



**Australian Government**  
**Medical Services Advisory Committee**

## **Public Summary Document**

### ***Supplement to Application No. 1585 – Addition of single gene testing for the diagnosis of heritable neuromuscular conditions***

**Applicant:** Royal College of Pathologists of Australasia

**Date of MSAC consideration:** MSAC Executive Meeting, 27 May 2022

### **1. Purpose of application**

Application 1585 was submitted in 2019 by the Royal College of Pathologists of Australasia (RCPA) to seek reimbursement of an amplicon-specific next generation sequencing (NGS) gene panel for the diagnosis of early-onset or heritable neuromuscular diseases (NMDs). MSAC recommended MBS reimbursement of the proposed gene panel, cascade testing, fetal testing, reproductive partner and re-analysis items at its July 2021 meeting, with the MSAC Executive finalising test fees and financial estimates at its September 2021 meeting, and minor amendments to item descriptors at its December 2021 meeting<sup>1</sup>.

There are a number of conditions with a NMD phenotype that are caused by variants not detectable using NGS methods, and so require standalone tests. The main assessment of Application 1585 did not encompass the relevant single gene tests (SGTs) that would be performed prior to the panel.

Following consultation between the Department and RCPA, in December 2021 the RCPA's neurogenetic experts (based at PathWest) provided a list of fifteen relevant single gene disorders, their respective genetic tests, cost per test and the estimated number of tests per year per condition based on test utilisation data from PathWest. This information forms the basis of the Department Overview for this assessment.

### **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 public funding for single gene testing for neuromuscular diseases, on the basis that the proposed testing is safe, effective and cost-effective, and will provide more effective testing at a net saving to the MBS compared to the muscle/nerve biopsies currently used to diagnose these patients.

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<sup>1</sup> Public Summary Document (PSD) for MSAC Application 1585 ([December 2021](#))

## **Consumer summary**

The Medical Services Advisory Committee (MSAC) previously supported public funding through the Medicare Benefits Schedule (MBS) for gene panel testing to diagnose neuromuscular disorders. However, there are some neuromuscular disorders caused by specific types of genetic variant that the gene panel test cannot detect. The Royal College of Pathologists of Australasia (RCPA) applied to MSAC for public funding through the MBS for single gene tests for fifteen neuromuscular disorders that cannot be detected by the gene panel test.

Neuromuscular disorders affect nerves and/or muscles and how they function. Single tests look for variants in one gene at a time, where the patient has specific signs and symptoms that mean they are likely to have disorder caused by a variant in that gene. Single gene tests 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. Where the variant is inherited in a recessive way, they could also consider testing reproductive partners, and prenatal testing, so that those planning a baby can make informed reproductive decisions.

MSAC recognised the clinical need for this type of genetic testing. Currently, neuromuscular disorders are diagnosed by muscle and/or nerve biopsies, though biopsies do not allow a genetic diagnosis to be made. MSAC considered single gene testing to be safer and more effective than biopsy. MSAC considered that the value for money of this testing was acceptable. MSAC considered that funding single gene testing would reduce biopsy costs to the MBS and would overall save money for the MBS.

### **MSAC's advice to the Commonwealth Minister for Health and Aged Care**

MSAC supported listing single gene testing for neuromuscular disorders on the MBS. MSAC considered the testing to be safe, effective, cost-effective, and with acceptable financial cost.

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

The MSAC Executive noted that SGTs had not been assessed as part of the main assessment of Application 1585, and that this Department Overview provided an assessment of NMD SGTs as a supplement to the main assessment, which focussed on the gene panel but also included cascade, reproductive partner and fetal testing, and re-analysis.

The MSAC Executive noted that currently these patients are tested with muscle or nerve biopsies. The MSAC Executive noted that a limited cost-effectiveness analysis was provided, with cost-effectiveness expressed in terms of cost per genetic diagnosis achieved, in line with the MSAC Executive's March 2021 reforms to the approach for the assessment of gene panel tests, and subsequent relevant assessments. The MSAC Executive considered that SGTs have superior effectiveness compared to biopsy, as biopsy cannot provide a genetic diagnosis. The MSAC Executive noted the cost-effectiveness was provided for diagnostic yields (DYs) ranging from 60% to 95%, given the uncertain but high DY anticipated for these tests based on specific signs and symptoms. The MSAC Executive noted that SGT for affected individuals only had dominant cost-effectiveness at all DYs, and that SGT for affected individuals plus cascade testing had ICERs ranging from \$115 to \$204 per genetic diagnosis achieved, depending on DY. The MSAC Executive noted this range is lower than the \$1,144 per diagnosis for the 1585 gene panel test.

The MSAC Executive noted that the population receiving SGTs does not overlap with those patients who can receive the gene panel upfront, as SGTs are proposed for fifteen NMDs that have relatively constrained phenotypes, in contrast to the gene panel for discriminating between phenotypes that cannot be readily distinguished. The MSAC Executive considered that clinical acumen would therefore be a component of the DY, which it noted was uncertain but estimated

at 60% to 95%. The MSAC Executive noted that where a patient tested negative on a SGT or SGTs, they may then proceed to the panel and test positive to a mimic condition there, so there would be some overlap with the population of patients eligible for the gene panel after first line SGT.

