response, the applicant stated that their intent was for this testing to use an NGS panel (i.e. a method with a full capture and sequencing background but with analysis restricted to a virtual panel), and not WES or WGS. MSAC agreed that AAAA should use methods that do not restrict library preparation and sequencing to a set of genes identified beforehand; i.e. should use methods with a full capture and sequencing background, with analysis restricted to a virtual panel.

The second DCAR stated that, noting the clinical algorithm indicates that only a subset of genes (i.e. within one of the two broad neurological or muscular panels) would be ordered initially, clarity is required as to whether re-analysis item FFFF is also intended to be used to report genes in the originally non-reported panel. The second DCAR stated that it is likely that a laboratory would be running a larger gene panel, with scope given the overlap in phenotypes, to report the remainder of the genes tested if the initial more focused test result is uninformative. It is not entirely clear whether expansion of the reporting of all genes in the panel would be performed/reported as part of the initial service, or whether this would constitute a re-analysis and require a request via Item FFFF. The second DCAR noted that the latter would approach the cost of upfront WES, which allows a more open-ended diagnostic enquiry into potential genetic variants responsible for the presentation and has been shown to improve diagnostic yield across a range of the conditions under consideration, compared with panel testing alone. The second DCAR noted that either panel testing or WES is approved within the NHS England's Genomic Directory[3] for the investigation of NMDs.

The second DCAR further noted that the descriptor for re-analysis item FFFF indicates this would be 're-analysis of whole exome data', yet item AAAA does not include wording or a fee to support WES or WGS.

The first DCAR noted that the reimbursement requested for item BBBB ($450) appeared higher than a private provider (Victorian Clinical Genetics Services, VCGS) which provides this test for $250. Similarly, the proposed rebate for CCCC ($1,000) was also noted to be a

[3] https://www.england.nhs.uk/publication/national-genomic-test-directories/ accessed 6 May 2021

higher than a similar test provided by VCGS which charges $600 for prenatal single gene testing for the *DMD* gene. ESC noted that MSAC had supported a fee of $1,200 for single gene sequencing reproductive partner testing items for MSAC applications 1599 and 1600 at its March/April 2021 meeting.

7. Summary of public consultation feedback/consumer Issues

Targeted consultation feedback was received from two genomics organisations and four individual clinicians, including one genetic counsellor. No consumer feedback/consumer comments were received for this application. Overall, feedback was supportive of public funding for genetic testing for the diagnosis of early onset or familial neuromuscular disorders.

Key benefits of the proposed genetic testing were identified as:

- Public funding would allow equitable access across Australia – at present provision of funding for testing is ad hoc and inconsistent between states. Some institutions triage children and test only those for whom genetic testing is most critical for ongoing clinical management.
- Avoiding a potentially lengthy diagnostic odyssey.
- Avoiding invasive procedures such as muscle or nerve biopsies.
- An accurate diagnosis allows therapeutic choices to be made, including informing drugs or other treatments to avoid.
- An earlier diagnosis can enable starting appropriate clinical management to prolong function, ease symptoms, and identify potential comorbidities requiring surveillance. Missing opportunities for effective treatment can have a profound impact on the child's ultimate outcome.
- Allowing the pre-symptomatic testing of other family members.
- Informing parents for potentially undiagnosed siblings and future family planning.
    - Genetic testing would allow an earlier diagnosis, whereas the present delay in diagnosis means that in some cases families can have multiple affected children before a specific diagnosis is made.
- Allows families to connect with disease support groups.
- A major advantage of this testing being MBS funded would be the requirement for testing to be carried out within Australia. This gives two-fold benefits: testing cannot be ordered from potentially lower quality laboratories overseas, and the data remaining at an Australian laboratory would facilitate reanalysis if required.
- A genetic diagnosis would permit early recruitment into relevant clinical trials.

Potential disadvantages of the proposed genetic testing were identified as:

- There are minimal safety disadvantages to the patient.
- There is the slight risk of an incidental funding unrelated to the original condition, however this is significantly minimised through the use of a panel of genes related to the phenotype being investigated.
- As outlined by the applicant, testing requests should only be permitted by suitable paediatric or adult specialists. This will require personal consultation to obtain informed consent, causing potential delays in instigation of testing, further exacerbated for rural patients.
- Consider limiting testing requests to subspecialists, or having all requests reviewed by a gatekeeper genetic counsellor/subspecialist, in order to ensure the correct test is requested.

- It can be traumatic for families to know a condition has been inherited, resulting in guilt or blame, and to have to communicate genetic information to other family members who may be at risk of having an affected child. However, this adjustment is generally made with support, and most families prefer knowledge over the diagnostic odyssey.

Other technical comments made in consultation feedback were:

- Strong support that genetic counselling be required, ideally prior to testing and certainly after a diagnosis, and especially where the result may have an impact beyond the family member being tested.
- Where provided by a non-genetic specialist, access to a genetic counsellor will be important to ensure patients and their families receive accurate advice and support.
- The population of patients includes those with neurological disorders for which genetic testing has proven utility, e.g. ataxias, spastic paraplegia, dystonia, dementias.
- Strong support for enabling methods with a full capture and sequencing background with virtual panel analysis, rather than only a genetic panel test.
    - Would prevent custom panels becoming outdated as new disease genes are identified.
    - Using full capture and sequencing methods for library preparation would allow reanalysis, overcoming potentially needing an additional test if a diagnosis was not made with the initial panel.
    - One possibility would be to include tiered analytical complexity options, with commensurate fees for each. This would allow analysis of a larger number of genes for patients with more complex presentations.
- A neuromuscular panel test is an inappropriate test when prenatal ultrasound finds abnormalities and there is no family history of a neuromuscular disorder and/or known genetic variant in a family. In this setting analysis of the whole exome/genome is the appropriate test, as there are causes for atypical ultrasound findings that will not be encompassed by a neuromuscular panel. For example, polyhydramnios can be due to a variant(s) in genes that underlie a variety of syndromes and brain disorders that are not included in a neuromuscular gene panel.
- The minimum gene list may need to be included in the MBS item descriptor, to ensure that laboratories performing the test have minimally equivalent tests.
- The proposed fee of $1,200 for item AAAA is in the appropriate range for panel testing, however if virtual panels on exomes/genomes are to be used then this fee would not cover the cost of testing. The fees for items BBBB and CCCC may be too high.

8. Proposed intervention's place in clinical management

Description of Proposed Intervention

The Applicant identified two populations for genetic testing for the diagnosis of NMDs: individuals where clinical criteria or a family history suggest a possible diagnosis of a neuromuscular disorder (including during prenatal assessments), and biological relatives of the index cases with a confirmed pathogenic variant identified in a gene known to be associated with a neuromuscular disease. In addition, the second DCAR noted that the first DCAR identified an additional population and need for expansion of the proposed item descriptors: for reproductive partners of individuals known to carry a recessive NMD pathogenic variant, as well as a population where re-analysis may be required when the initial gene panel test result is uninformative.

The first DCAR stated that both panel tests and variant-specific testing are currently provided through private laboratories or through state-funded hospital pathology departments. Similarly, single gene tests for those NMD-associated variants that are not detectable using NGS methods are not MBS reimbursed but are available privately or through state-funded hospital pathology departments. Challenges in NMD diagnosis include the large number of causative genes across both the broad disease categories (muscular and neurological), and multiple causal genes within a phenotypic diagnosis (genetic heterogeneity), the association of genes with multiple phenotypes (phenotypic heterogeneity), occurrence of various number and types of pathogenic variants along the length of each gene (allelic heterogeneity), and the significantly larger sizes of most NMD genes, including *Dystrophin (DMD)*, *Dysferlin (DYSF), Titin (TTN), Lamin A/C (LMNA)*. The total proposed panel comprises over 500 genes.

Gene panels developed by clinical molecular laboratories can simultaneously assess for multiple pathogenic variants causal for a suspected NMD and are claimed to reduce the number, cost, and time of diagnostic tests. Gene panels are useful in refining the diagnosis among heritable disorders with genetic and clinical heterogeneity. Methodologically, testing could be a gene panel test, or library preparation using a full capture and sequencing method with analysis restricted to a virtual panel.

