Australian Government

Department of Health

RATIFIED PICO

Application 1585:

Genomic testing for the diagnosis of neuromuscular disorders (NMDs)

Background

PASC's First Consideration (December 2019)

PASC requested the revised Draft PICO return to PASC before it can proceed to the Evaluation Sub-Committee (ESC) stage.

PASC recommended that, once the PICO is revised and ratified (after its second consideration by PASC), it is appropriate for the assessment to follow the Clinical Utility Card (CUC) approach, with one or more 'star performers'.

PASC's Second Consideration (April 2020)

This application was reconsidered by PASC for a second time in April 2020. PASC's April 2020 advice is included in *italics*, distinguishing it from the advice provided during its first consideration in December 2019.

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Please note: In line with gender-neutral policies and practices, references to 'female and male' are used for ease of interpretation. Gender-neutral language are usually used in any final item descriptors where appropriate.

Component	Description

Patients	• Broad gene panel testing for:
	  ○ Individuals with suspected NMD
	  ○ Pregnant females with a fetus with suspected NMD and with no family history of NMD (including the family history of the reproductive male partner)
	• Variant-specific detection for:
	  ○ Biologic relatives of an individual with an actionable pathogenic variant of NMD
	  ○ Reproductive partner of an individual with an identified recessive gene variant of NMD, for the purpose of pre-pregnancy planning
	  ○ Pregnant females with a family history of an actionable pathogenic variant of NMD (including the family history of the reproductive male partner)

Prior tests	None
Intervention	A gene panel test (either myopathy panel and/or neuropathy panel) or variant-specific testing, that are in-vitro diagnostic (IVD) tests, which are used to detect genetic variants from a peripheral blood sample, saliva sample, buccal swab, amniotic fluid or chorionic villi sample (CVS) to assess whether there is an actionable pathogenic variant of NMD. Requested only by specialist paediatricians, neurologists, clinical geneticists or obstetricians.
Comparator	No genetic test
Outcomes	<u>Safety</u> • Adverse events from obtaining a sample for testing • Psychological adverse events from genetic testing or no genetic testing • Psychological effects of false positives or false negatives <u>Effectiveness</u> • Impact on clinical management • Health-related quality of life • Impact on decisions for future reproduction • Termination rate due to presence of specific genetic variants • Reduction in proportion of children born with NMD <u>Analytical validity</u>[1] • Analytical sensitivity and specificity • Likelihood ratios • Rate of repeat testing • Rate of repeat data analysis <u>Clinical validity</u>[2]

Component	Description
	• Clinical specificity and sensitivity • Positive and negative predictor values <u>Healthcare resources</u> • Cost of gene panel test or variant specific test • Number of, and cost associated with obtaining an appropriate sample • Additional medical practitioner consultations • Cost of re-testing and/or data reanalysis • Cost of genetic counselling • Cost offset by reducing number of diagnostic tests • Cost of targeted therapies • Cost of pregnancy termination • Cost offset by the effect of reducing number of births with NMDs • Cost per quality-adjusted life year • Total Australian Government healthcare costs

POPULATION

<u>Please note</u>: As per the Human Genome Variation Society (HGVS) recommendations (den Dunnen et al. 2016), the term 'variant' should be (and has been) used to replace the outdated term 'mutation'

PASC's First Consideration (December 2019)

PASC noted the difficulty of accurately estimating prevalence and incidence of the included conditions. Although most of the individual conditions are relatively rare, they are (as a group) common.

PASC confirmed it is unlikely to be appropriate to restrict the population to a certain age group – while the majority of patients will present early (early age of onset is often a predictor of more severe disease), some might present later in life.

PASC identified numerous neuromuscular disorders (NMDs) that should be excluded from the proposed medical service, because some NMDs are not detectable using next-generation sequencing (NGS) - e.g. Charcot-Marie-Tooth type 1 and Huntington disease, which require copy-number testing. PASC therefore advised that the target population needs to be defined more carefully, either by using more focussed terminology, or listing all exclusions.

The applicant stated that, while this is correct, it is a complex issue, specifically regarding inclusion of MBS item 73294. The Department is of the view that, given the small number of specifically-funded tests, this use could be described in the Practice Note.

The applicant responded that inclusion of an appropriate Practice Note for the proposed MBS item may negate concerns around testing for late-onset Charcot-Marie-Tooth disease type 1A (CMT1A) and the use of MBS item 73294 (genetic testing for PMP22 for the diagnosis of CMT1A). The applicant added that testing for CMT1A may be a first-line test in some patients (prior to testing with the proposed NMD panel). The applicant reiterated that this is a complex issue that needs resolving. The Department confirmed that, as it stood, the proposed algorithm did not include single gene testing prior to the proposed panel.

The Department agreed there may be exceptional specific instances where a single gene test may be preferentially performed ahead of an NM panel (with PMP22 testing), noting Royal College of Pathologists of Australasia (RCPA) advice that this would only relate to a very few clinical instances.

Hence, it has not been included as a standard step in the algorithm (i.e. the algorithms remain unaltered on this point).

PASC noted that, if certain conditions are excluded (because NGS is not a suitable technology for all NMDs, or they are already covered by other MBS items), they will fall outside the scope of the evaluation. This will have a large impact on the economic evaluation and financial estimates. The proposed intervention is test agnostic, in order to capture NMDs that cannot be diagnosed via NGS. This is documented in the PICO under the heading 'Intervention' (included under variant-specific testing, 2nd para). Mitochondrial myopathies are out of scope for this application.

PASC also noted hereditary neuropathy can be a component of several autosomal recessive neurometabolic disorders (such as Refsum disease, metachromatic leukodystrophy and Krabbe disease), so appropriate testing should be performed if indicated. Other conditions associated with neuropathy include mitochondrial diseases, Friedreich ataxia, X-linked adrenomyeloneuropathy, and Pelizaeus-Merzbacher disease (PMD) (X-linked). Such disorders do not appear to have been considered in this application.

The applicant advised that Friedreich ataxia is mostly due to a trinucleotide repeat expansion, and PMD frequently associated with copy number variant (CNV). While CNV detection is possible with the use of a gene panel, currently repeat expansions represent a challenge. The applicant added that proposed MBS item AAAA clearly states "a genetic neuromuscular disorder other than those associated with variants that are not detected by massively parallel sequencing". The applicant is of the view that it will be cumbersome to list all exclusions, rather than having the generic statement. In addition, technologies/analyses change, and sensitivity is likely to improve in the future.

There is broad agreement (between the applicant, assessment group and Department) that the proposed MBS item should be silent on genes that are not detectable by massively parallel sequencing.

The applicant advised that genes for X-linked adrenomyeloneuropathy, and Pelizaeus-Merzbacher disease (X-linked), are on the panel. However, mitochondrial disorders are not detected by the panel. It is noted later in this PICO that mitochondrial DNA is not tested.

PASC advised that redrafting the application to address these issues would require different algorithms to cover the different approaches.

PASC advised that, for conditions that are autosomal recessive, an MBS item for reproductive partner testing will be required. An estimate of the size of this population is required, and will need to be included in financial estimates. A statement on genetic testing of reproductive partners for autosomal recessive conditions has been added to the intervention.

The applicant agreed that item BBBB should be amended to reflect partner testing for recessive conditions. The assessment group has added a separate MBS item to cover this group.

An estimate of size of the population needing reproductive partner testing for autosomal recessive conditions has not been completed. The applicant will need to advise whether a new MBS item is required for reproductive partner testing of autosomal recessive conditions or if proposed MBS item 'CCCC' will capture this population subgroup.

Neuromuscular disorders (NMDs) are a broad range of generally progressive disorders affecting the peripheral nervous system and muscle and neuromuscular junctions. Although grouped under a single name, individuals present with a high level of clinical and genetic heterogeneity along with overlapping phenotypes[3]. A common aspect of all NMDs is abnormal muscle function with associated clinical burden. The clinical and genetic heterogeneities of NMDs make disease diagnosis complicated and expensive, often involving multiple tests[4]. While treatment options for NMD were historically poor, new developments offer curative interventions or improvements decreasing morbidity and mortality[5]. However, novel treatments for NMD are guided by the underlying molecular pathology and establishment of a specific genetic diagnosis.