The MSAC Executive noted that the estimated total financial cost of SGTs for the fifteen conditions ranges from \$5.2 million to \$9.9 million over a six-year period, depending on DY (highest estimate and lowest estimate of DY, respectively). In the base case with highest DY, this is comprised of a net cost to the MBS of \$12.9 million over six years, and a cost-offset of biopsy day admission costs of -\$7.7 million over six years. The MSAC Executive considered that the cost-offsets have likely been over-estimated, as some patients would test negative on both SGT and the gene panel, and so will still receive a muscle/nerve biopsy. If the DY is towards the lower end of the estimated range, the proportion of offsets that are unrealised would still be moderate, as there would be an estimated 664 of the 2,076 patients remaining without a genetic diagnosis eligible for biopsy. Nevertheless, the MSAC Executive advised the net financial impact to be acceptable.

The MSAC Executive noted that the items MSAC had previously supported under the main 1585 assessment are scheduled to be listed on the MBS on 1 November 2022, and considered that it was important that the SGT (or SGTs) be conducted prior to the gene panel test, where applicable. The MSAC Executive noted that this would be addressed by the practice note already supported for gene panel testing item (AAAA in the 1585 main assessment):

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.

The MSAC Executive noted the proposed item descriptors grouped together the SGTs for multiple NMDs, and that it had been presented with the option for *DUX4* testing to be provided separately, or alternatively for it to be combined in a single item descriptor with the other NMD SGTs. The MSAC Executive noted the disparity between the fees proposed for the two items, and the RCPA's justification for the increased fee for Southern blotting of *DUX4* compared to *FMR1* (\$202.65, MBS item 73305) based on it being more complex and more time- and labour-consuming. The MSAC Executive noted that *DUX4* Southern blotting is only provided in one lab in Australia at present, and that the providers intend to lodge an MSAC application when the methodology used for this testing advances. The MSAC Executive considered that a combined item would have a significant chance of co-payments being charged to patients for *DUX4* Southern blotting, given the cost to conduct this test is nearly three-fold higher than the other tests. The MSAC Executive also noted that test methods for *DUX4* may change from Southern blotting in the future, and that *DUX4* testing was proposed to have a relatively low number of services per year. On balance, the MSAC Executive advised that *DUX4* Southern blotting should be separated out from the other NMD SGTs, to avoid the risk of patient co-payments.

The MSAC Executive considered that reproductive partner testing is only appropriate where the pathogenic or likely pathogenic variant identified in the proband has a recessive mode of inheritance, and requested that XXXX specify this.

The MSAC Executive noted the RCPA's comment on the public summary document (PSD), that while reproductive partners may carry variants of the type tested by for by the relevant SGT (e.g. triplet repeat expansions), other types of sequence variation (e.g. point variants) may also be relevant. The MSAC Executive considered that for reproductive partner testing items MSAC has recently supported, it had supported a fee commensurate with gene sequencing because its intent was that reproductive partner testing should detect all variants in the relevant gene, to enable patients to make fully informed reproductive decisions. The MSAC Executive considered that in this case, a SGT and gene sequencing would be required to detect all relevant variants in

the reproductive partner. The MSAC Executive noted the RCPA’s recommendation that first-tier testing of reproductive partners eligible under XXXX should use the SGT and second-tier testing should use gene sequencing, and considered this to be reasonable given the higher fee for gene sequencing.

The MSAC Executive considered the financial impact of this proposal to be very low given the estimated number of reproductive partner tests (8-13 tests in the first year, depending on DY – incremental cost to the MBS only \$13,955 in the first year at 95% DY), however was concerned the addition of gene sequencing to reproductive partner testing may not be cost-effective, given the rarity of point variants. The MSAC Executive noted the Department estimated the cost-effectiveness of reproductive partner testing using only SGTs was \$19,600 per carrier couple identified, whereas the cost-effectiveness of the RCPA’s proposal would be an additional \$2,584,615 per additional carrier couple identified, from pragmatic cost-effectiveness analyses of the cost of testing (Table 1).

**Table 1 Assessment of the cost-effectiveness of adding gene sequencing to reproductive partner testing using SGTs. Effectiveness is expressed in terms of cost of testing per carrier couple identified.**

|               | <b>Intervention: reproductive partner testing using SGT and gene sequencing</b> | <b>Comparator: reproductive partner testing using SGT</b> | <b>Increment</b> | <b>ICER</b> |
|---------------|---|---|------------------|-------------|
| Cost          | \$1,568   | \$392   | \$1,176          | \$2,584,615 |
| Effectiveness | 0.020455  | 0.020000  | 0.000455         |             |

ICER = incremental cost-effectiveness ratio; SGT = single gene testing. Reproductive partners were assumed to have the carrier frequency of the general population: as detailed in section 10 for variants detected using SGTs, and for point variants 1:5000 for FA<sup>2</sup> and 1:1600 for SMA<sup>3</sup>.

The MSAC Executive considered that adding gene sequencing would be pragmatic based on the very low financial impact and risk, and that the poor cost-effectiveness was uniquely acceptable in this specific situation, and therefore advised that on balance it supported the RCPA’s proposal to use gene sequencing in addition to SGTs for reproductive partner testing. The MSAC Executive therefore advised it would be appropriate to also make gene sequencing of the relevant gene/s available to reproductive partners of patients in whom a recessive variant has been identified using XXXX. The 1585 reproductive partner testing item EEEE should therefore be expanded (“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, or XXXX where XXXX has not identified a relevant variant in the reproductive partner”), and a practice note be added to XXXX:

Where a recessive variant has been identified using XXXX, reproductive partners should first be tested using XXXX, prior to gene sequencing under EEEE where no relevant variant was detected by XXXX.