Samples for testing adults and children can be from blood, saliva, or buccal swabs, and for fetal testing from amniotic fluid or chorionic villi samples. Each patient tested would have one pathology sample taken from which the full virtual gene panel could be assessed. Depending on the phenotypic features, either the neurological or myopathy panel will be requested by the clinician. Bioinformatic filters can be used to restrict analysis to a subpanel of genes associated with each clinical phenotype. If there is remaining diagnostic uncertainty, the remaining panel can then also be reported. This is thought to be not that likely due to the small overlap of genes on the muscular and neuropathy panel. There are 269 genes unique to the proposed muscular panel, 326 genes unique to the proposed neuropathy panel, and 49 genes common between the two panels. Later re-analysis of genetic data is also proposed.

Description of Medical Condition

NMDs are a broad range of generally progressive disorders affecting the peripheral nervous system, muscle, or neuromuscular junction, that present with a high level of clinical and genetic heterogeneity and overlapping phenotypes[4]. The common aspect of all NMDs is abnormal muscle function with associated clinical burden. At the most severe end of the spectrum, onset can be in utero leading to fetal akinesia, paralysis or reduced movement in utero leading to fetal death[5]. Paediatric patients may present with early onset symptoms that include a delay in motor milestones, hypotonia, abnormal gait characteristics, frequent falls, respiratory difficulties, and difficulty ascending stairs or arising from the floor; such conditions may be fatal or result in severe morbidity. Late onset or adult patients may present with loss of strength, fatigue, episodic weakness, muscle cramps, falls and difficulties with speech and swallowing[6]. Many inherited NMDs are multi-systemic, involving cardiac,

[4] Fattahi Z, et al. Improved diagnostic yield of neuromuscular disorders applying clinical exome sequencing in patients arising from a consanguineous population. Clinical Genetics. 2017;91(3):386-402.
[5] Beecroft S, et al. Genetics of neuromuscular fetal akinesia in the genomics era. J Med Genet. 2018; 55 (8): 505-514.
[6] McDonald C. Clinical Approach to the Diagnostic Evaluation of Heritary and Acquired Neuromuscular Diseases. Phys Med Rehabil Clin N Am. 2012;23(3):495-563.

respiratory, and other organ systems[7]. The significant life-long morbidities of NMD are frequently severely disabling and associated with premature mortality.

The clinical and genetic heterogeneities of NMDs make disease diagnosis complicated and expensive, often involving multiple tests[8]. While historically treatment options for NMD were poor, potential treatments are under development – though curative interventions or improvements decreasing morbidity and mortality remain experimental[9]. However, novel treatments for NMDs are guided by the underlying molecular pathology and establishment of a specific genetic diagnosis. A definitive genetic diagnostic result may also, separately, provide prognostic information for an affected individual.

Neuromuscular disorders can be roughly allocated into broad four categories: muscle disorders such as muscular dystrophies (e.g. Duchenne muscular dystrophy (DMD)), myotonias, myopathies, motor neurone disorders including spinal muscular atrophies (SMAs); neuropathies such as Charcot-Marie-Tooth disease (CMT); and neuromuscular junction disorders[10]. Genetic heterogeneity exists not only for NMDs as a group but also within the subgroups. For example, there are over 20 genes implicated in autosomal recessive limb-girdle muscular dystrophy[11]. NMDs tend to be mostly genetic in origin, and can be inherited as autosomal dominant, autosomal recessive, X-linked or mitochondrial traits, however, *de novo* pathogenic variants are relatively common (up to 30% for DMD[12,13]). Approximately 761 different NMD disorders exist, associated with over 500 known genes[14,15].

The first DCAR stated that the clinical management algorithms presented in the first DCAR are not the same as those in the ratified PICO, because the populations have been reorganised to reflect testing firstly in a population symptomatic of NMD and then secondly in the biological relatives of the index cases. Clinical management algorithms are presented for affected individuals (Figure 2), pregnancies with symptomatic fetuses (Figure 3) and other biological relatives and reproductive partners of index cases (Figure 4).

The first DCAR stated that for affected individual testing, the proposed algorithm uses gene panel test as first line testing to establish a genetic diagnosis (item AAAA). Currently, diagnostic testing is available that may provide a phenotypic diagnosis but will not identify the gene variant responsible for the condition. Genetic testing would be used to replace existing tests where a genetic variant is found, and in patients in whom no variant is identified it would be used in addition to existing testing.

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[7] Kassardjian C, et al. The utility of genetic testing in neuromuscular disease: A consensus statement from the AANEM on the clinical utility of genetic testing in diagnosis of neuromuscular disease. Muscle Disease. 2016; 54 (6):1007-1009.
[8] Ankala A, et al. A Comprehensive Genomic Approach for Neuromuscular Diseases Gives a High Diagnostic Yield. Ann Neurol. 2015;77:206-214.
[9] Dowling J, et al. Treating pediatric neuromuscular disorders: The future is now. Am J Med Genet. 2018;176(4):804-841.
[10] Arnold W & Flanigan K. A practicular approach to molecular diagnostic testing in neuromuscular diseases. 2012;23(3):589-608.
[11] Efthymiou S, Manole A, & Houlden H. Next-generation sequencing in neuromuscular diseases. Curr Opin Neurol. 2016;29:527-536.
[12] Darras B, Urion D & Ghosh P. Dystrophinopathies [Internet]. University of Washington, 2018. Available from: www.ncbi.nlm.nih.gov/books/NBK1119 [Accessed 26/10/2020].
[13] Laing N. Genetics of neuromuscular disorders. Crit Rev Clin Lab Sci. 2012;49(2), 33-48.
[14] Fattahi Z, et al. Improved diagnostic yield of neuromuscular disorders applying clinical exome sequencing in patients arising from a consanguineous population. Clinical Genetics. 2017;91(3):386-402.
[15] GeneTable of Neuromuscular Disorders. Available: http://www.musclegenetable.fr/

The second DCAR noted that gene panel testing was proposed by the applicant to be preceded by (where appropriate) differential testing that requires separate single gene tests (Figure 1), as there are some NMDs caused by genetic variants that are not detectable using NGS methods.