Neuromuscular disorders can be allocated into four broad categories:

1. Muscle disorders, comprising myopathies, myotonias and muscular dystrophies
2. Motor neuron disorders
3. Peripheral neuropathies
4. Neuromuscular junction disorders (Arnold & Flanigan 2012)

It should be noted that genetic heterogeneity exists not only for NMDs as a group, but also within subgroups. Genetic variants are seen within subgroups, and they may have varying phenotypes.

The applicant confirmed that, given demyelinating peripheral neuropathies are not usually considered motor neuron diseases (and hereditary sensory neuropathies usually come under the heading of neuromuscular disorders [and are also not motor neuron diseases], neuropathies should be included as a category. This also applies to ataxias.

NMDs tend to be genetic in origin and can be inherited as autosomal dominant, autosomal recessive, X-linked or mitochondrial traits, however, de novo pathogenic variants are also common (up to 30% for Duchenne muscular dystrophy [DMD])[67]. At least 761 different NMD disorders exist associated with >500 known genes[8] (refer to Neuromuscular Disorders Gene Table website www.musclegenetable.fr).

According to the Muscular Dystrophy Foundation Australia, more than 20,000 people are affected nationally with some form of NMD and many more are undiagnosed[9]. Individually, these diseases are rare, but as a group, NMD prevalence is greater than 33 per 100,000. For myopathy related NMD, the incidence of common muscular dystrophies is estimated to be between 13.0 and 17.9 per 100,000 and the prevalence of all other myopathies in the United States is estimated to be 2.0 per 100,000, although both are seen to be underestimates of their respective rates[10,11]. Table 1 provides the published incidence rates for thirteen of the most common disorders.

The populations included in the proposed intervention are:

1. People with suspected NMD.
2. Biological relatives of an individual with an actionable pathogenic variant of NMD.
3. Pregnant females with a family history (including the family history of the reproductive male partner) of an actionable pathogenic variant of NMD.
4. Pregnant females where their fetus has suspected NMD and with no family history of NMD (including the family history of the reproductive male partner).

The applicant agreed that this wording should be amended to reflect the need for reproductive partner testing for recessive conditions, as this is not covered by current wording ("biological relative"). The applicant agreed this could be incorporated into proposed MBS item BBBB (or it could equally sit within a separate item). The applicant suggested consideration be given to a generic MBS item for testing partners of those found to be carrying a recessive disease.

Table 2 describes the estimated demand for the proposed genetic test based on national data from the NMD testing laboratory in Western Australia (WA) over the past two years and further extrapolated to 2021. The values provided are based on the number of tests for NMD for patients from Queensland, New South Wales, South Australia, Victoria, and WA. While they represent the majority of the current national genetic testing demand, they do not represent the volume of services potentially required should genetic testing become more generally available.

The applicant advised that many conditions in Table 1 (below) do not have a genetic basis (e.g. Guillain-Barré syndrome and dermatomyositis). The applicant added that most NMDs listed in Table 1 are not monogenic (and although conditions such as Friedreich ataxia have a genetic cause, they may not be detected by NGS panel, as described in this application). The title of Table 1 has been amended to reflect these are heritable and acquired conditions.

It is therefore important to note that the applicant believes the incidence rates described in Table 1 are probably misleading, inflating the number of cases likely to be tested. The applicant advises that the best estimate is the number of samples currently tested at PathWest, being the Australian 'centre of excellence' for NMD testing.

Table 1: Global incidence rates for 13 heritable and acquired neuromuscular disorders (Bhatt 2016; Deenen et al 2015)

Disorder	Incidence range per 100,000 per year*
Anterior horn cells	
Type I spinal muscular atrophy	3.53 to 9.8
All spinal muscular atrophy	3.53 to 14.9
Amyotrophic lateral sclerosis	0.42 to 5.3
Peripheral nerve	
Chronic inflammatory demyelinating polyneuropathy	0.35 to 1.6
Guillain-Barré syndrome	0.4 to 3.0
Friedreich Ataxia	2.7 to 6.19
Neuromuscular junction	
Myasthenia Gravis	0.3 to 2.8 (11.8 reported by one study in Japan)
Lambert-Eaton myasthenic syndrome	0.05
Muscular	
Duchenne muscular dystrophy	2.0 to 34.7 per 100,000 males
Becker muscular dystrophy	1.06 to 7.2 per 100,000 males
Limb-girdle muscular dystrophy	0.7
Polymyositis	0.27 to 3.80
Dermatomyositis	0.08 to 1.78
Inclusion body myositis	0.09 to 0.79
TOTAL	**11.95 to 82.8**

Assumptions from Table 2:

- Based on data provided, 29% and 24% of patients with NMD tested positive for a genetic cause of their NMD in years 2017 and 2018, respectively. The overall proportion of individuals testing positive for a genetic variant was 26% across the two years. This static value has been applied to the modelled estimates (years 2019 to 2021).

- The number of family members tested per index case was 1.12 in 2017, and 1.3 in 2018. To estimate the number of family members' cascade tests for future years (2019 to 2021), the number of NMD cases with an identified genetic cause is multiplied by the ratio of the number of family cascade tests and the number positive test results (1.21) observed in the 2017 and 2018 data.

- The 8.4% increase in total volume of NMD genetic tests observed between 2017 and 2018 has been applied annually for the modelled values (years 2019 to 2021).

Table 2: Estimated number of NMD genetic tests from 2017 to 2021

Parameter	2017	2018	2019*	2020*	2021*
Number of suspected NMD index cases	944	1,023	1,108	1,200	1,300
Number of positive NMD cases	276	242	293	316	342
Number of cascade tests per positive case	1.12	1.30	1.21	1.21	1.21
Total number of family cascade tests	310	330	354	382	413
Number of prenatal diagnosis	13	19	-	-	-

Source: Application Form 1585
Notes: based on 2017-2018 data from the national NMD testing laboratory in WA
*Estimated population based on linear projection of 8.4% (change from 2017-2018)

Table 3 applies each of the assumptions set out Table 2, but does so starting from an estimated population incidence rate for the most commonly occurring NMDs.

- The current application provides a minimum and maximum incidence for thirteen NMDs reported in peer-reviewed studies (see Table 1). The wide range is attributable to differences in NMD diagnostic definitions and heritability, as well as a general paucity of data to inform estimates. The cumulative prevalence estimates provided in Table 1 were used as the basis for assessing likely population demand for testing (see section labelled 'scenario A' in Table 3). The lower incidence estimate was set at 12.0/100,000, while the upper estimate was set at 82.8/100,000, both being the simple additive sum of rates of each individual NMD included in Table 1. It is acknowledged that the list of disorders is not complete, and the incidence rates provided are likely to underestimate the true incidence (due to incomplete case ascertainment).

- In addition to the two incidence rates provided in the application, another set of models has been developed, assuming an incidence rate of 100/100,000. This was indicated to be the likely NMD incidence rate on the Muscular Dystrophy Foundation Australia website[12]. It is assumed this estimate attempts to correct/address the two factors discussed above (incomplete list of NMD disorders and incomplete case ascertainment), although no peer reviewed document is cited in connection with the estimate.

- With the range of incidence rates established, assumptions based on data from Table 2 were used to estimate the likely number of tests conducted on suspected NMD index cases in Table 3. Data from Table 2 indicated that for every single confirmed case, approximately 2.8 suspected index cases would be tested. Scenario B in Table 3 provides the estimated number of tests required, assuming the same ratio of suspected test cases to true cases (based on the three incidence estimates[13]).

- Using data in Table 2, the observed increase in the rate of testing (8.4%) annually was applied to the modelled estimates (section 'Scenario C' in Table 3), building on previous scenarios.[14] It should be noted that, for the upper incidence estimate and the alternative incidence estimates in Scenario C, the estimate of number of tests required are similar to the observed and modelled volume of tests currently recorded for the national NMD testing laboratory in WA.

- In order to assess the number of pregnant females with a family history (who may require genetic testing), the carrier frequency was calculated based on NMD incidence rates provided, assuming an autosomal recessive pattern of inheritance[15]. An uptake percentage of 5% was then applied, based on a large-scale study which found only 5% of individuals were referred to SMA testing based on their family history [16]. Calculating the carrier frequencies for the lower bound, upper bound, and alternative incidence estimates, yielded a carrier to population ratio of 1:38, 1:18, 1:13, respectively. The total number of pregnancies were multiplied by these ratios, and 5% of the product was reported (see results under Scenario D). It should be noted that this would markedly increase the number of individuals who would require testing, more than doubling the number of tests to be conducted for each incidence estimate.