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<sup>2</sup> Delatycki MB, Williamson R, Forrest SM (2000). Friedreich ataxia: an overview. *J Med Genet*, **37**:1-8.

<sup>3</sup> Keinath MC, Prior DE, Prior TW. (2021). Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. *Appl Clin Genet*, **14**:11-25.

**Table 2 MSAC’s supported MBS item descriptors**

|   |
|---|
| Category 6 – Pathology Services – Group P7 Genetics   |
| <p>Item XXXX</p> <p>Detection of pathogenic or likely pathogenic gene variants in a patient with suspected neuromuscular disorder (NMD), a relative of a patient with a pathogenic or likely pathogenic germline gene variant confirmed by laboratory findings, or the reproductive partner of a patient with a recessive pathogenic or likely pathogenic germline gene variant confirmed by laboratory findings (requested by specialist or consultant physician):</p> <p>a) in any one of the following genes: <i>DMPK, CNBP, HTT, PABPN1, C9orf72, AR, SMN1, PRNP, MT-ND1, MT-ND4, MT-ND4L, MT-ND6, MT-TK, MT-TL1, MT-ATP6, FXN, ATN1</i>; or</p> <p>b) all five of the following genes: <i>ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7</i></p> <p>Subject to rule 25 – once per gene per lifetime</p> <p><b>Fee:</b> \$392.00      <b>Benefit:</b> 75% = \$310.50      85% = \$333.20</p> |
| Category 6 – Pathology Services – Group P7 Genetics   |
| <p>Item YYYY</p> <p>Detection of pathogenic or likely pathogenic <i>DUX4</i> gene variants in a patient with suspected neuromuscular disorder, or a relative of a patient with a pathogenic or likely pathogenic germline gene variant confirmed by laboratory findings (requested by specialist or consultant physician).</p> <p>Subject to rule 25 – once per gene per lifetime</p> <p><b>Fee:</b> \$1000.00      <b>Benefit:</b> 75% = \$750.00      85% = \$912.10</p>  |

Where applicable the 85% benefit reflects the greatest permissible gap of \$87.90, as of 1 November 2021.

The MSAC Executive noted that the Murdoch Children’s Research Institute (MCRI) is also a key stakeholder in NMD genetic testing, and requested the Department consult with the MCRI on its supported item descriptors.

Given the uncertainty in the DY, the MSAC Executive requested these items be reviewed two years after listing. The MSAC Executive advised that ideally review should be concurrent with review of the items listed for the main 1585 assessment.

The MSAC Executive endorsed publishing the Department Overview assessment, along with its consideration and advice, as a PSD on the MSAC website.

## 4. Background

MSAC previously supported gene panel testing for neuromuscular diseases under the main assessment of Application 1585, along with cascade, reproductive partner and fetal testing, and re-analysis. This Department Overview provided an assessment of NMD SGTs as a supplement to the main assessment.

## 5. Proposal for public funding

The list of conditions and associated SGTs relevant for the diagnosis of the NMDs identified by the applicant are shown in Table 3. Given the heritable nature of each of the conditions in scope, where an individual is identified as being affected by the condition, cascade testing of their relatives is also required to provide information on personal risk, and reproductive partner testing for future pregnancy decision-making. In addition, the diagnosis of a potentially affected fetus where the parents have not had the opportunity, or choose not to, undergo pre-implantation genetic diagnosis is also required to ensure comprehensive test coverage in this population. The fee for each of the fetal test item and gene panel test supported under 1585 are considered the same for testing arising from SGTs for the purposes of this assessment.

**Table 3 Heritable neuromuscular conditions requiring single gene diagnostic testing, proposed test fee and estimated test volume and cost per year**