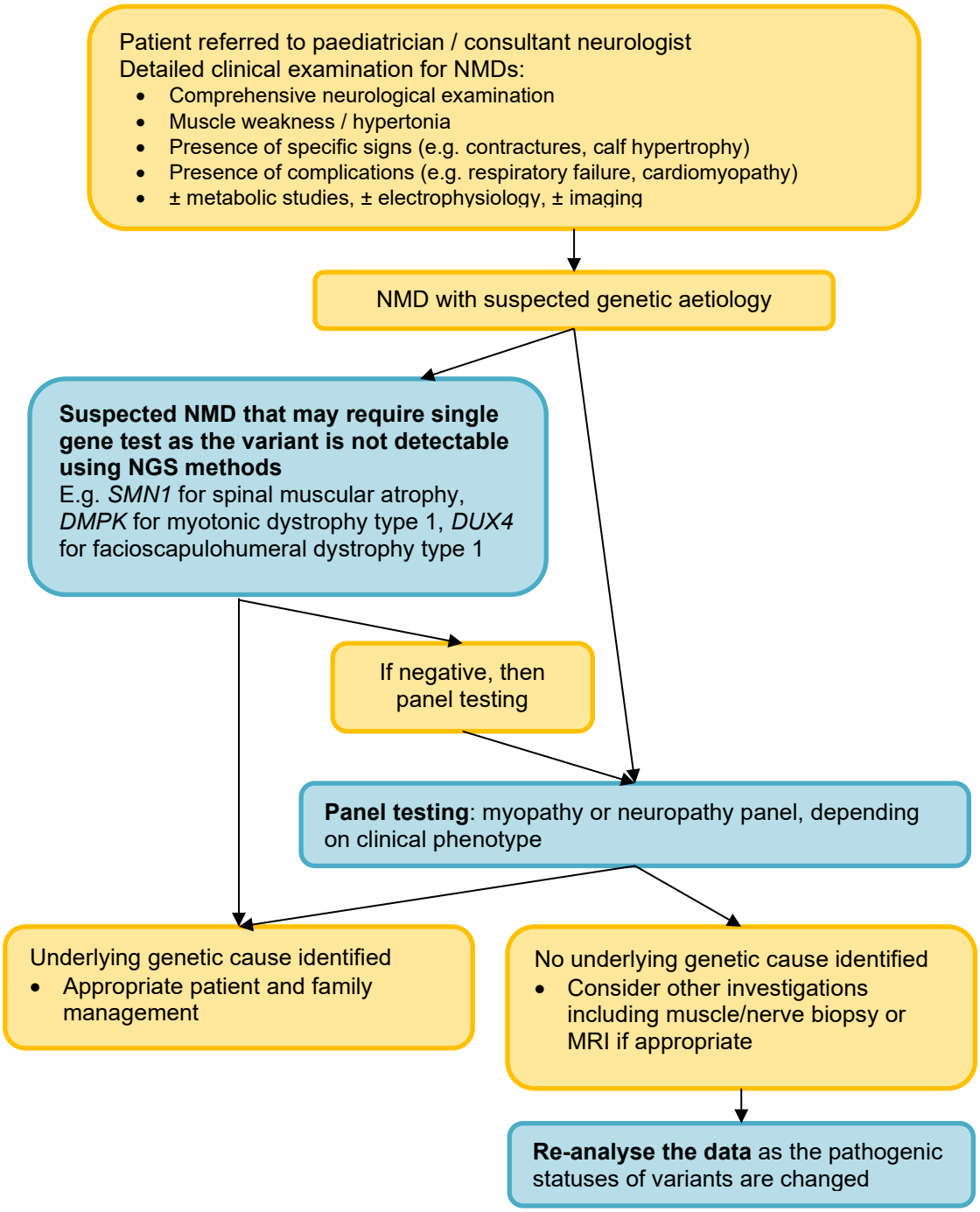
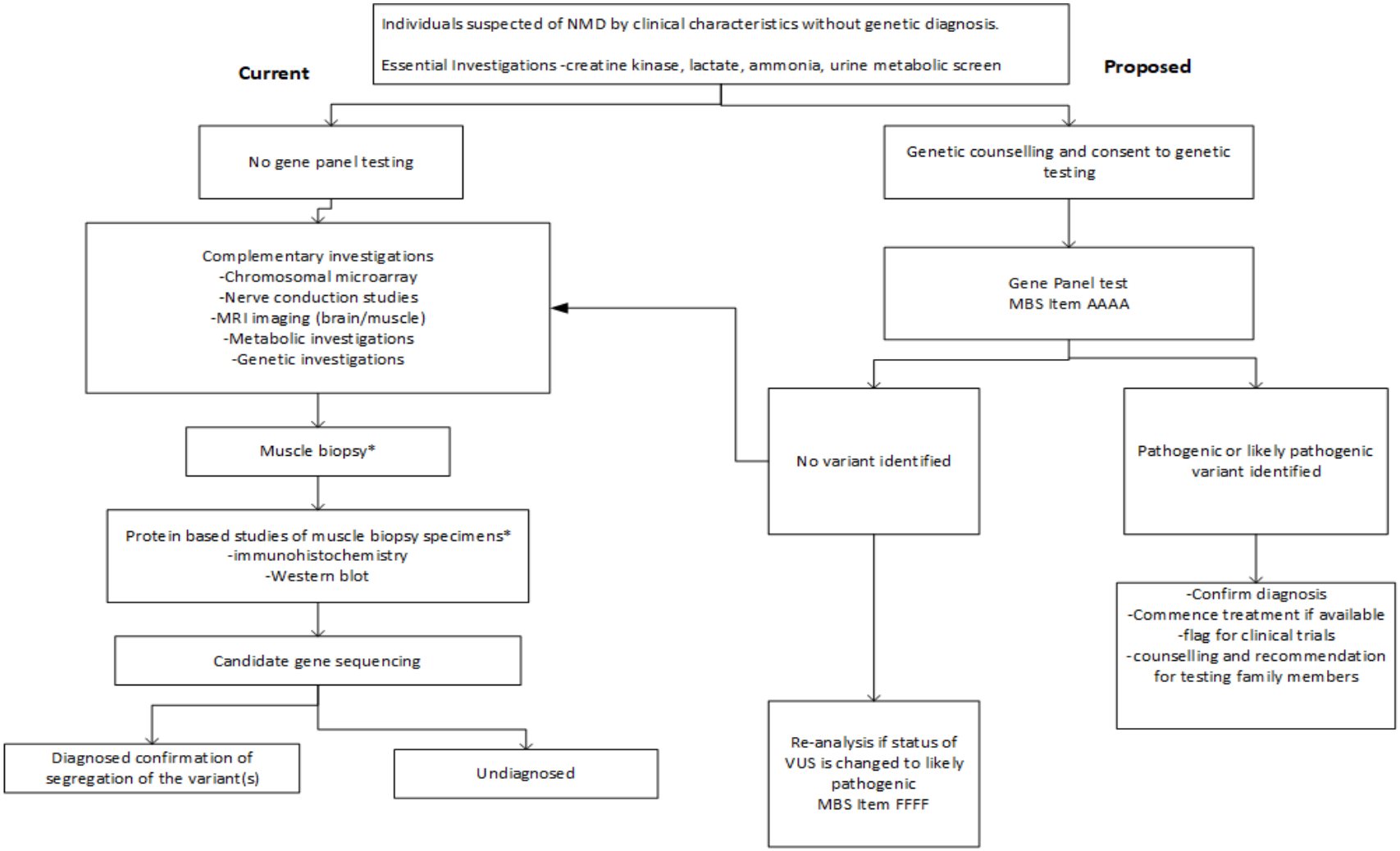


Figure 1 Clinical algorithm including proposed NMD genetic testing.
Source: Based on Second DCAR Figure 1, from Application form Figure 2 (page 21).