- The applicant importantly stated that, if Table 1 was used to calculate the carrier rate, this figure will also be erroneous and inflated. The applicant advised that only a small number of NMD conditions have an autosomal recessive pattern of inheritance.

- Scenario E builds on scenario D by adding the number of cascade tests required, relative to the number of likely cases testing positive. The estimate of 1.21 cascade tests is applied for every incident case (Scenario A), as provided in the observed testing volume.

- Scenario F addresses the number of individuals who require *de novo* testing. It should be noted that this has already been partially integrated into existing modelling by the inclusion of tests conducted on suspected cases (Scenario B). In an attempt to mitigate double counting of testing requirements, the number of suspected cases added was 30% of incidence estimates outlined in Scenario A. The integration of these assumptions add very few tests to the testing requirements, and the addition is tentative, based on uncertainty surrounding other assumptions preceding scenario F.

- Three aspects <u>not</u> considered in the modelling above were:
    1. the initial need to test existing prevalent cases who may gain access to testing as a result of listing the services on the MBS;
    2. individuals who may require re-testing due to inaccurate/inconclusive results, or individuals who require re-testing due to a previous negative result (who may benefit from testing with an expanded testing battery of genetic variants); and
    3. pregnant females where the fetus has suspected NMD, with no family history (including the family history of the reproductive male partner). These are likely to be included in current estimates, based on the number of initial suspected cases, but the number of individuals tested may increase, based on increased availability of the proposed testing.

- The applicant confirmed that the modelling should include pregnancies. In relation to de novo variants, proposed MBS item DDDD would cover de novo, if presented in utero; however, conditions such as DMD do not present in utero, but may be detected by ultrasound.

Modelling in the application is likely to underestimate potential uptake of genetic testing, as it only accounts for current volume and observed increases (prior to wide-scale accessibility of testing). It is likely that the true uptake of genetic testing will be between the lowest and highest estimates in Table 4, aligned with the middle estimate provided.

PASC's Second Consideration (April 2020)

PASC confirmed the proposed populations.

PASC agreed that the estimated numbers for testing (2,000 ± 500) were uncertain and if possible should be better defined. PASC noted that current MBS items are not specific for NMDs, which makes it difficult to use MBS claiming data to estimate the population numbers.

The applicant noted, that in the absence of refined population data on incidence and prevalence of genetically determined NMD, the estimated numbers for testing are approximate; the data from multi-ethnic populations such as those in New Zealand, Canada, and UK could be used as proxies.

The applicant provided three recent articles related to incidence and/or prevalence of NMD in these countries. The incidence in Canada[1] was quoted as 10.6/100,000 adults when relying on data from ED or hospital admissions. Considering clinician billing, the incidence in Canada was estimated at 182/100,000 adults (including ~50% non-monogenic causes). The applicant noted these numbers do not seem to be far from the assumption of an incidence of ~100/100,000 in the MSAC application. Further, the applicant stated, the collective prevalence of genetically determined NMD in UK[2] would not also exceed 100/100,000, and the numbers from New Zealand[3] are consistent with this trend (but only for genetic muscle disorders).

In summary, the applicant concluded the numbers from these articles supported the existing estimates in the application. The applicant considered the PASC's advice regarding the estimated population numbers may relate to the fact that the number 2000+/- 500 reflects the potential total of all items (AAAA-EEEE), rather than breaking down numbers into their specific categories (index patients, relatives etc.).

[1] Rose L, McKim D, Leasa D, Nonoyama M, Tandon A, Bai YQ, et al. (2019) Trends in incidence, prevalence, and mortality of neuromuscular disease in Ontario, Canada: A population-based retrospective cohort study (2003-2014). PLoS ONE 14(3): e0210574. https:// doi.org/10.1371/journal.pone.0210574

[2] Bargiela, D., Yu-Wai-Man, P., Keogh, M., Horvath, R., & Chinnery, P. F. (2015). Prevalence of neurogenetic disorders in the North of England. Neurology, 10-1212.

[3] Theadom, A., Rodrigues, M., Poke, G., O'Grady, G., Love, D., Hammond-Tooke, G., ... & Te Ao, B. (2019). A Nationwide, population-based prevalence study of genetic muscle disorders. Neuroepidemiology, 52(3-4), 128-135.

Table 3: Likely testing requirements based on population incidence

		2017	2018	2019*	2020*	2021*
Number of births		309,142	323,481	330,239	336,833	343,033
Number of pregnancies		366,224	368,976	371,728	374,480	377,232
Incidence Estimates						
Scenario A: • Base Incidence Rate	Lower Incidence Estimate (12.0/100,000)	37	39	39	40	41
	Upper Incidence Estimate (82.8/100,000)	256	268	273	279	284
	Alternative Incidence Estimate (100/100,000)	309	323	330	337	343
Scenario B: • Incidence • Number of tests conducted on suspected cases	Lower Incidence Estimate (12.0/100,000)	140	147	150	153	156
	Upper Incidence Estimate (82.8/100,000)	973	1,018	1,039	1,060	1,079
	Alternative Incidence Estimate (100/100,000)	1,175	1,229	1,255	1,280	1,304
Scenario C: • Incidence • Number of tests conducted on suspected cases • proposed annual increase (8.4%)	Lower Incidence Estimate (12.0/100,000)	152	159	163	166	169
	Upper Incidence Estimate (82.8/100,000)	1,054	1,103	1,126	1,149	1,170
	Alternative Incidence Estimate (100/100,000)	1,273	1,332	1,360	1,387	1,413
Scenario D: • Incidence • Number of tests conducted on suspected cases • Proposed annual increase (8.4%) • Likely screening requirements based on carrier frequency	Lower Incidence Estimate (12.0/100,000)	634	645	652	659	665
	Upper Incidence Estimate (82.8/100,000)	2,072	2,128	2,159	2,189	2,218
	Alternative Incidence Estimate (100/100,000)	2,682	2,752	2,790	2,828	2,864
Scenario E • Incidence • Number of tests conducted on suspected cases • Proposed annual increase (8.4%) • Likely screening requirements based on carrier frequency • Cascade Tests	Lower Incidence Estimate (12.0/100,000)	679	692	699	707	715
	Upper Incidence Estimate (82.8/100,000)	2,381	2,452	2,490	2,527	2,562
	Alternative Incidence Estimate (100/100,000)	3,056	3,143	3,190	3,235	3,279
Scenario F • Incidence • Number of tests conducted on suspected cases • Proposed annual increase (8.4%) • Likely screening requirements based on carrier frequency • Cascade Tests • de novo testing	Lower Incidence Estimate (12.0/100,000)	690	703	711	719	727
	Upper Incidence Estimate (82.8/100,000)	2,458	2,533	2,572	2,610	2,647
	Alternative Incidence Estimate (100/100,000)	3,149	3,240	3,289	3,336	3,382

Sources: Application Form 1585, ABS 3222.0 - Population Projections, Australia, 2017 (base) - 2066
*Estimated population

Table 4: Likely testing volumes across three scenarios

Parameter	2017	2018	2019*	2020*	2021*
Number of suspected NMD index cases +cascade testing- original modelling	944+310= **1,254**	1,023+330= **1,353**	1,108+354= **1,462**	1,200+382= **1,582**	1,300+413= **1,713**
Screening Requirements (upper incidence estimates, Scenario D)	**2,072**	**2,128**	**2,159**	**2,189**	**2,218**
Screening Requirements (upper incidence estimates, Scenario E)	**2,381**	**2,452**	**2,490**	**2,527**	**2,562**

Source: Refer to Table 2 and 3

Prior test

No prior tests are required for the proposed genetic test.

INTERVENTION

PASC's First Consideration (December 2019)

PASC noted this application is for a targeted gene panel test (myopathy and/or neuropathy panel), using next generation sequencing (NGS). This will exclude some NMDs (e.g. SMA, CMT). PASC had stated that NGS will also not reliably detect myotonic dystrophy, facioscapulohumeral dystrophy and Duchenne muscular dystrophy (but not because these disorders are due to copy-number variants). PASC advised that, excluding these conditions, will complicate the issue of incidence and prevalence, because remaining conditions will all be rare.