| Condition   | Gene(s)                                    | Mode of inheritance    | RCPA proposed test fee | WA test volume per year | Estimated national total test number | Test method                  | Estimated total cost of SGT nationally, per test methodology, first year |
|---|--|------------------------|------------------------|-------------------------|--------------------------------------|------------------------------|--|
| Myotonic dystrophy type 1   | <i>DMPK</i>                                | AD                     | \$400                  | 10                      | 96                                   | RT-PCR                       | \$366,364  |
| Myotonic dystrophy type 2   | <i>CNBP</i>                                | AD                     | \$400                  | 4                       | 40                                   |                              |  |
| Huntington disease  | <i>HTT</i>                                 | AD                     | \$400                  | 40                      | 384                                  |                              |  |
| Oculopharyngeal muscular dystrophy  | <i>PABPN1</i>                              | AD                     | \$400                  | 5                       | 48                                   |                              |  |
| Motor Neuron Disease  | <i>C9orf72</i>                             | AD                     | \$400                  | 30                      | 300                                  |                              |  |
| Spinal and bulbar muscular atrophy (SBMA)   | <i>AR</i>                                  | X-linked               | \$200                  | 10                      | 96                                   |                              |  |
| Spinal muscular atrophy   | <i>SMN1</i>                                | AR                     | \$300                  | 15                      | 144                                  | MLPA                         | \$43,193   |
| Facioscapulohumeral dystrophy type 1 (FSHD1)  | <i>DUX4</i>                                | AD                     | \$1000                 | 8                       | 77                                   | Southern blot                | \$76,788   |
| Familial prion disease  | <i>PRNP</i>                                | AD                     | \$300                  | 3                       | 30                                   | Sanger sequencing            | \$85,788   |
| Leber's Hereditary Optic Neuropathy (LHON)  | <i>MT-ND1, MT-ND4, MT-ND4L, MT-ND6</i>     | Maternal mitochondrial | \$600                  | 10                      | 96                                   |                              |  |
| Mitochondrial myopathy encephalopathy, lactic acidosis and stroke (MELAS) or Myoclonic epilepsy associated with ragged red fibres (MERFF) | <i>MT-TK, MT-TL1</i>                       | Maternal mitochondrial | \$300                  | 20                      | 192                                  | Fluorescent PCR/RE digest    | \$71,989   |
| Neuropathy, ataxia and retinitis pigmentosa   | <i>MT-ATP6</i>                             | Maternal mitochondrial | \$300                  | 5                       | 48                                   |                              |  |
| Friedreich's ataxia   | <i>FXN</i>                                 | AR                     | \$300                  | 10                      | 96                                   | Fluorescent + long-range PCR | \$28,795   |
| Spinocerebellar ataxia SCA1, 2, 3, 6, 7 (all five together)   | <i>ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7</i> | AD                     | \$500                  | 40                      | 400                                  | STR PCR                      | \$205,759  |
| Dentatorubral-pallidoluysian atrophy  | <i>ATN1</i>                                | AD                     | \$200                  | 3                       | 29                                   |                              |  |
| <b>Total</b>  |  |                        |                        | <b>213</b>              | <b>2076</b>                          |                              | <b>\$859,479</b><br>(weighted average SGT cost = \$414)                  |

AD = autosomal dominant; AR = autosomal recessive; MLPA = Multiplex ligation-dependent probe amplification; PCR = polymerase chain reaction; RE = restriction enzyme; STR PCR = short tandem repeat polymerase chain reaction

In the correspondence received, the RCPA's experts confirmed that the gene panel would be used in the diagnosis of: childhood onset dystonia, chorea or related movement disorder, early onset or syndromic epilepsy, hereditary neuropathy or pain disorder (not *PMP22*-related), malignant hyperthermia, ataxia telangiectasia, or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. The RCPA's experts also advised that multiplex ligation-dependent probe amplification (MLPA) for *DMD* is no longer required as a standalone test, because there is good copy number variant (CNV) coverage from the NGS panel, so it is no longer used as a first line test prior to the panel. The RCPA's experts advised that testing for spinocerebellar ataxias (SCAs) is not conducted individually but rather as a panel of five genes, however in WA the NGS gene panel is always run first and will only reflex to the SCA panel if there is a specific indication to do so – though the SCA panel remains included in the proposed SGTs as other states may differ in their approach.

The intervention, SGT, is proposed to also include cascade testing of relatives, and reproductive partner and fetal testing.

The draft item descriptors proposed for the MSAC Executive's consideration are provided below (Table 4). The item descriptors encompass affected individual, cascade, and reproductive partner testing; fetal testing is proposed to be provided through amendment to previously supported items.

**Table 4 Proposed MBS item descriptors.** The proposed item descriptors encompass options for both separate testing of *DUX4* (items XXXX and YYYY), or alternatively a single item for all NMD SGTs including *DUX4* Southern blotting (item XXXX2), for which the proposed fee is the weighted average.

|   |
|---|
| Category 6 – Pathology Services – Group P7 Genetics   |
| Item XXXX   |
| Detection of pathogenic or likely pathogenic gene variants in a patient with suspected neuromuscular disorder (NMD), a relative of a patient with a pathogenic or likely pathogenic germline gene variant confirmed by laboratory findings or their reproductive partner (requested by specialist or consultant physician): |
| <ul style="list-style-type: none"> <li>a) in any one of the following genes: <i>DMPK, CNBP, HTT, PABPN1, C9orf72, AR, SMN1, PRNP, MT-ND1, MT-ND4, MT-ND4L, MT-ND6, MT-TK, MT-TL1, MT-ATP6, FXN, ATN1</i>; or</li> <li>b) all five of the following genes: <i>ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7</i></li> </ul>             |
| Subject to rule 25 – once per gene per lifetime   |
| <b>Fee:</b> \$392.00 <b>Benefit:</b> 75% = \$310.50      85% = \$333.20   |
| Category 6 – Pathology Services – Group P7 Genetics   |
| Item YYYY   |
| Detection of pathogenic or likely pathogenic <i>DUX4</i> gene variants in a patient with suspected neuromuscular disorder, or a relative of a patient with a pathogenic or likely pathogenic germline gene variant confirmed by laboratory findings (requested by specialist or consultant physician).                      |
| Subject to rule 25 – once per gene per lifetime   |
| <b>Fee:</b> \$1000.00 <b>Benefit:</b> 75% = \$750.00      85% = \$912.10  |
| Category 6 – Pathology Services – Group P7 Genetics   |
| Item XXXX2  |
| Detection of pathogenic or likely pathogenic gene variants in a patient with suspected neuromuscular disorder (NMD), a relative of a patient with a pathogenic or likely pathogenic germline gene variant confirmed by laboratory findings or their reproductive partner (requested by specialist or consultant physician): |
| <ul style="list-style-type: none"> <li>a) in any one of the following genes: <i>DMPK, CNBP, HTT, PABPN1, C9orf72, AR, SMN1, PRNP, MT-ND1, MT-ND4, MT-ND4L, MT-ND6, MT-TK, MT-TL1, MT-ATP6, FXN, ATN1, DUX4</i>; or</li> <li>b) all five of the following genes: <i>ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7</i></li> </ul>       |
| Subject to rule 25 – once per gene per lifetime   |
| <b>Fee:</b> \$414.00 <b>Benefit:</b> 75% = \$331.20      85% = \$351.90   |

Where applicable the 85% benefit reflects the greatest permissible gap of \$87.90, as of 1 November 2021.