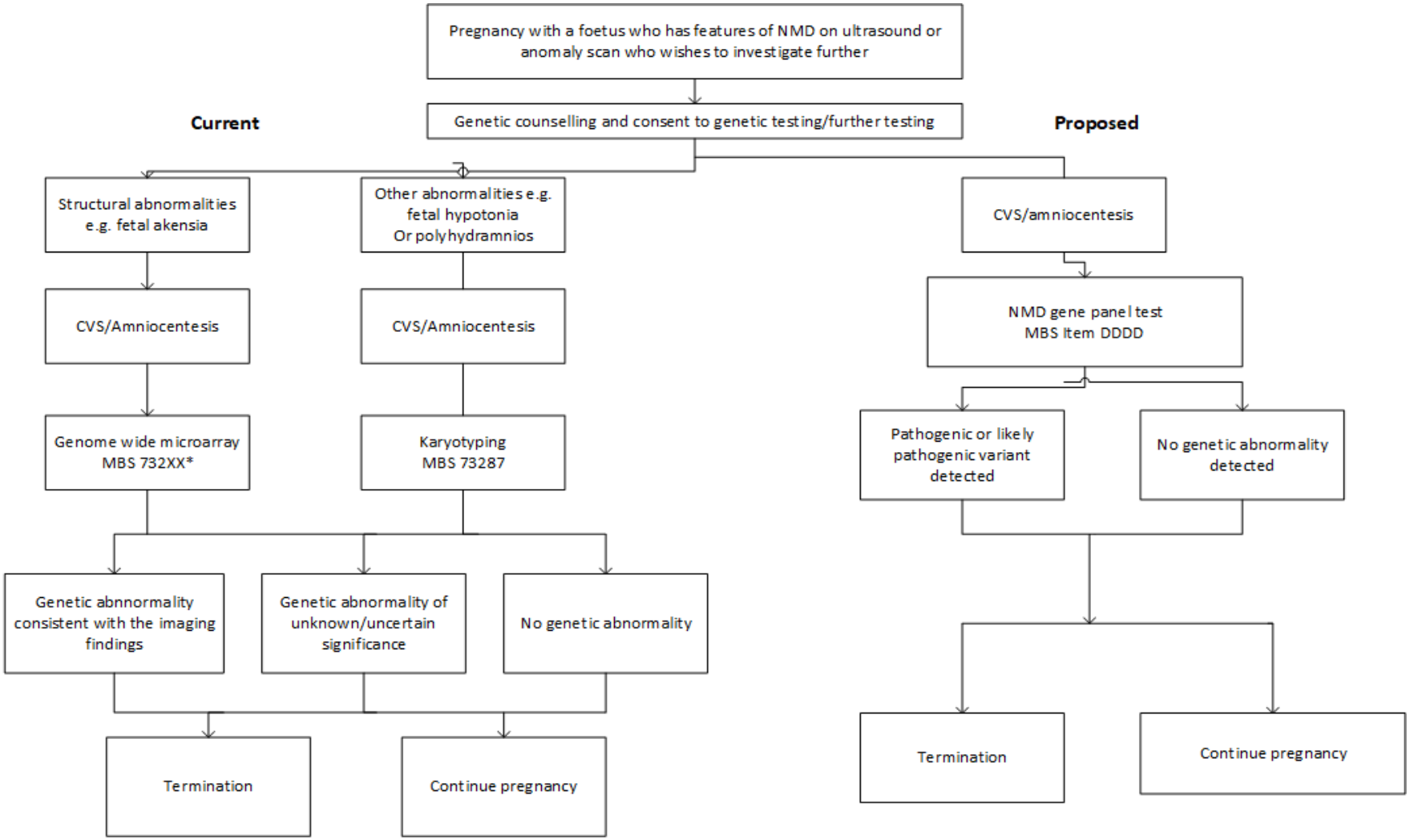
The first DCAR stated that for patients who have no pathogenic variant identified by panel testing, re-analysis of their stored data (item FFFF) can reoccur twice per lifetime in the event that new evidence is produced that changes the status of a variant from variant of uncertain significance (VUS) to likely pathogenic or pathogenic, and/or additional genes are found to be likely pathogenic or pathogenic.

For a pregnancy where the fetus has been identified on ultrasound or anomaly scan with either structural abnormalities or other signs suggestive of NMD, currently, a sample will be obtained via amniocentesis or chorionic villi sampling (CVS) and tested using genome wide microarraying or karyotyping (depending on the abnormality detected). The proposed pathway will not completely replace the genome wide microarray or karyotype test with the gene panel test (item DDDD). Where the gene panel test detects a pathogenic or likely pathogenic variant the mother/parents will need to decide whether to continue with the pregnancy.

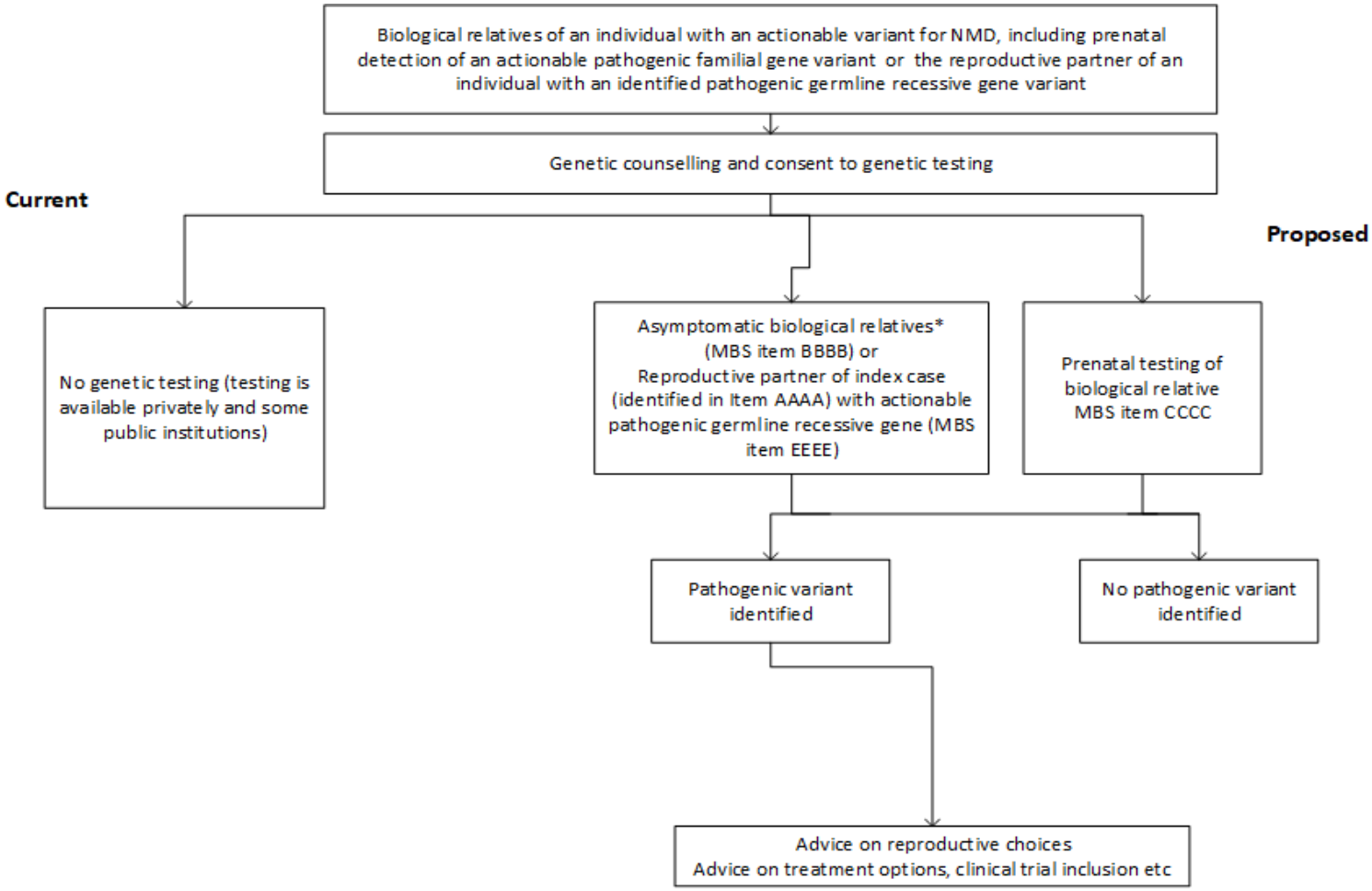
Currently, biological relatives and reproductive partners of index cases do not have access to variant-specific gene testing (except privately or through some public institutions). The proposed pathway would allow biological relatives (including parents of an index case) to access variant-specific testing (items BBBB, CCCC) for actionable pathogenic gene variant(s) previously identified in an index patient (through item AAAA or DDDD). This information would allow for disease surveillance and reproductive choice. Where the inheritance pattern is recessive, genetic testing would be available for the reproductive partner for couples wishing to reproduce (item EEEE).



* MBS items 30075, 72844, 72846 are tests that will be used to obtain a diagnosis for some clinical phenotypes.
VUS = variant of uncertain significance.
Source: First DCAR, Figure 1.



* Has been recommended for listing but is yet to have an MBS item.
CVS = chorionic villus sampling.
Source: First DCAR, Figure 2.



* The degree of testing, whether the first degree, second degree etc. will depend on the mode of inheritance of the actionable pathogenic variant.
Source: First DCAR, Figure 3

9. Comparator

The first DCAR stated that the comparator to the gene panel test for affected individuals is no genetic testing, and the comparator to variant-specific testing (for cascade testing of biological relatives, reproductive partners and fetuses) is no genetic testing.

10. Comparative safety

The first DCAR stated that genetic testing for NMDs has inferior safety compared to no genetic testing. The claim of inferior safety is due to an intervention being done (taking a buccal swab, blood test etc.) versus no testing; the safety risk is small but exists.