The applicant advised that this was incorrect. The applicant advised that the panel is capable of detecting copy number variants. For example, the PMP22 copy number variants should be detected by the panel. Given DMD variant is comprehensively analysed by the proposed panel, the applicant was unsure why this conclusion was made.

The applicant requested that the PICO document reiterated that disorders that cannot be assessed by the proposed technology are specifically mentioned, as outlined on page 11, paragraph 6 of the original PASC Outcome document (i.e. "Some NMD variants, like spinal muscular atrophy type 1 (SMN1), myotonic dystrophy type 1 (DM1) and facioscapulohumeral muscular dystrophy type 1 (FSHD1), are not detected by NGS." The applicant advised that the comment following this statement (i.e. "If there is a strong clinical suspicion of these disorders, a patient or fetus will undergo variant-specific testing for the relevant genes, covered by separate MBS items") is incorrect. The applicant confirmed there are no MBS items that cover testing for these disorders, with the exception of PMP22 (MBS item 73294).

In light of the applicant's comments, and subject to PASC's advice, the statements identified by the applicant as incorrect were removed from the PICO document.

The applicant advised that the current technology (involving multiple short reads) may be substituted in the near future by a different approach (i.e. multiple long reads). In addition,

bioinformatic approaches may change, and future gene panels may be able to detect more/different gene variants. The applicant was of the view that the MBS items should be agnostic to technology and should not be restrictive. The Department agreed with this, noting the proposed MBS items are method agnostic.

PASC agreed with the applicant that a broad panel of genes is preferred.

PASC advised that the two panels do not include the mitochondrial genome, so mitochondrial myopathies are out of the scope of this application. A sentence was added to the intervention section to address this.

PASC recommended the need for clarity about whether gene panel testing would replace existing MBS items, or be an additional test. PASC recommended reviewing whether tests already MBS funded could be rolled into this application. Current MBS items that would not be replaced by a potential amalgamation would need to remain. This application relates to NGS, so it is important to ensure existing MBS items cover syndromes for which NGS is unsuitable.

The applicant reiterated (as detailed in their comments in the 'Population' section of this PICO), that given there is no age restriction in the current application, existing MBS item 73294 could be considered amalgamated. However, the applicant believes item 73294 should remain on the MBS as a first-line test for some patients. Other MBS items detailed in this application (biopsy, etc) will need to remain available for patients. The Department agrees that item 73294 should remain separate, in order to allow single-gene testing in selected patients.

The applicant advised that (in most cases) the proposed intervention will replace existing MBS items 30075 (diagnostic biopsy), 72844 (enzyme histochemistry) and 72846 (immunohistochemistry).

Based on the proposed clinical algorithm, if a person initially declines genetic testing, these existing MBS items will be used for diagnosis. Based on results obtained through currently-funded MBS tests, the person may then choose to undertake genetic testing (if the test is warranted and offered by a specialist). In such scenarios, the person may utilise the current MBS items and the proposed intervention. There may also be scenarios where a person refuses genetic testing, despite positive (MBS-funded) biopsy results.

The proposed intervention includes two types of genetic testing:

1. gene panel testing
2. variant-specific testing.

The type of NMD genetic test is based on whether there is a known pathogenic gene variant in the person's biological family members.

Mitochondrial myopathies are out of scope of this application.

Gene panel testing

Gene panels capture all known pathogenic variants of NMD that are detectable by next generation sequencing (NGS). After a clinical examination to rule out other non-genetic causes of NMD, patients will undergo genetic testing by either the myopathy or neuropathy gene panel. The choice of panel used is decided by the referring medical practitioner and is based on clinical presentation. In some circumstances, both panels will be used, owing to difficulty in determining a diagnosis based on clinical examination. Based on current data held by the applicant, this occurs in about 1% of gene panel tests (40 out of 4000 tests).

The gene panel test is suitable for a patient or fetus with suspected NMD, who does not have a documented family history of an NMD gene variant. Biological parents of those individuals with a positive genetic panel test result, will then also be screened, using a specific genetic test to determine whether the pathogenic variant was inherited or *de novo.*

Patients with a negative genetic test result may undergo a muscle or nerve biopsy, in order to characterise their disease (as currently happens), and in future, may obtain re-analysis of their genetic data (e.g. if new genes are identified and/or added to the panel). Other tests (such as histology or biochemistry analysis) may also be used for diagnosis. The number and type of tests used for patients with a negative genetic test result is based on disease phenotype.

A description of the 'exemplar' genes with defined diagnostic, prognostic and predictive utilities in the neuromuscular panel was provided by the applicant in Appendix A of the Amended Application Form (provided to the Department on 6 April, 2020). These should include at least one gene for each of the four groups per page 5. If there are conditions in each category which are exemplars for childhood-onset disorders, these should also be described.

The applicant confirmed that for each patient tested, they will have one pathology sample taken from which the full virtual gene panel will be assessed, but depending on the clinical features, either the neurological or muscular panel will be reported to the clinician. In the event there is residual clinical uncertainty, the remaining panel can then be reported.

Variant-specific testing

Sanger sequencing or other technologies (e.g. multiplex ligation-dependent probe amplification (MLPA)) is used for variant-specific genetic testing. This cascade test is proposed to be performed for a patient or fetus with a biological family history of an actionable pathogenic variant of NMD. If the variant-specific genetic test is negative, further tests like broad gene panel testing and/or biopsy may be warranted, but only if the patient develops signs and symptoms later in their life.

Some NMD variants, like spinal muscular atrophy type 1 (*SMN1*), myotonic dystrophy type 1 (*DM1*) and facioscapulohumeral muscular dystrophy type 1 (*FSHD1*), are not detected by NGS. If there is a strong clinical suspicion of these disorders, a patient or fetus could undergo variant-specific testing for the relevant genes, if separate MBS items were listed.

Genetic test results are obtained within two to four months, although urgent cases can be processed within one to two weeks. Prenatal genetic test results for known familial variants can be obtained within four to seven days.

Patients and parents of a fetus identified with an NMD are offered genetic counselling (which may be provided by a genetic counsellor, a specialist physician, or both), as well as being referred to other healthcare clinicians, such as neurologists, cardiologists, physiotherapists, respiratory therapists, etc. Disorder-specific treatment is commenced in a timely manner, and advice is provided on family planning options.

The gene panel test and variant-specific testing are not currently funded on the MBS, but are accessed on a user-pay basis.

Some non-genetic NMD diagnostic procedures and tests are currently subsidised on the MBS:

- **Item 30075:** Diagnostic biopsy of lymph gland, muscle or other deep tissue or organ, as an independent procedure, if the biopsy specimen is sent for pathological examination.
- **Item 72846:** Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 antibodies except those listed in 72848.
- **Item 72844:** Enzyme histochemistry of skeletal muscle for investigation of primary degenerative or metabolic muscle diseases or of muscle abnormalities secondary to disease of the central or peripheral nervous system - 1 or more tests[17].

In addition, patients with a family history of suspected NMD currently undergo several diagnostic tests such as nerve conduction studies, blood tests to measure creatine kinase and other biomarkers, electromyography, and nerve and muscle biopsies[18]. These diagnostic tests, especially nerve and muscle biopsies, are invasive and often painful.

Genetic testing helps to identify the putative causative gene variant of the clinical phenotype so that treatment and counselling is targeted and can be commenced early, and patients can be advised on family planning, prognosis, and other long-term management plans[19]. Single gene testing of specimens can be done currently, but given the number of genetic variants, it is implausible to perform these for each patient.

The proposed intervention is less painful and invasive when compared with muscle and nerve biopsies and may help patients avoid further time consuming and expensive tests such as nerve or muscle imaging, blood and cerebrospinal fluid testing, Sanger sequencing and other additional tests for family members (e.g. cascade testing).