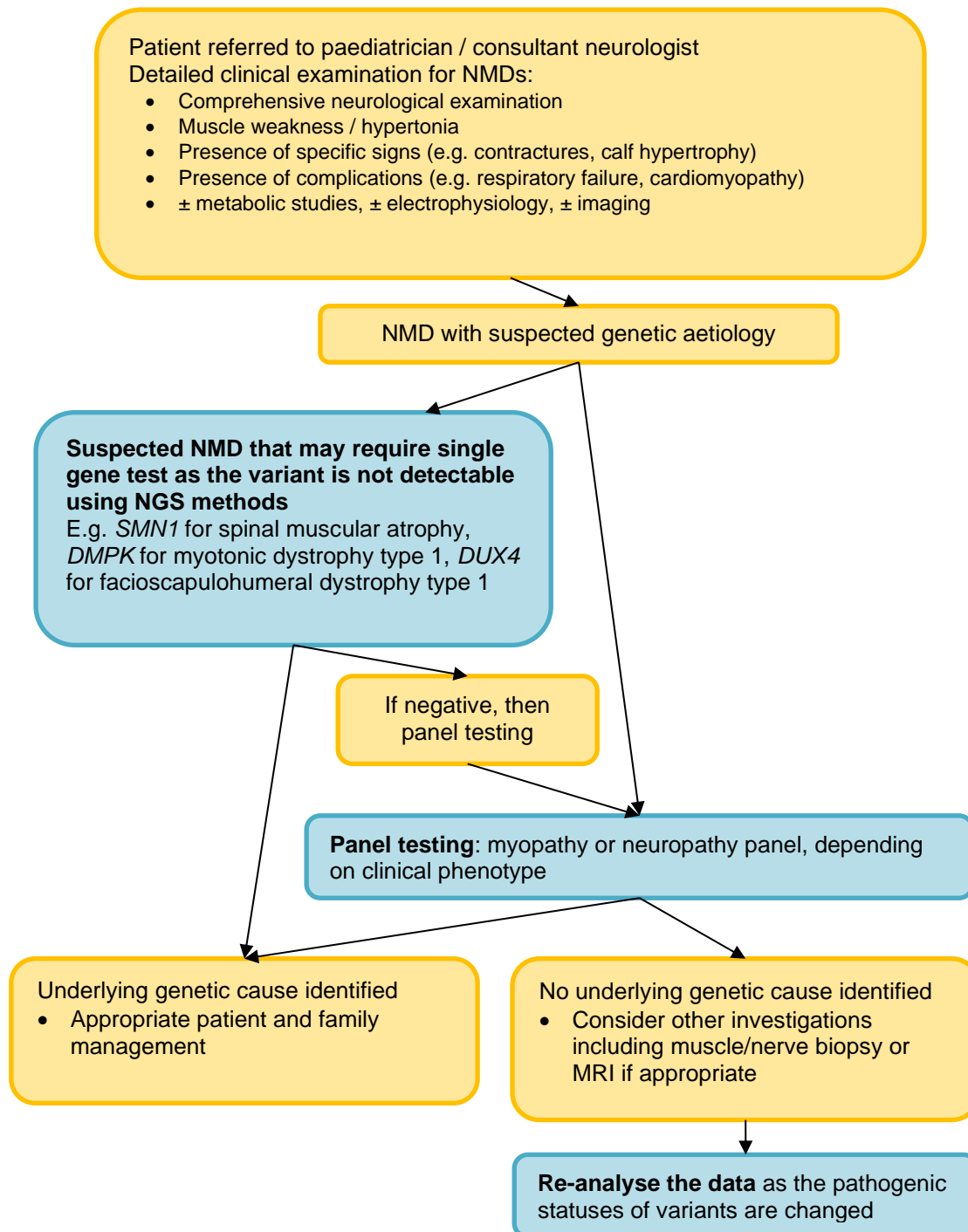
## 6. Population

The neuromuscular conditions encompassed by the gene panel described in the main assessment of MSAC Application 1585 were noted to be heterogeneous in terms of their phenotype, inheritance pattern, clinical management and prognosis. The place of the gene panel in the diagnostic pathway was defined as for use in individuals in whom there is a clinical diagnosis of a neuromuscular condition, but that requires further delineation, or amendment, by genetic diagnosis. Given the indistinct phenotype(s) of many of the conditions, or where the phenotype is relatively clinically defined but has a diverse range of causal genetic variants and inheritance patterns (such as in Charcot-Marie-Tooth) the only method of refining or accurately ascertaining a diagnosis is by genetic testing. As a consequence of making a diagnosis of a heritable NMD, cascade testing, reproductive partner testing and fetal testing items were considered, and all recommended for MBS reimbursement.