The first DCAR identified no studies that reported on the safety of the use of NMD panels. No safety issues exist, beyond those associated with taking blood samples of buccal swabs for the purpose of DNA extraction.

11. Comparative effectiveness

Clinical claim
The first DCAR stated that the clinical claim is that genetic testing for NMDs is inferior in terms of safety and superior in terms of clinical effectiveness, compared to no genetic testing, for the proposed population.

The claim of clinical superiority is because patients may get a genetic diagnosis that agrees with their phenotype, or the genetic diagnosis refutes the phenotypic diagnosis. A genetic diagnosis in an affected individual permits further prognostication, and permits cascade testing, that would otherwise not be possible.

Analytical validity
MSAC advised at its March/April 2021 meeting that the second DCAR's assessment of this application should use a revised streamlined approach, including no requirement to assess analytical validity. MSAC advised that analytical validity does not need to be assessed for applications for expanded indications for genomic tests (including large panels, WES and WGS), because NGS is used extensively by laboratories and is not inferior to Sanger sequencing. NGS is more reproducible and for many (larger) genes is cheaper than Sanger sequencing. Analytical validity is already captured by the laboratory's own quality control processes and NATA accreditation to the standards set by the NPAAC.

Clinical validity
The first DCAR stated that for Charcot-Marie-Tooth (CMT) disease, penetrance in verified variant carriers is almost 100%[16], although the condition is variable both within and between families. For Duchenne muscular dystrophy (DMD), 91-96% of patients who have an out-of-frame variant in the *DMD* gene will develop DMD, otherwise Becker muscular dystrophy may develop depending on the variant[17]. If the variant is known to cause DMD in other family members, the chance of the index patient developing DMD is close to 100%.

[16] Aretz S, Rautenstrauss B, Timmerman V. Clinical utility gene card for: HMSN/HNPP HMSN types 1, 2, 3, 6 (CMT1,2,4, DSN, CHN, GAN, CCFDN, HNA); HNPP. European Journal of Human Genetics: 2010;18(9).
[17] Coote DJ, et al. CUGC for Duchenne muscular dystrophy (DMD). European Journal of Human Genetics. 2018, 26:749–757.

Clinical utility
The second DCAR stated that the clinical utility of genetic testing over and above the added value of achieving a diagnosis using genetic testing of the affected individual is that it allows predictive testing for family members who may be asymptomatic carriers and planning a family, and who would wish to take advantage of reproductive interventions to manage the risk of this condition being passed on to any children.

12. Economic evaluation

MSAC advised at its March/April 2021 meeting that the second DCAR's assessment should use a revised streamlined approach, including truncated examination of the cost-effectiveness of testing if the total financial implications of this testing were not too high. MSAC discussed the value of economic modelling in the assessment of large genetic tests, noting there are several limitations to incremental cost-effectiveness ratios (ICERs) in these applications. In particular, the economic evaluation is often based on assumptions for which there are little or no data, or that the data cannot be generalised to all conditions tested. MSAC considered it may be more valuable to compare costs per diagnostic yield unit outcome (e.g. cost per trisomy detected, cost per pathogenic/likely pathogenic variant detected, as per previous MSAC considerations), which could remove many assumptions and uncertainties that complicate its decision-making. This could provide a quantitative basis for benchmarking against previously supported total financial impacts of testing.

MSAC advised at its July 2021 meeting that, in the context of clear clinical utility and likely low total financial cost of testing overall, a full economic evaluation was not warranted for this application. MSAC advised that the cost-effectiveness was likely within an acceptable range, though asked the Department to conduct more analyses so it could confirm this.

The Department's analyses provided to the MSAC Executive showed an estimated cost-effectiveness of the proposed testing of $1,444 per proband diagnosed.

13. Financial/budgetary impacts

Utilisation
The utilisation of testing depends on the incidence and prevalence of NMDs in Australia. The second DCAR stated that the first DCAR estimated the likely population for NMDs using literature estimates, and assessed the proportions of patients considered likely to access the various tests if made available under the proposed item descriptors. The first DCAR's figures were calculated assuming an incidence of 10.6/100,000 and prevalence of 80/100,000. The first DCAR indicated that its figures for the estimated use of gene panel testing were likely to be an overestimate.

The second DCAR calculated alternative utilisation figures (Table 5) based on the PathWest data included in the Application form, as these are real-world data available for Australia. The second DCAR calculated the incidence from PathWest data to be 3.6/100,000, which it considered likely to be an underestimate. The incidence and total number of tests ordered from the PathWest data were extrapolated *pro rata* to estimate the total number of tests that might be ordered in Australia. It is uncertain how many samples are sent overseas for analysis, so the estimated nationwide figure was then increased by 10%. The second DCAR considered extrapolation beyond 2021 likely to be inaccurate because it is not certain what impact listing of the NMD genetic testing would have on testing rates, noting there appears to be a budget allocated in some states for accessing this service already, according to the first DCAR.

The second DCAR's utilisation estimates used a diagnostic yield amongst affected individuals of 20% – based on PathWest data showing a diagnostic yield of 19.7% in 2019 and 18.3% in 2020. Extrapolation of PathWest data to 2021 (including nationwide extrapolation and estimate of overseas patients) gives a diagnostic yield of 18.4%.

Table 5 Estimated total gene tests and outcomes from genetic testing for patients with suspected NMD in Australia in 2020, with extrapolation to 2021

Parameter	Extrapolated PathWest for 2020 excl ACT, NT, TAS	Estimated total tests or outcomes for all of Australia 2020 incl ACT, NT, TAS	Estimated total tests or outcomes from overseas tests*	Estimated total tests and outcomes in 2020	Estimated total tests and outcomes in 2021**
Number of suspected NMD affected individuals	1296	1360	136	1496	1586
Number of positive NMD cases (i.e., index cases)	238	250	25	275	292
Total number of family cascade tests	257	270	27	297	315
Number of prenatal diagnoses	10	11	0	11	12

* 10% of total ordered in Australia; overseas tests for prenatal diagnoses are considered unlikely to be undertaken due to turnaround time.
** 2021 estimates based on 6% increase in testing rates and outcomes compared with 2020
Source: Second DCAR, Table 7.

The second DCAR presented utilisation estimates based on an epidemiological approach incorporating various incidence/prevalence estimates, against likely resulting diagnosis numbers based on various diagnostic yield values. After ESC, the assessment group for the second DCAR updated the analysis to include the diagnostic yield from PathWest real-world utilisation data (Table 6).

Table 6 Estimates of test population size, and those with an informative result according to diagnostic yield for 2021

	Estimated Australian testing PathWest data 2021	Epidemiological approach			
		Prevalence 60/100,000		Prevalence 80/100,000	
		Incidence 3.6/100,000	Incidence 10.6/100,000	Incidence 3.6/100,000	Incidence 10.6/100,000
Number tested	1586 (Test positive = 292, DY = 18.4%)	2,466	4,334	2,887	4,755
Number with a diagnosis (DY 20%)	-	493	867	577	951
Number with a diagnosis (DY 26%)	-	641	1,127	751	1,236

Diagnostic yield (DY) = 18.4%, from PathWest data extrapolated to 2021 including estimated overseas testing.
Source: provided by the assessment group for the second DCAR after the June 2021 ESC meeting. Modified from Second DCAR Table 11, including estimated overseas testing.

Cost-offsets

The second DCAR stated that the cost-offsets of testing can be broken down across the timeframe of the cost-offsets, with only the immediate test items able to be factored into an estimated financial impact. One such immediate cost-offset was identified in the revised estimation of financial impact: muscle or nerve biopsy and associated procedures necessary to undertake this (Table 7). This may not always be avoided, for example where there is still

some uncertainty about the correlation between an identified gene variant and the observed phenotype, correlation may expand the understanding of the disease phenotype[18].