The proposed genetic tests, amalgamated in panels (which would replace the current diagnostic testing processes described above, and single-gene tests for some index patients), would be accessible via a referral from a specialist paediatrician, neurologist, clinical geneticist or obstetrician. DNA is obtained from a peripheral blood sample, saliva sample or buccal swab for paediatric and adult patients, and amniocentesis or CVS is obtained for prenatal genetic tests. The samples are delivered to a NATA-accredited pathology laboratory for analysis, and interpretation is undertaken by accredited pathologists or medical scientists.

If a patient has a positive diagnosis for an autosomal recessive NMD, their reproductive partner will also require variant-specific testing for the putative causative gene variant. NMD genetic tests are a once-off diagnostic test per patient. Re-testing and data re-analysis can be requested by the laboratory (if required), in consultation with the requesting clinician. This may be applicable for people with a negative test result, based on current gene panel composition, when new genes and associated phenotypes are discovered and reported.

PASC's Second Consideration (April 2020)

PASC confirmed the interventions.

PASC noted the applicant previously provided additional information about the exemplar and facilitated genes for the nominated exemplar diseases in each of the 4 categories, which will allow the assessment group to do the analysis based on the Clinical Utility Card approach.

PASC advised that most of the testing would be in a non-hospital setting, making this testing suitable for the MBS.

PASC noted the issues relating to inequity of access for this application, including jurisdictional variation.

COMPARATOR

PASC confirmed that the appropriate comparator is no genetic testing.

No gene panel test or variant-specific test is the proposed comparator.

Diagnosis of NMD is currently informed by MBS subsidised diagnostic tests that are available for patients with suspected NMD. These tests are not suitable comparators since they do not provide a definitive diagnosis and are unable to specify the genetic pathogenic variant of NMD. However diagnostic tests will not be required if the proposed interventions are introduced on the MBS.

It is important to note that, in current clinical practice, clinicians may request sequential series of single gene tests (funded outside the MBS on either a user-pay basis or utilising state/territory health department funding, etc). This is in addition to, or in replace of, requesting MBS-subsidised diagnostic tests. However, it was deemed not suitable for single-gene testing to be compared to broad panel testing. This is because neither are currently available on the MBS, and the application includes the use of single-gene testing (i.e. variant-specific testing) for a defined cohort, compared to use of the broad panel for a different cohort.

OUTCOMES

PASC confirmed the proposed outcomes.

Patient-relevant outcomes

From a patient perspective, NMD genetic tests may offer a definitive diagnosis without the need for multiple tests that can be time consuming, painful, and invasive. Patients can commence targeted treatments earlier which can offer symptom relief, slow disease progression, and improve quality of life (QoL). This intervention detects pathogenic variants of NMD in asymptomatic family members and foeti which can help in early education and monitoring of signs and symptoms of the disorder.

Pregnant couples (and those planning a pregnancy) can be advised on reproductive options and pregnancy termination to avoid having children with these diseases. High risk couples (reproductive couples with a pathogenic variant of NMD or with a family history of pathogenic NMD), and females with a fetus with NMD who choose to have children without considering alternative options, would be able to prepare and inform themselves prior to birth, by seeking frequent monitoring and early treatments.

From a clinical perspective, an accurate assignment of genomic variant is important, because of prognostic and therapeutic implications for the patient. Clinicians can reach a definitive diagnosis earlier; they can provide patient-centred monitoring and therapy; and (if necessary) refer patient/s to other relevant healthcare services and clinicians. Also, genetic counselling services will be targeted to the disorder, and clinicians will be able to provide relevant information on prognosis, family planning and long-term management.

The following outcomes are considered relevant to the assessment of the comparative effectiveness and safety for a person or fetus with suspected NMD and those with a family history of an actionable pathogenic variant.

Effectiveness:

- Impact on clinical management
- Health-related quality of life
- Impact on decisions for future reproduction
- Termination rate due to presence of specific genetic variants
- Reduction in proportion of children born with NMD

Safety:

- Adverse events from obtaining a sample for testing
- Adverse effects of targeted drug therapy
- Psychological adverse events from genetic testing or not genetic testing
- Psychological effects of false positives or false negatives

Analytical validity[20]:

- Analytical sensitivity and specificity
- Likelihood ratios
- Rate of repeat testing
- Rate of repeat genetic data analysis

Clinical validity[21]:

- Clinical sensitivity and specificity
- Positive and negative predictive values

Healthcare system outcomes

Availability of genetic testing for people with suspected NMD (and cascade testing of family members and fetuses) will have implications for the Australian healthcare system.

Availability of NMD gene panel and variant-specific tests will likely involve additional consultations with clinicians, so people and pregnant females with suspected NMD, and those with a family history of these disorders, understand what the testing provides and the implications for patients and their families. Positive results of these genetic tests will result in referrals to other healthcare clinicians and consultations at genetic counselling services. Where a gene has been identified as a causal variant, the genetic test provides a definitive diagnosis. It is therefore expected there will be fewer specialist appointments, especially for diagnostic purposes, before appropriate treatment can be commenced (where a known variant is detected).

The applicant claims that equal access to NMD genetic tests, via MBS funding, will minimise the cost of other diagnostic tests and decrease the risk of treatment with inappropriate therapies. NMD genetic panel tests could therefore have a lower cost than multiple sequential genetic and non-genetic diagnostic tests, and reduce the costs associated with inappropriate treatment (for the therapy and associated adverse events).

Couples will be able to choose other reproductive options. If so, this would result in a cost-saving for the MBS, PBS and other healthcare use (e.g. public/private hospitalisation and/or non-admitted patient sessions, private health insurance). For people or fetuses with a negative NMD genetic test result, the impact on healthcare resources will be the cost of the test or MBS fee.

Healthcare resources:

- Cost of gene panel test or variant-specific test
- Number of samples, and the cost associated with obtaining them
- Additional medical practitioner consultations
- Cost of retesting and/or data reanalysis
- Cost of genetic counselling
- Cost offset by reducing number of diagnostic tests
- Cost of targeted therapies
- Cost of pregnancy termination
- Cost offset by reducing number of births with NMD
- Costs of pre-implantation genetic diagnosis for couples with a previously affected infant, or who are known carriers
- Cost per quality-adjusted life year
- Total Australian Government healthcare costs

Current and proposed clinical management algorithms

Current clinical management algorithm for identified population

Under the current clinical management pathway, people with suspected NMD, pregnant females with a fetus with signs of NMD and those with a family history of these disorders, are referred for genetic testing by their medical practitioner. If they accept to be tested, the service is currently performed on a user-pay basis.

Figure 1 and Figure 2 present the current clinical management algorithm for NMD genetic testing in the proposed population. A multidisciplinary healthcare team treats the patient as they progress with age. These diseases significantly affect quality of life and are associated with increased healthcare costs.