However, as was noted in the second assessment of 1585, the NMD gene panel is not proposed to be used in individuals with a clinical phenotype associated with a genetic variant that cannot be detected using NGS methods – this caveat is explicit within MSAC-supported 1585 item AAAA. Given the stated clinical difficulty in ascertaining a comprehensive diagnosis, it is proposed that the individuals who undergo a SGT, but are not assigned a genetic diagnosis, could then proceed to the NMD gene panel. As with the NMD gene panel, the use of the SGT would obviate the need for invasive phenotype tests, such as a nerve or muscle biopsy among those individuals in whom a diagnosis of a heritable NMD is made.

The clinical algorithm for the place of the gene panel in clinical management was described in the main assessment of 1585, shown in Figure 1. This algorithm demonstrates the prior tests (requested by a consultant paediatrician or neurologist) before either SGT or gene panel testing, and the need for individuals with an uninformative SGT to then proceed to the gene panel. For individuals who cannot be assigned a diagnosis of a heritable NMD, they would proceed to a nerve or muscle biopsy and other investigations.





**Figure 1 Clinical management algorithm including gene panel testing for application 1585**

For each of the nominated conditions in this assessment, the gene test for diagnosis of an affected individual will be the same test (and fee) that is required for cascade testing (consistent with MBS item 73294 for *PMP22* testing). The Department notes MSAC has previously explicitly preferred whole gene sequencing for reproductive partner testing (likely using NGS methods), however the test methods utilised in these proposed tests are the same non-NGS method used for affected individual testing of each specified gene, such as MLPA.

Reproductive partner testing of individuals identified with a variant in the *SMN1* gene is also provided under supported MSAC application 1573, however for a separate population of reproductive partners identified via reproductive carrier testing rather affected individual testing. Reproductive partner testing is therefore relevant for partners of individuals with Friedreich's

Ataxia and Spinal Muscular Atrophy, and is proposed to use the same method as for the test for affected individuals.

The fee for testing a potentially affected fetus, irrespective of the condition, is the same as recommended in the main assessment of 1585, at \$1600 for fetal testing for known familial variants (item CCCC).

## 7. Comparator

The comparator is (phenotypic) nerve/muscle biopsy at a cost of \$1378 (full MBS fees and a day admission) for either biopsy type, as calculated in the 1585 main assessment.

## 8. Comparative safety

The use of a diagnostic SGT from blood is considered to have at least non-inferior safety compared to nerve/muscle biopsy.

## 9. Comparative effectiveness

The nominated SGTs are considered to have superior effectiveness to tissue biopsy, as biopsy is incapable of providing a genetic diagnosis. Biopsy is therefore also not able to provide a basis for cascade testing, or testing of reproductive partners and fetuses to enable informed reproductive decision-making.

The overall clinical claim is for superiority of SGT compared to tissue biopsy (with no single gene testing) for each of the fifteen heritable conditions described.

## 10. Economic evaluation

The Department Overview has undertaken a limited cost-effectiveness assessment of the proposed tests, consistent with previous assessments of genetic testing considered by MSAC.

Cost-effectiveness of affected individual testing in terms of cost of testing per genetic diagnosis achieved is provided in Table 5. This analysis assumes all individuals with a non-diagnostic SGT result proceed to gene panel testing, and that the DY of the gene panel is then the same as for the previous assessment, at 20%. The analysis showed SGT in affected individuals is overall cost-saving and more effective than tissue biopsy.

**Table 5 Assessment of the cost-effectiveness of SGT in affected individuals. Effectiveness is expressed in terms of genetic diagnoses achieved.**

| DY of SGT |               | Intervention: SGT available | Comparator: SGT not available | Increment | ICER         |
|-----------|---------------|-----------------------------|-------------------------------|-----------|--------------|
| 95%       | Cost          | \$474                       | \$1,378                       | -\$904    | SGT dominant |
|           | Effectiveness | 0.96                        | 0                             | 0.96      |              |
| 90%       | Cost          | \$534                       | \$1,378                       | -\$844    | SGT dominant |
|           | Effectiveness | 0.92                        | 0                             | 0.92      |              |
| 80%       | Cost          | \$654                       | \$1,378                       | -\$724    | SGT dominant |
|           | Effectiveness | 0.84                        | 0                             | 0.84      |              |
| 70%       | Cost          | \$774                       | \$1,378                       | -\$604    | SGT dominant |
|           | Effectiveness | 0.76                        | 0                             | 0.76      |              |
| 60%       | Cost          | \$894                       | \$1,378                       | -\$484    | SGT dominant |
|           | Effectiveness | 0.68                        | 0                             | 0.68      |              |

DY = diagnostic yield; ICER = incremental cost-effectiveness ratio; SGT = single gene testing.

The cost-effectiveness of including cascade testing in terms of cost of testing per genetic diagnosis achieved is provided in Table 6. The analysis showed SGT in affected individuals and first-degree relatives (FDRs; assumed 3 per proband) ranged in cost-effectiveness from \$126 to \$214 per genetic diagnosis achieved. By comparison, in the assessment of the NMD gene panel, the cost per diagnosis stated is \$1,444. The analysis assumed cascade testing would use the same methodology as the affected individual test. A weighted average DY for cascade testing of 55% was used based on the estimated test numbers provided, assuming diagnostic yield in relatives appropriate to the mode of inheritance, i.e. 50% (AD), 25% (AR), and 100% (mitochondrial). FDRs are assumed to not have biopsies in the absence of SGT.