Table 7 Costs included in assessment of cost-offset for muscle biopsy no longer required if genetic testing available for initial diagnosis

Intervention	MBS Item number	Cost
Anaesthetic consultation	17615	$89.95
General anaesthetic	21997	$81.60
Spinal/epidural infusion for analgesia	18216	$195.85
Muscle (or nerve) biopsy	30075	$154.45
Histology (Level 5) (same for muscle or nerve)	72380	$274.15
Skeletal muscle enzyme IHC	72884	$30.75
Day Admission		$552
Total		$1378

Source: Second DCAR Table 8, based on email communication from the Department

The second DCAR stated that longer term cost-offsets may arise from a decline in NMD incidence with the availability of genetic testing of individuals (including prenatally detected cases), cascade testing and reproductive partner testing. Other potential cost-offsets may arise but are difficult to identify and quantify, especially for such a heterogeneous group of diseases of varying severity. The cost offsets for prenatal tests only included the avoidance of muscle biopsies, whereas some of these pregnancies will not result in live births.
The second DCAR stated that the other tests proposed in the clinical algorithm are still likely to be required for the diagnosis and management of NMDs. The first DCAR included the cost of one genetic counselling session as an associated cost, but this was specifically not included in the second DCAR's estimation of financial impact as it considered this would likely be more than offset by the shortened time to diagnosis, and uncertainty about the capacity and availability of such services as proposed. Though the second DCAR noted it is likely that genetic counselling appointments would be required for non-urgent testing, such as cascade testing for biological relatives. The assessment group for the second DCAR stated in their post-ESC analyses that the costs associated with genetic counselling of index cases and family members will be offset by the reduction in clinic visits and diagnostic tests due to an earlier diagnosis with genetic testing of the index case.

Financial implications
The second DCAR noted that the first DCAR's estimated financial impact of testing affected individuals did not take into account the cost-offset of no longer requiring a muscle (or nerve) biopsy. The second DCAR revised the estimated financial impact taking into account that those cases diagnosed using genetic testing upfront would no longer need a muscle (or nerve) biopsy, costed at $1378 for each affected individual diagnosed by genetic testing (Table 7). The second DCAR presented this with sensitivity analyses across a range of diagnostic yields to determine the potential range of any estimated financial impact per patient with an informative genetic test result (Figure 5).

[18] Savarese M, et al. The genetic basis of undiagnosed muscular dystrophies and myopathies: Results from 504 patients. Neurology. 2016 Jul 5;87(1):71-6. Erratum in: Neurology. 2018 Jun 5;90(23):1084. Erratum in: Neurology. 2019 Aug 20;93(8):371

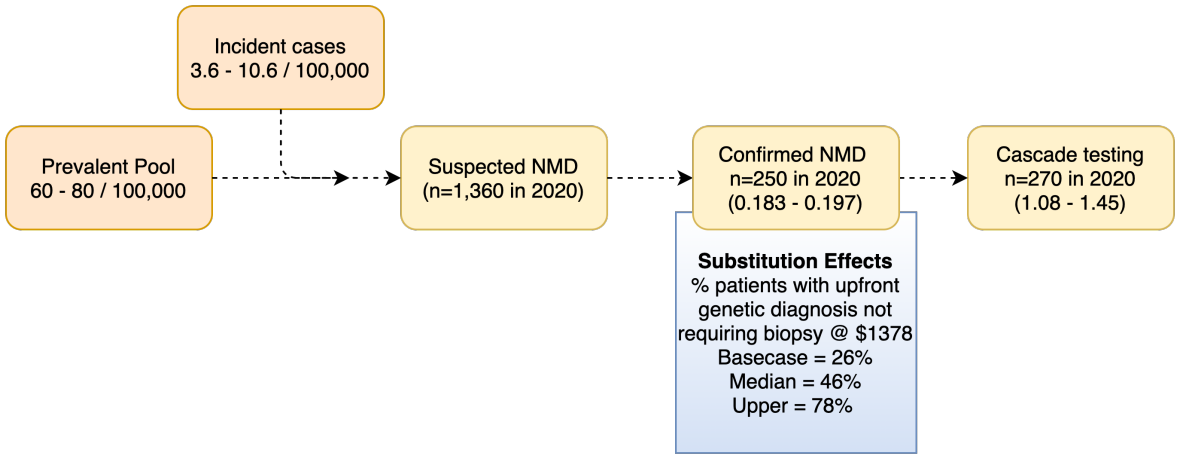


Figure 5 Model used for the Second DCAR's financial impact calculations.
Source: ESC.

A wide range of diagnostic yields were reported, so analyses incorporating a range from 26% to 78% were included in the second DCAR for a prevalence of 60/100,000 and 80/100,000. The upper estimate of the diagnostic yield of 78% was ascertained from the references excluded from the first DCAR's literature search, being the upper quartile of the range of values and from a highly selected/enriched population.

The assessment group for the second DCAR noted that it had taken a pragmatic approach to determining cost offsets, seeking to find those generalisations that would hold sufficiently to have a meaningful impact on the cost of testing. Using the above numbers of individuals to be tested (Table 6), Table 8 shows the estimated total cost of testing before any offsets (Row One), and the cost of testing including offset of the cost of muscle or nerve biopsy (assumed in all patients; Row Two). ESC considered that the most realistic estimated financial impact, which was based on extrapolated PathWest data and incorporating cost-offsets, was **$2,115,190**. The second DCAR stated that the figure for cascade testing was not adjusted given there were large uncertainties about the proportion of patients likely to be tested. MSAC requested that the Department revise the financial analyses incorporating its updated fees, and bring the results for it to confirm the total budget impact is within an acceptable range.

The revised financial analyses incorporating MSAC's revised fees are shown below, for the estimated cost of genetic testing only over five years (Table 8), and updated net cost including offsets (Table 9).

Table 8 Revised cost of NMD genetic testing over five years (testing only), using MSAC's supported fees

	Fee	Yr1	Yr2	Yr3	Yr4	Yr5
		2021-22	**2022-23**	**2023-24**	**2024-25**	**2025-26**
No. AAAA tests		4472	5106	5454	5499	5285
Cost of AAAA tests	$1200	$5,366,219	$6,127,713	$6,545,153	$6,598,385	$6,341,749
No. BBBB tests		2285	2593	2762	2787	2687
Cost of BBBB tests	$500	$1,142,446	$1,296,289	$1,381,209	$1,393,325	$1,343,379
No. CCCC tests		112	112	112	112	112
Cost of CCCC tests	$1600	$179,001	$179,001	$179,001	$179,001	$179,001
No. DDDD1 tests*		38	39	40	40	41
No. DDDD2 tests*		245	250	255	260	265
Cost of DDDD1 tests	$1800*	$90,992	$92,849	$94,729	$96,527	$98,458
Cost of DDDD2 tests	$2400*	$588,418	$600,421	$612,582	$624,211	$636,694
No. EEEE tests		251	270	282	286	283
Cost of EEEE tests	$1200	$301,279	$324,175	$338,487	$343,268	$339,801
No. FFFF tests		N/R	N/R	N/R	N/R	N/R
Total services		7403	8400	8936	9014	8704
New total cost		**$7,668,355**	**$8,620,448**	**$9,151,161**	**$9,234,717**	**$8,939,082**

* MSAC advised that proposed item DDDD should be separated into singleton and trio tests. The table's calculations assume 13.4% singleton vs 86.6% trio tests, as observed in the 2020-21 financial year for childhood syndromes MBS items 73358 and 73359.
Source: modified by the Department to incorporate MSAC's supported fees, based on Second DCAR Table 12.