Figure 1: Current clinical algorithm – variant-specific NMD genetic test

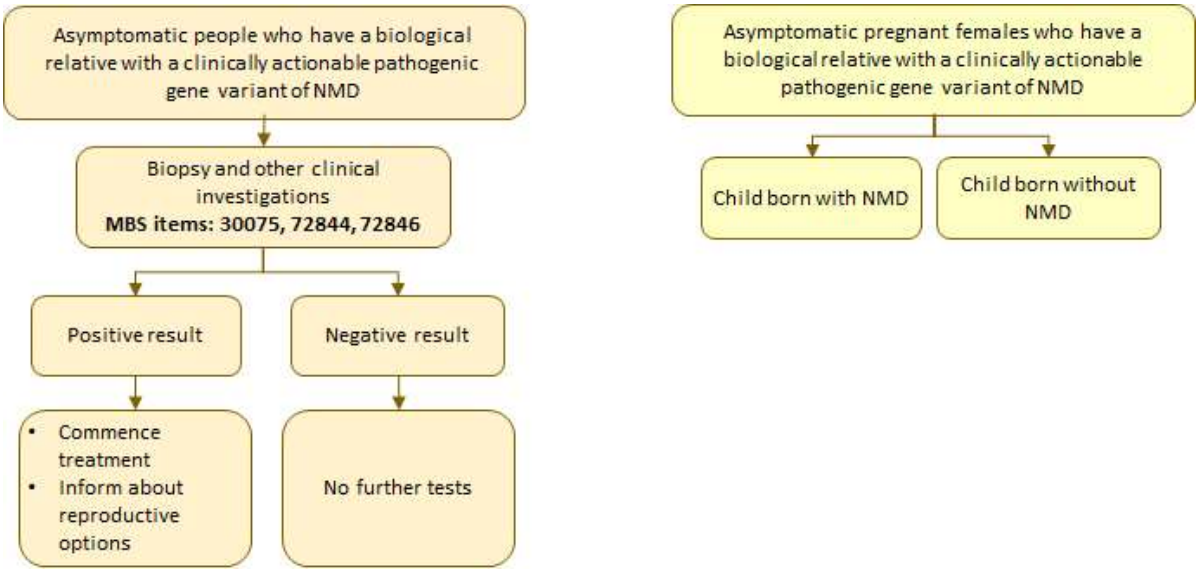
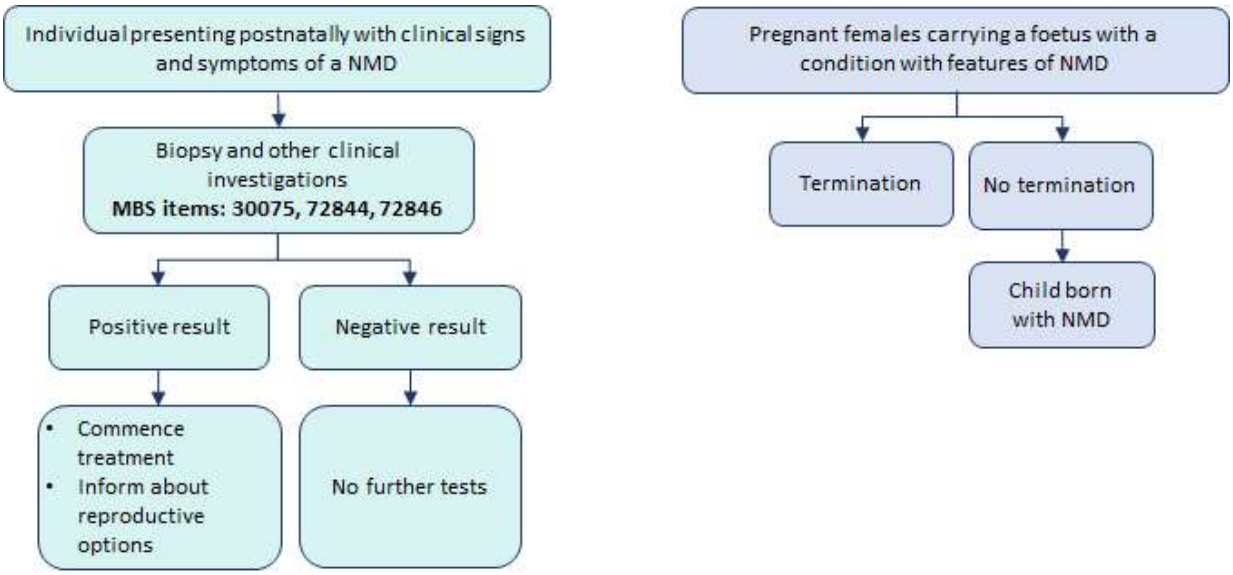


Figure 2: Current clinical algorithm – NMD gene panel test (myopathy and/or neuropathy)



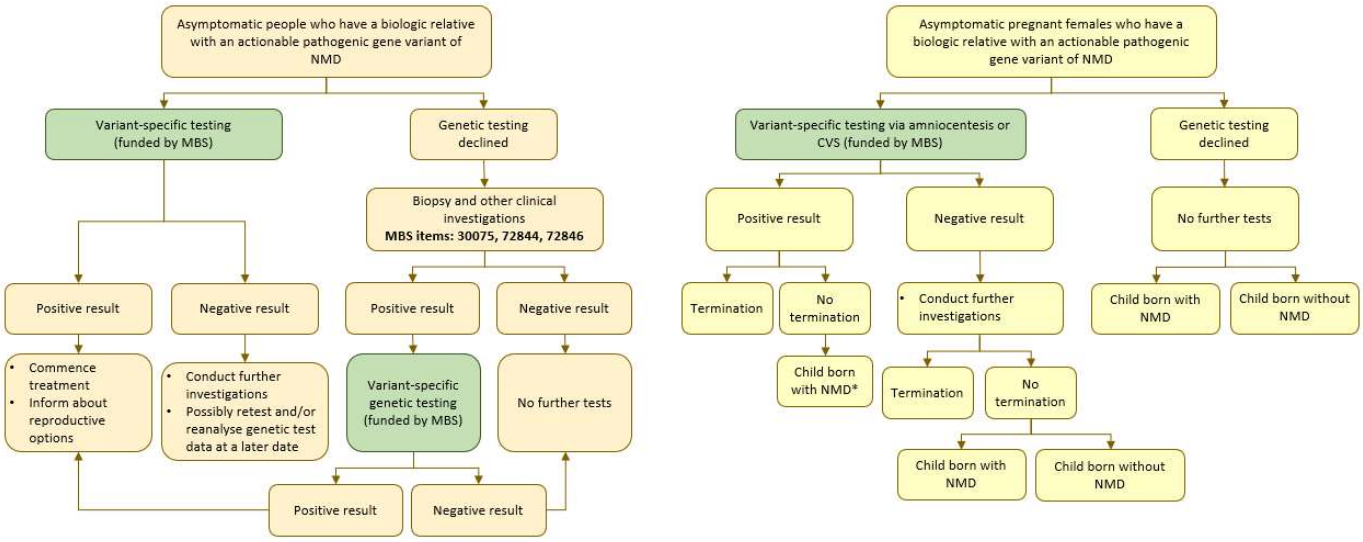
Proposed clinical management algorithm for identified population

Figure 3 and Figure 4 present the proposed clinical management algorithm for NMD genetic testing in the proposed population. The main difference between the current and proposed clinical algorithm is that NMD genetic testing is MBS subsidised (for the proposed clinical management algorithm), rather than on a user-pay basis (current clinical management algorithm). If genetic testing is undertaken (noting some individuals may object to genetic testing), current diagnostic processes funded under the MBS may not be required.

PASC noted the management algorithms were complex and heterogeneous, involving a multi-disciplinary approach (including counselling and referral to a neuromuscular specialist, in addition to paediatricians, respiratory therapists and cardiologists). The applicant would like clarification on whether genetic counselling should be reflected in the proposed algorithms (while noting it is funded outside the MBS in the public sector).This doesn't need to be included as a specific step in the algorithm, but should be noted in the PICO that 'genetic counselling' may be performed by either a genetic counsellor, or by a specialist physician, or both. A change has been made to the text on page 14 which clarifies who can provide the genetic counselling required (genetic counsellor, specialist physician, or both).

PASC noted an incorrect loopback in the flowchart for an "individual presenting post-natally, with clinical signs and symptoms of an NMD" (Figure 4). This needs to be corrected – i.e. in the "Genetic testing declined" arm of the chart, the arrow from a positive result following variant-specific gene testing should not lead back to myopathy/neuropathy panel testing. The applicant agreed with the suggested changes to the algorithms, noting Figures 2 and 4 contain the same erroneous loop back. The applicant repeated that the correct term is 'variant', not 'mutation'.