**Table 6 Assessment of the cost-effectiveness of SGT, in affected individuals and first-degree relatives. Effectiveness is expressed in terms of genetic diagnoses achieved.**

| DY of SGT |               | Intervention: SGT available | Comparator: SGT not available | Increment | ICER  |
|-----------|---------------|-----------------------------|-------------------------------|-----------|-------|
| 95%       | Cost          | \$1,701                     | \$1,378                       | \$323     | \$115 |
|           | Effectiveness | 2.50                        | 0                             | 2.50      |       |
| 90%       | Cost          | \$1,710                     | \$1,378                       | \$332     | \$125 |
|           | Effectiveness | 2.40                        | 0                             | 2.40      |       |
| 80%       | Cost          | \$1,729                     | \$1,378                       | \$351     | \$146 |
|           | Effectiveness | 2.19                        | 0                             | 2.19      |       |
| 70%       | Cost          | \$1,747                     | \$1,378                       | \$369     | \$172 |
|           | Effectiveness | 1.98                        | 0                             | 1.98      |       |
| 60%       | Cost          | \$1,766                     | \$1,378                       | \$388     | \$204 |
|           | Effectiveness | 1.77                        | 0                             | 1.77      |       |

DY = diagnostic yield; ICER = incremental cost-effectiveness ratio; SGT = single gene testing.

The cost-effectiveness of reproductive partner testing in terms of cost of testing per carrier couple identified is provided in Table 7. Reproductive partners were assumed to have the carrier frequency of the general population (1:80 for FA<sup>4</sup>, 1:40 for SMA as per the 1573 economic model).

**Table 7 Assessment of the cost-effectiveness of reproductive partner testing using SGTs. Effectiveness is expressed in terms of cost of testing per carrier couple identified.**

|               | Intervention: reproductive partner testing using SGT | Comparator: No reproductive partner testing | Increment | ICER     |
|---------------|--|---|-----------|----------|
| Cost          | \$392  | \$0   | \$392     | \$19,600 |
| Effectiveness | 0.02   | 0   | 0.02      |          |

ICER = incremental cost-effectiveness ratio; SGT = single gene testing.

## 11. Financial/budgetary impacts

A market share approach has been used to estimate the utilisation and therefore financial implications of listing the proposed SGTs on the MBS, based on the list of conditions, the relevant gene(s), test methodology, test fee and estimated test utilisation (extrapolated from that provided by PathWest) shown in Table 3. The generalised outcome of single gene testing shown in Figure 1 has been used to calculate the costs of first-line single gene testing, and second-line gene panel testing (GPT).

<sup>4</sup> Bidichandani SI & Delatycki MB (2017). GeneReviews: Friedreich Ataxia. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1281/>. 1:80 used as the midpoint of "1:60-1:100".

Australian Bureau of Statistics data were used to extrapolate proportionally from Western Australia testing data to estimate 2,076 tests will be performed annually nationally. Of the total single gene tests in the first year, 77 are estimated to be for FSHD1, and the remainder being for all other nominated conditions. The estimated total annual cost of all the proposed first line SGTs, without any offset costs, is \$736,299 in the first year (at MBS fees of \$1000 for YYYY and \$392 for XXXX).

As with the assessment of the gene panel, there is uncertainty in the expected cumulative diagnostic yield of the SGTs, therefore a range of diagnostic yields have been used to assess the financial impact of single gene testing. However, by comparison with the use of the gene panel, the nominated conditions are expected to have a strong phenotype-to-genotype relationship, given the degree of penetrance of the nominated genes. Thus, the assessment has used higher estimates of DY to inform the financial impact of single gene testing, with the base case of 95% (in contrast to the 20% estimate of DY in the assessment of the gene panel).

The estimated number of services for each of the proposed tests is shown in Table 8 over a six-year time period. The ratio of cascade tests, prenatal diagnostic tests and reproductive partner tests per diagnostic test result is the same as was used in the assessment of the gene panel test – cascade testing was estimated using a ratio of 1:3 diagnoses to cascade tests, consistent with the ratio used in previous MSAC considerations, fetal testing was estimated using 1:0.04 diagnoses to fetal tests, and reproductive partner testing used 5.6% of probands having a reproductive partner tested per year from the gene panel test assessment. Reproductive partner testing has been estimated for patients with recessive variants only, i.e. for Friedreich’s Ataxia and Spinal Muscular Atrophy only.

**Table 8 Estimated service volumes of the proposed tests over a six-year timeframe, base case 95% diagnostic yield from SGT**

| Parameter  |  | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|--|--|--------|--------|--------|--------|--------|--------|
| <b>Estimated use of the proposed health technology</b> |  |        |        |        |        |        |        |
| Affected individuals                                   | Total SGT for affected individuals   | 2076   | 2367   | 2528   | 2548   | 2446   | 2553   |
|  | XXXX (all conditions other than FSHD1)                                     | 1999   | 2279   | 2434   | 2453   | 2355   | 2459   |
|  | YYYY (FSHD1)   | 77     | 88     | 94     | 94     | 91     | 95     |
| Cascade testing  | Total SGT for cascade testing  | 5917   | 6745   | 7204   | 7261   | 6971   | 7277   |
|  | XXXX (all conditions other than FSHD1)                                     | 5697   | 6495   | 6936   | 6992   | 6712   | 7008   |
|  | YYYY (FSHD1)   | 219    | 250    | 267    | 269    | 259    | 270    |
| Reproductive partner testing                           | SGT for reproductive partners - XXXX only (because FA & SMA both use XXXX) | 13     | 15     | 16     | 16     | 15     | 16     |
| <b>Change in use of other health technologies</b>      |  |        |        |        |        |        |        |
| Affected individuals                                   | Gene panel test (1585 AAAA) after SGT negative                             | 104    | 118    | 126    | 127    | 122    | 128    |
|  | Biopsy (where SGT & gene panel both negative)                              | -1993  | -2272  | -2426  | -2446  | -2348  | -2451  |
| Fetal  | Fetal testing (1585 CCCC)  | 79     | 90     | 96     | 97     | 93     | 97     |