Table 9 Revised estimated total cost of testing according to incidence and prevalence, and cost of testing according to diagnostic yield with cost-offsets from avoided muscle biopsy costs, using MSAC's supported fees

	Estimated 2021 testing based on PathWest data	Epidemiological approach			
		Prevalence 60/100,000		Prevalence 80/100,000	
		Incidence 3.6/100,000	Incidence 10.6/100,000	Incidence 3.6/100,000	Incidence 10.6/100,000
Total cost of testing, **without offset** ($) ($1200 for test AAAA, $1800 and $2400 for DDDD1 and DDDD2 respectively – assume 10% of all tested under DDDD)	$2,065,770	$3,210,951	$5,642,700	$3,759,050	$6,191,220
Cost of testing **with offset for avoided muscle biopsy** ($) (Diagnostic yield 20% where epidemiological approach used)	**$1,652,616**	$2,568,761	$4,370,160	$3,007,240	**$4,952,976**
Cost of testing **with offset for avoided muscle biopsies** ($) (Diagnostic yield = 26% where epidemiological approach used)		$2,376,104	$4,514,139	$2,781,697	$4,581,502
Cost of testing BBBB $500	$157,500 (315 tests)	$1,142,466 (2285 tests)	$1,142,466 (2285 tests)	$1,142,466 (2285 tests)	$1,142,466 (2285 tests)
Cost of testing CCCC $1,600	$179,001 (112 tests)	$179,001 (112 tests)	$179,001 (112 tests)	$179,001 (112 tests)	$179,001 (112 tests)
Cost of testing EEEE $1200	$301,200 (251 tests)	$301,200 (251 tests)	$301,200 (251 tests)	$301,200 (251 tests)	$301,200 (251 tests)
Cost of FFFF	Not estimable	Not estimable	Not estimable	Not estimable	Not estimable
Total cost	**$2,290,317**	$4,191,408 (DY 20%) $3,998,751 (DY 26%)	$6,136,807 (DY 20%) $5,798,245 (DY 26%)	$4,629,887 (DY 20%) $4,404,344 (DY 26%)	$6,575,623 (DY 20%) $6,204,149 (DY 26%)

Bold font indicates the highest and lowest potential financial costs, across the various estimates of incidence/prevalence presented.
⁺ represents diagnostic yield (DY) of 18.4%, as per PathWest data extrapolated to 2021 including estimated overseas testing.
* using fee of $1200, based on MSAC's March/April 2021 advice on the fee for single gene testing of reproductive partner items in MSAC applications 1599 and 1600.
** As taken from First DCAR Table 51 and based on incidence 10.6/100,000 and prevalence 80/100,000
Source: modified by the Department to incorporate MSAC's revised fees, based on the table provided by the assessment group for the Second DCAR after the June 2021 ESC meeting.

14. Key Issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Incidence and prevalence estimates are highly uncertain	The second DCAR used both published estimates of incidence and prevalence plus the current testing figures from PathWest. In the absence of registry data, prevalence is highly uncertain, as is the proportion of the prevalent population who may undergo testing. The uncertainty in these estimates makes the size of the testable population uncertain. The epidemiological approach used is reasonable. However, the estimated incidence of 3.6/100,000 is probably an underestimate. The proportion of the incident population that does not undergo testing currently cannot be categorically established. Each of these issues also contributes to uncertainty in the total budget estimate.
AAAA test method	Panel testing for affected individuals should require the use of wet-lab methods that involve a full capture and sequencing background, to allow full ascertainment then narrow bioinformatics, and ensure future data re-analysis is possible.
MBS item descriptors are reasonable	The proposed changes to the original MBS descriptors seem reasonable. The cost of genetic counselling was not included in the second DCAR.
Lack of availability or access to genetic counsellors	Genetic counselling is currently included in the item descriptor as a testing pre-requisite, but is not sufficiently widely available for this to be feasible in all circumstances. It is suggested that this wording is removed. A consistent policy approach to the MBS wording relating to this issue is required.
Some proposed fees seem inflated	The fees for BBBB and CCCC are above current market pricing in Australia and could be revised downwards ($450 currently versus $250 in laboratories).
Proposed budget impact is reasonable	The revised costs estimates were based on a conservative diagnostic yield of 26%. ESC considered the 26% value to be reasonable (as it was based on the most representative value from the literature search), given the significant heterogeneity between studies and frequency of NMD subtypes. Consideration of diagnostic yields of 46% and 78%, which were reported in literature excluded from the first DCAR, were also modelled in the second DCAR.
Restrict testing to subspecialists	General paediatricians are unlikely to have the relevant subspecialist knowledge to order the appropriate genetic test. ESC noted that the MSAC Executive considered that access to testing could be via clinical genetics clinics or relevant sub-specialty clinics.
Item FFFF	Should item FFFF for re-analysis be method-agnostic? Noting that there is the potential that this item could be used to access WES. There are little data to guide the likely number of tests and costs for this item, which are therefore highly uncertain.
Single gene tests prior to panel testing	The application requested single gene tests for those genes whose variants are not detectable by NGS methods, prior to panel testing, where those NMDs are suspected. ESC noted that the list of such disorders would likely be very long, and requested MSAC consider how to best address the need for single gene tests prior to panel testing for some patients.

ESC Discussion

ESC noted that this application was for Medicare Benefits Schedule (MBS) listing of genetic testing for NMDs. ESC noted that the assessment comprised a first DCAR dated December

2020, discussion at the February 2021 MSAC Executive meeting, discussion at the March/April 2021 MSAC meeting, and a second DCAR dated March 2021.

ESC noted that there is enormous clinical heterogeneity both between and within the disorders encompassed by the application. There is also substantial genetic heterogeneity – the same variant may result in a different phenotype, which precludes making a definitive diagnosis and assessment of risk to other family members. Individually, the 761+ NMDs able to be characterised are individually rare, but from the included literature have an estimated cumulative prevalence of 33/100,000.

ESC noted MSAC's advice on streamlining the approach to the assessment of large genomic panels, WES and WGS, at its meeting of March/April 2021:

- disaggregating the gene panel and making funding decisions on the basis of assessments of the exemplar genes alone inadequately captures the clinical benefits and utilities of using a large panel where the intent is to make a diagnosis among a population tested. MSAC instead suggested that the test population's diagnostic yield is relevant and not disaggregating the genes within these panels would be a better and more patient-centred approach.
- genomic testing is already the standard of care for complex NMDs where there is no readily identifiable phenotype to direct condition-specific genetic testing.
- a more pragmatic approach is needed to assess large genomic panels, WES and WGS.
- cost per informative diagnostic test result should be considered, which includes the proportions of both "variant detected" and "no variant detected", as both outcomes have relevance.
- clinical utility, underpinning the value proposition, may additionally be assessed more qualitatively rather than quantitatively.
- Assessment of analytical validity is no longer required for these tests.

ESC noted the consumer support for the application, which included considering the 'value of knowing', avoiding tests and biopsies, and truncating the 'diagnostic odyssey'. ESC noted regarding clinical utility that there is no treatment for the vast majority of NMDs, and noted the MSAC Executive's advice that the clinical utility for genomic tests can be assessed more qualitatively than quantitatively. ESC considered that the major benefit of testing is in the 'value of knowing', rather than commencement of targeted therapies.

ESC noted the proposed MBS items for testing the affected individual would (at least) obviate the need for muscle or nerve biopsy collection and testing. The six proposed MBS items are:

- AAAA – genetic testing of the affected individual using gene panels
- BBBB – genetic testing of relatives of the proband
- CCCC, DDDD – prenatal genetic testing of a fetus for known, and unknown variant(s), respectively
- EEEE – genetic testing of the proband's reproductive partner
- FFFF – re-analysis of whole exome data

ESC considered that it may be appropriate to restrict use of biopsies (MBS items 30075, 72844 and 72846) if the proposed item AAAA was used as an alternative diagnostic test. ESC advised that item AAAA requestors were not restricted by subspeciality, and that this item be applicable once per lifetime. ESC considered that an explanatory note may be needed

to list the exclusions for genes whose variants are known not to be detectable using NGS methods.