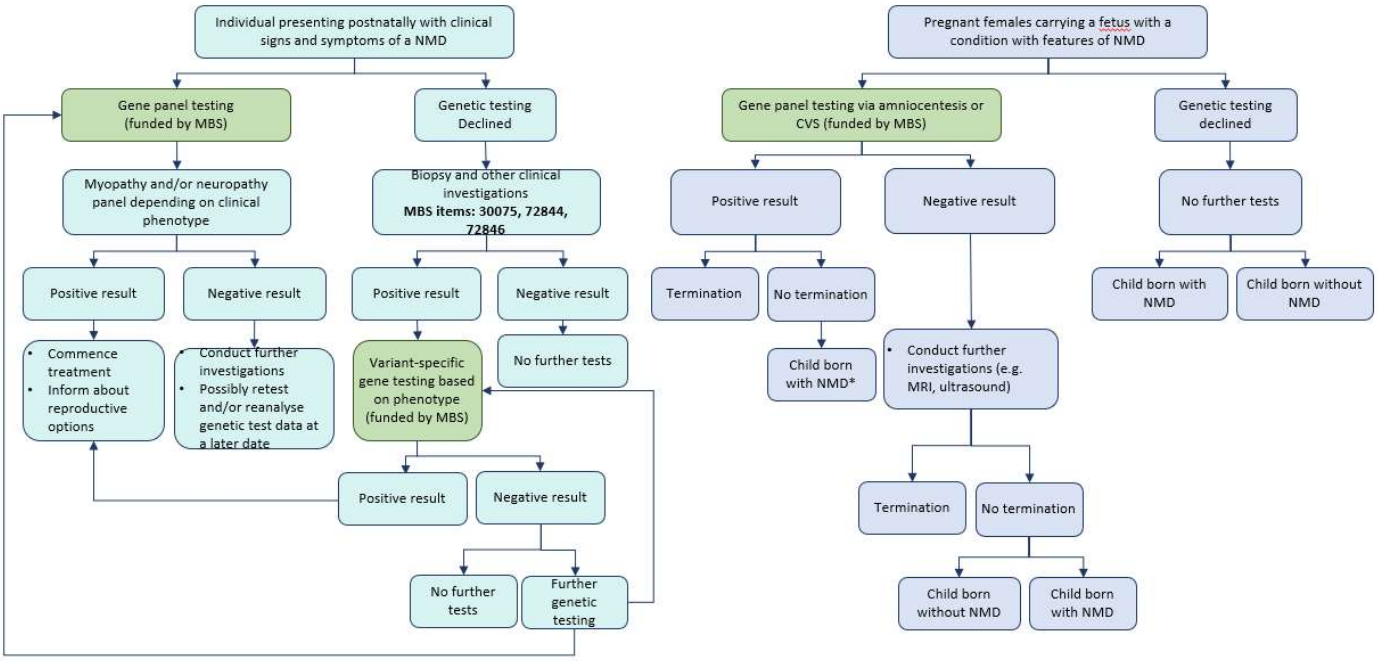
Figure 3: Proposed clinical algorithm – Variant-specific NMD genetic test



*Assuming 100% sensitivity and specificity of the Variant-specific test

Updated based on PASC advice that, 'mutation-specific testing' should be changed to 'variant-specific testing'.

Figure 4: Proposed clinical algorithm – NMD gene panel test (myopathy and/or neuropathy)



*Assuming 100% sensitivity and specificty of the gene panel test

Updated based on PASC advice that, 'mutation-specific testing' should be changed to 'variant-specific testing'.

Proposed economic evaluation

PASC's First Consideration (December 2019)

PASC questioned whether a cost-consequence analysis may be more appropriate than cost-effectiveness. However, PASC noted that cost-consequence analysis would create problems for ESC and MSAC (in terms of judging value propositions). PASC concluded that a cost-consequence analysis could be supplemented with a cost-utility framework. A sentence surrounding the supplementation of a cost utility framework surrounding the cost consequence analysis has been added.

PASC stressed the importance of identifying the tests that would replace current MBS-funded tests, and tests that would be additional, noting this would affect the economics considerably. The applicant advised that the proposed intervention will replace current MBS-funded tests (30075, 72844 and 72846) in some circumstances. The applicant elaborated that there will be some circumstances where both current MBS-funded tests and the proposed interventions will be used. Current MBS-funded tests may also be required if a person declines genetic testing.

PASC noted that targeted gene panel test testing could shorten the diagnostic pathway and reduce utilisation of other tests. This is a clear cost offset (not cost utility) that is within scope of the evaluation, but for which evidentiary demands are not trivial. A paragraph surrounding the possibility of a shortened diagnostic pathway has been added.

The applicant supplied an article by Schofield et al (2017) - "Cost-effectiveness of massively parallel sequencing for diagnosis of paediatric muscle diseases". The applicant advised that this article should be referenced in the PICO, which it has.

PASC acknowledged that obtaining accurate utilisation data will be key for this application, because Australian incidence and prevalence data for NMDs are lacking. PASC noted that the currently accepted method to sample fetal DNA is by CVS or amniocentesis.

PASC noted leakage may be an issue for cascade and pre-natal testing. The applicant advised that, given proposed MBS item descriptors BBBB and CCCC are conditional on positive findings from AAAA or DDDD, there should be minimal leakage (if items BBBB and CCCC are strictly followed in practice).

PASC advised that costs used in the evaluation will need to be closely analysed, noting that patient out-of-pocket costs may be:

- more than the 15% not reimbursed by Medicare (i.e. based on the 85% MBS rebate for non-admitted [out-of-hospital] patients) OR
- more than the Greatest Permissible Gap (GPG) amount. From 1 November 2019, the GPG is set at $84.70, which means that all out-of-hospital Medicare services which have an MBS fee of $565.00 or more will attract a benefit that is greater than 85% of the MBS fee. If, for example, the schedule fee for a service is $1,000, then the 85% benefit would be $850 which means that the gap is $150. In this case, the GPG would apply and the patient would receive a Medicare benefit of $915.30, not $850 (i.e. $1,000 minus the GPG of $84.70). **Source: MBS Online**

PASC's Second Consideration (April 2020)

PASC confirmed that the analysis should be a cost-effectiveness and/or cost-utility analysis.

PASC agreed with the consultation feedback, that 'In children, nerve and muscle biopsies are done under general anaesthesia. This cost should therefore include that of a hospital day-stay admission and general anaesthetic, and has been under-estimated.' This should be considered in the economic evaluation.

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

According to the *Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee: Investigative*, the required economic analysis is therefore a cost-effectiveness and/or cost-utility analysis. This type of analysis will determine the incremental cost per extra unit of health outcome achieved, expressed in quality-adjusted life years (QALYs) because of a reduction in the number of further diagnostic tests, early treatment and fewer number of babies born with NMD. A cost-consequence analysis could be supplemented with the cost-utility framework.

Targeted gene panel test testing could shorten the diagnostic pathway and reduce utilisation of other tests. This is a clear cost offset (not cost utility) that is within scope of the evaluation, but for which evidentiary demands are not trivial.

For the economic evaluation, QALYs should be calculated for each of the endpoint outcomes. If QALYs cannot be calculated, then the measure of effectiveness can be expressed in life years or other outcomes.

An Australian cost-effective analysis study of 56 patients compared the costs involved with traditional NMD diagnostic tests and an NMD gene panel test. The results revealed that the NMD gene panel was more cost effective. Traditional diagnostic tests on average cost AUD$10,491 per patient and AUD$22,596 per successful diagnosis. The NMD gene panel cost $6,683 less than traditional diagnostic tests, per patient. This reduction in the cost per patient was statistically significant at 5% level of significance[22].

Proposed MBS item descriptor/s and MBS fees (if relevant)

PASC's First Consideration (December 2019)

PASC agreed the MBS item descriptors need to be clear about what conditions are being investigated (and how).

PASC agreed that 'requesters' for the test should be specialists, due to the need for genetic counselling. PASC agreed that, if GPs were granted the ability to request the test, it should not be for cascade testing (and only in consultation with a relevant specialist, being a neurologist, paediatrician or clinical geneticist). PASC advised that restrictions on requesting the test need to be clear.

The applicant advised that they agree with PASC that the requester should be a specialist, and that re-wording of proposed item descriptors has been achieved (as presented below).

PASC noted the amendments to MBS item descriptors and fees below, proposed by the Department.

PASC noted that, for item DDDD, the MBS fee appeared to be incorrect in the Draft PICO (i.e. it should be $1,000, not $1,600). The applicant advised that the proposed fee for item DDDD encompasses testing for variant detection **in addition to** testing for maternal cell contamination (which is required in the context of prenatal testing). The applicant advised that the fee **cannot** be the same or lower than that for item AAAA, because item DDDD includes variant detection and maternal cell contamination. The applicant is of the view that, because the original proposed fee of $1,600 is inclusive of both tests, and is below a reasonable fee that includes both tests, it should stand.

The Department is of the view that there is justification for an increased fee for item DDDD (i.e. higher than $1,000) to account for cell contamination, but the ultimate decision will be made by MSAC.

PASC noted that the changes to MBS fees (proposed by the Department prior to PASC's first consideration) reflect fees for current MBS items for genetic testing.

The Department is of the view that an additional MBS item (EEEE) would be appropriate for partner testing (see draft item EEEE below). This could be a generalised item, as per the applicant's feedback since PASC's first consideration. Further discussion is needed on this issue at PASC's second consideration, followed by ESC and MSAC.

Rather than the proposed additional item EEEE, consideration could be given to a 'catch-all' item (for future use), along the following lines:

> Detection of a single identified gene variant requested by a specialist or consultant physician and after appropriate genetic counselling, in a reproductive partner of an individual with a documented and actionable pathogenic germline recessive gene variant identified under MBS items A, B, C … X, Y, Z, etc.

PASC's Second Consideration (April 2020)

PASC noted that the items descriptors were unchanged from the previous consideration and confirmed them.

PASC advised that MSAC will need to consider the rebates for the items (see 'Consultation Feedback').

Four separate MBS items are proposed. Two items for paediatric and adult detection (suspected NMD, and asymptomatic paediatric and adult with a family history of NMD), and a subsequent two items for prenatal detection (suspected NMD, and asymptomatic fetus with a family history of NMD).

Item AAAA	Category 6 (Pathology Services) – Group P7 Genetics
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. **Fee**: $1,200 **Benefit:** 75% = $825 85% = $935	

Item BBBB	Category 6 (Pathology Services) – Group P7 Genetics
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. **Fee:** $400 **Benefit:** 75% = $337.50 85% = $382.50	

Item CCCC	Category 6 (Pathology Services) – Group P7 Genetics
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. **Fee:** $400 **Benefit:** 75% = $750 85% =$ 850	

Item DDDD	Category 6 (Pathology Services) – Group P7 Genetics
Prenatal detection of unknown gene variant(s) 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. **Fee:** $1,000 **Benefit:** 75% = $750 85% =$ 850	

Proposed additional item, following PASC's first consideration (see comments above regarding a generalised item)

Item EEEE	***Category 6 (Pathology Services) – Group P7 Genetics***
Detection of a single identified gene variant requested by a specialist or consultant physician and after appropriate genetic counselling, in a reproductive partner of an individual with a documented and actionable pathogenic germline recessive gene variant for a neuromuscular disorder identified by item number AAAA or DDDD. ***Fee: $450 Benefit: 75% = $337.50 85% = $382.50***	

Practice note:

The laboratory used to undertake gene panel tests for items AAAA and DDDD must use a methodology with sufficient diagnostic range and sensitivity to detect all known pathogenic gene variants of NMD.

The Applicant noted that the revised item numbers as outlined below are erroneous and do not account for the cost of testing for maternal cell contamination in items CCCC and DDDD in addition to testing for the variant (s).

The Applicant proposed the following revised fees for items CCCC and DDDD:

- *Item CCCC: $,1000*
- *Item DDDD: $1,600 (benefit: 75% = $1,2000 and 85% = $1,360)*

Consultation feedback

PASC's First Consideration (December 2019)

PASC noted the consultation feedback.

PASC noted feedback that stated a specific minimum list of genes should be included in the MBS descriptor (or in advisory notes that accompany the MBS descriptor), to ensure laboratories have equivalent tests. The applicant is expected to provide a minimum list of genes.

PASC agreed with feedback that the item descriptor should be agnostic about the panel, in order to future-proof against outdated panels (as new disease genes are identified).

PASC's Second Consideration (April 2020)

PASC noted the consultation feedback and general support of the application.

PASC noted the feedback that proposed rebates for items BBBB and CCCC 'seem a bit high'.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as a DCAR (Department-contracted assessment report).

PASC advised that the clinical utility card (CUC) format is suitable for this application.

References

[1] Analytical validity: the reproducibility and repeatability of the assay, that is, the ability of the test to measure gene expression accurately and reliably.

[2] Clinical validity: measures the test's ability to predict the presence or absence of disease, that is, the sensitivity, specificity, and positive and negative predictive values, in this case

[3] Fattahi, Z., Kalhor, Z. et al (2017). 'Improved diagnostic yield of neuromuscular disorders applying clinical exome sequencing in patients arising from a consanguineous population', *Clin Genet,* 91 (3), 386-402.

[4] Ankala, A., da Silva, C. et al (2015). 'A comprehensive genomic approach for neuromuscular diseases gives a high diagnostic yield', *Ann Neurol,* 77 (2), 206-214.

[5] Dowling, J. J., H, D. G. et al (2018). 'Treating pediatric neuromuscular disorders: The future is now', *Am J Med Genet A,* 176 (4), 804-841.

[6] Darras, B. T., Urion, D. K. & Ghosh, P. S. (2018). *Dystrophinopathies* [Internet]. University of Washington. Retreived 19/09/2019, from: https://www.ncbi.nlm.nih.gov/books/NBK1119/

[7] Laing, N. G. (2012). 'Genetics of neuromuscular disorders', *Crit Rev Clin Lab Sci,* 49 (2), 33-48.

[8] Fattahi, Z., Kalhor, Z. et al (2017). 'Improved diagnostic yield of neuromuscular disorders applying clinical exome sequencing in patients arising from a consanguineous population', *Clin Genet,* 91 (3), 386-402.

[9] Muscular Dystrophy Foundation Australia. (2016). "What is MD?" Retrieved 19/09/2019, from https://mdaustralia.org.au/neuromuscular-condition/what-is-md/.

[10] Centers for Disease Control and Prevention. (2009). Prevalence of Duchenne/Becker muscular dystrophy among males aged 5-24 years—four states, 2007. *MMWR Morbidity and Mortality Weekly Report,* 58, 1119-1122. Retrieved 08/10/2019, from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5840a1.htm

[11] Kurtzke JF: Neuroepidemiology. Ann Neurol 1984;16:265-277

[12] Muscular Dystrophy Foundation Australia. "What is MD?" Retrieved 25/09/2019, from https://mdaustralia.org.au/neuromuscular-condition/what-is-md/

[13] It should be noted that for this calculation we have assumed a 100% detection rate; implying no need for re-testing) Published estimates for the detection rates for disorders such as spinal muscular atrophy (SMA) range from 71% to 95%, although it is also acknowledged that other studies have reported much lower rates of identification for causal genetic variants (some estimates have reported that the causative genes were only identified in 45.2% of cases using next gen sequencing). It is therefore likely that some individuals would require re-testing at a later date, either due to incomplete detection or re-testing when the number of genes tested for is expanded to include additional conditions.

[14] It was assumed that the increase observed from 2017 to 2018 largely relates to improved detection as well as increases in clinical uptake and referral rather than an increase in incidence rates.

[15] The assumption is based on calculations assuming Harvey-Weinberg equilibrium.

[16] Sugarman EA, Nagan N, Zhu H, Akmaev VR, Zhou Z, Rohlfs EM, Flynn K, Hendrickson BC, Scholl T, Sirko-Osadsa DA, Allitto BA. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet. 2012 Jan;20(1):27-32.

[17] Australian Government Department of Health. "MBS Online: Medicare Benefits Schedule." Retrieved 20/09/2019, from http://www9.health.gov.au/mbs/search.cfm.

[18] The Department of Health and Human Services. (2014). "Neuromuscular Disorders." Retrieved 20/09/2019, from https://www.betterhealth.vic.gov.au/health/ConditionsAndTreatments/neuromuscular-disorders.

[19] Tian, X., W.-C. Liang, Y. Feng, J. Wang, V. W. Zhang, C.-H. Chou, H.-D. Huang, C. W. Lam, Y.-Y. Hsu, T.-S. Lin, W.-T. Chen, L.-J. Wong and Y.-J. Jong (2015). "Expanding genotype/phenotype of neuromuscular diseases by comprehensive target capture/NGS." Neurology Genetics 1(2): e14.

[20] Analytical validity: the reproducibility and repeatability of the assay, that is, the ability of the test to measure gene expression accurately and reliably.

[21] Clinical validity: measures the test's ability to predict the presence or absence of disease, that is, the sensitivity, specificity, and positive and negative predictive values, in this case.

[22] Schofield, D., K. Alam, L. Douglas, R. Shrestha, D. G. MacArthur, M. Davis, N. G. Laing, N. F. Clarke, J. Burns, S. T. Cooper, K. N. North, S. A. Sandaradura and G. O'Grady (2017). "Cost-effectiveness of massively parallel sequencing for diagnosis of paediatric muscle diseases." npj Genomic Medicine 2(4).