ESC noted the applicant's request for the panel test AAAA and re-analysis item FFFF be method-agnostic, yet noted that FFFF depends on AAAA having previously used a method that includes a full capture and sequencing background (such as a virtual panel on an exome background). ESC noted that if the descriptor is method-agnostic, small laboratories may perform cheaper tests and bioinformatic analyses on small gene panels, which would constitute less comprehensive initial testing and preclude item FFFF from being performed at a later time. Whereas if a virtual panel on a full capture and sequencing background is required for AAAA, then the fee might need to be increased from $1,200 (for example to $2,100 in line with the implemented fee for similar MBS items), which would then need to be reflected in a revised budget impact. ESC noted that a virtual panel on a full capture and sequencing background is an accepted methodology for NMD gene panel testing in other jurisdictions. ESC stated that MSAC may want to consider suggesting a minimum gene set for item AAAA, but noted the application references panels reported at www.muslcegenetable.fr; alternative panels are reported in PanelApp Australia (https://panelapp.agha.umccr.org/). ESC noted that leaving FFFF as method-agnostic may lead to it being used as a 'mop-up item' for access to exome sequencing with a virtual panel, which is more costly, and so the financial impact would increase. ESC therefore explicitly assumed that panel testing under AAAA would require the use of broader wet-lab ascertainment methodologies followed by narrow bioinformatics (i.e. WES/WGS library preparation and sequencing, with a virtual panel), similar to how a range of biochemical tests are done then only a subset reported. This would ensure re-analysis was always available afterwards.

ESC noted that it was not clear how to incorporate single gene tests for those genes whose variants are not detectable by NGS methods (where suspected) prior to panel testing, such as *DUX4* for facioscapulohumeral dystrophy. ESC requested MSAC's advice on how best to address this testing, including whether it should be part of this application or be considered as a separate application.

For proposed item BBBB, ESC noted that "biological relatives" needs specifically defining and suggested using first-degree relatives instead. ESC also noted that the proposed fee for BBBB of $450 appeared to be inflated: the Victorian Clinical Genetics Services charges about $250 for this test. ESC noted similar feedback regarding the fee ($1,000) for proposed item CCCC – PathWest charges about $600 for this test.

ESC noted that proposed item EEEE was test methodology agnostic and there were no real-world data to inform the fee for this test. ESC also queried whether clinicians would want to know if there was another variant that might result in biallelic loss and subsequent risk of an NMD. ESC advised that reproductive partner testing must assess all variants within the gene, and therefore be single gene sequencing rather than single variant testing. ESC noted that MSAC had supported a fee of $1,200 for single gene sequencing reproductive partner testing items for applications 1599 and 1600 at its March/April 2021 meeting. MSAC justified this increase from the originally proposed $500 fee (for these items in both 1599 and 1600) based on the complexity of sequencing the genes on these panels being greater than the simpler cystic fibrosis gene, which has a fee of $500. For proposed item EEEE the budget impact used a fee of $450, which would need to be adjusted if MSAC decided that the higher fee was more appropriate. This was performed in post-ESC analyses.

In its pre-ESC response, the applicant noted that re-analysing a sample with the same panel composition is rare.

ESC noted the two sources for population estimates, resulting in different total budget calculations. From the literature, Rose 2019[19] suggested an incidence of 10.6/100,0000 and a prevalence of 80/100,000, which the first DCAR used to calculate the budget impact. However, current testing data from PathWest suggested an incidence of 3.6/100,000, and a sensitivity analysis using prevalence of 60/100,000 was used in the second DCAR's budget impact. ESC noted that the PathWest data represent only some states and so were extrapolated to include nationwide testing and some overseas testing. ESC noted that cost-effectiveness was not requested to be modelled in the second DCAR. Thus, the budget impacts presented in the second DCAR used the incidence from the literature (10.6/100,000) and an alternative incidence based on PathWest data (3.6/100,000).

The first DCAR presented net costs to the MBS (including counselling) ranging from a saving of $5.07 million to additional expenditure of $4.48 million, which ESC considered to be highly uncertain. The second DCAR, using various diagnostic yields (26% representing current testing yields, and 46% and 78% representing the estimates from selected populations in the literature), along with two different prevalence estimates (60 and 80/100,000) and two different incidence estimates (3.6 and 10.6/100,000), provided budget impacts (including the cost-offsets of avoided muscle or nerve biopsies, but excluding counselling) that found net cost estimates ranging from $0.3 million to $4.2 million per year. ESC considered the second DCAR's net cost estimates to be less uncertain. ESC noted that the first DCAR had estimated the annual cost of counselling to be $1.17 million. ESC considered the second DCAR's $4.2 million per year estimate (based on 26% diagnostic yield, 10.6/100,000 incidence and 60/100,000 prevalence) to be "conservative" and its $2.4 million per year cost estimate (based on a 26% diagnostic yield, 3.6/100,000 incidence and 80/100,000 prevalence) to be "realistic". Analyses provided by the assessment group for the second DCAR after the ESC meeting subsequently slightly revised these estimates (see Table 8). ESC noted that the cost-offsets might have been underestimated due to the cost per reproductive decision made not being considered, but may also have been overestimated as the incidence of these conditions may reduce over time. It was noted that cascade testing is not expected to reduce the incidence of *de novo* disease. In its pre-ESC response to the second DCAR, the applicant suggested that cost-offsets should include hospitalisations and downstream carers' costs for children. The rejoinder noted that there is not a 'typical' patient population affected by the conditions tested for, and therefore these costs are extremely difficult to quantify.

ESC noted strong support in consultation feedback for provision of counselling with genetic testing, given the potential impact for other family members. ESC discussed whether genetic counselling should be mandated in the item descriptor, and noted that all patients who are recommended for genetic testing receive a certain amount of counselling from a specialist in order to obtain informed consent for testing, and for pre- and post-test delivery of information and assembling each pedigree. ESC noted that genetic counsellors are in high demand and that mandating genetic counselling in the item descriptor may result in exceptionally long wait times for genetic counsellors and testing, which is not acceptable if reproductive testing is urgently required, and may create inequity. ESC considered that it may be more appropriate to include counselling in a practice note instead, so that access to testing is not restricted by access to formal genetic counselling, and advised the requirement for genetic

[19] Rose L, et al. Trends in incidence, prevalence, and mortality of neuromuscular disease in Ontario, Canada: A population-based retrospective cohort study (2003-2014). PLoS One. 2019; 14(3): e0210574.

counselling be removed from within the item descriptor. ESC considered that some type of subspecialty contribution would be advantageous. ESC also noted that the first DCAR included counselling in the financial costings whereas the second DCAR excluded it, and advised that the inclusion (or not) of counselling costs needs to be clarified for MSAC.

15. Other significant factors

Nil

16. Applicant comments on MSAC's Public Summary Document

Firstly, the College would like to take this opportunity to thank the Department and the MSAC for their assistance in moving this application forward to a successful outcome, giving all NMD patients equitable access to a test that may provide a definitive diagnosis and end their diagnostic odyssey.

Whilst the PSD is a thorough document, the College has several concerns, many of which were addressed in the College's ESC response (15th July 2021):

i. There is still confusion around the wording of the requested item numbers. Testing described in item number AAAA *will not* use exome sequencing in order to avoid inherent issues with exome sequencing, in particular, unreliable copy number variant (CNV) analysis, important for over 8 percent of diagnoses. Item number AAAA should remain technology agnostic.
ii. Regardless of technology used, the College is concerned that item number AAAA stipulates that testing is "*applicable once per lifetime*." Future technology updates may mean that individuals who had tested negative should be able to access further testing. The College suggests the following wording for AAAA "*Available up to twice per lifetime where the second service is at least 5 years after the first and a different or updated technology is used*."
iii. Following on from this, there is a disconnect between the proposed items AAAA and FFFF. Item number FFFF, which was proposed by the Department, incorrectly states that it is for the re-analysis of whole exome data from item AAAA, and that the use of WES or WGS would allow for reanalysis. Application 1585 is for a *gene panel*, not for WES or WGS, and therefore item FFFF should remain technology agnostic. As it is written, item number FFFF in effect forces AAAA to be technology biased, not technology agnostic. Item number FFFF should read:
Re-analysis of ~~whole exome~~ data obtained in performing a service to which item AAAA applies, ~~after appropriate genetic counselling~~, for characterisation of previously unreported pathogenic gene variants related to the clinical phenotype.
iv. It should also be noted that laboratories are not obliged to ensure that appropriate consent has been obtained for level 1 testing (i.e. testing under item AAAA), contrary to what is stated on p. 2, last paragraph. In addition, the requirement for genetic counselling in the item numbers should be removed and added as a practice note.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website