FA = Friedreich’s Ataxia; FSHD1 = Facioscapulohumeral dystrophy type 1; GPT = gene panel testing; NMD = neuromuscular disease; SGT = single gene testing; SMA = Spinal Muscular Atrophy. Table incorporates post-MSAC Executive corrections to the analyses.

The total financial costs to the MBS of single gene testing, gene panel testing, cascade testing, reproductive partner testing, fetal testing and offset biopsy costs are shown in Table 9. Costs to the MBS are based on genetic testing being conducted on an outpatient basis (85% benefit, including the greatest permissible gap where applicable), and biopsies on an inpatient basis (75% benefit).

**Table 9 Net financial implications of SGT to the MBS by year, and cumulative total cost, using the base case of 95% diagnostic yield from SGT, and offset from all biopsies avoided**

| Parameter  | Year 1             | Year 2             | Year 3             | Year 4             | Year 5             | Year 6             | Total (yrs 1-6)     |
|--|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|---------------------|
| <b>Estimated cost of the proposed health technology</b>      |                    |                    |                    |                    |                    |                    |                     |
| XXXX (Affected individuals + cascade + reproductive partner) | \$2,568,624        | \$2,928,231        | \$3,127,351        | \$3,152,369        | \$3,026,275        | \$3,159,431        | \$17,962,280        |
| YYYY (Affected individuals + cascade)                        | \$270,392          | \$308,247          | \$329,208          | \$331,841          | \$318,568          | \$332,585          | \$1,890,841         |
| <b>Change in cost of other health technologies</b>           |                    |                    |                    |                    |                    |                    |                     |
| 1585 AAAA  | \$115,436          | \$131,597          | \$140,546          | \$141,670          | \$136,003          | \$141,987          | \$807,239           |
| 1585 CCCC  | \$119,287          | \$135,987          | \$145,234          | \$146,396          | \$140,540          | \$146,724          | \$834,166           |
| Biopsy – MBS items   | -\$1,234,639       | -\$1,407,488       | -\$1,503,197       | -\$1,515,223       | -\$1,454,614       | -\$1,518,617       | -\$8,633,778        |
| <b>Net financial impact to the MBS</b>                       | <b>\$1,839,099</b> | <b>\$2,096,573</b> | <b>\$2,239,140</b> | <b>\$2,257,054</b> | <b>\$2,166,771</b> | <b>\$2,262,109</b> | <b>\$12,860,748</b> |

Table incorporates post-MSAC Executive corrections to the analyses.

In addition to the costs to the MBS, a biopsy also includes a \$522 day admission cost to the insurer or the patient (Table 10), as per the gene panel assessment (1585 PSD Table 7).

**Table 10 Net financial implications of SGT to other health budgets**

|   | Year 1           | Year 2           | Year 3           | Year 4           | Year 5           | Year 6           | Total (yrs 1-6)    |
|---|------------------|------------------|------------------|------------------|------------------|------------------|--------------------|
| <b>Cost to the insurer or patient</b>             |                  |                  |                  |                  |                  |                  |                    |
| Biopsy – day admission                            | -\$1,100,114     | -\$1,254,130     | -\$1,339,411     | -\$1,350,126     | -\$1,296,121     | -\$1,353,150     | -\$7,693,052       |
| Net cost to the MBS                               | \$1,839,099      | \$2,096,573      | \$2,239,140      | \$2,257,054      | \$2,166,771      | \$2,262,109      | \$12,860,748       |
| <b>Net financial impact to all health budgets</b> | <b>\$738,986</b> | <b>\$842,444</b> | <b>\$899,730</b> | <b>\$906,928</b> | <b>\$870,650</b> | <b>\$908,959</b> | <b>\$5,167,696</b> |

Table incorporates post-MSAC Executive corrections to the analyses.

Sensitivity analyses were undertaken to explore the effect of uncertain variables on the net financial impact to the MBS (Table 11), to show the effect of:

- (i) a change in diagnostic yield of single gene testing from 95% to 60%
- (ii) a change in the proportion of individuals who did not have a diagnostic genetic test result that proceeded to a biopsy
- (iii) the RCPA's proposal to add gene sequencing (1585 EEEE) to reproductive partner testing, given the small proportion of cases where sequence variation may also be relevant.

**Table 11 Sensitivity analyses on the net financial cost to the MBS**

|   | Year 1      | Year 2      | Year 3      | Year 4      | Year 5      | Year 6      | Total (yrs 1-6) | Change from base case (%) |
|---|-------------|-------------|-------------|-------------|-------------|-------------|-----------------|---------------------------|
| Base case   | \$1,839,099 | \$2,096,573 | \$2,239,140 | \$2,257,054 | \$2,166,771 | \$2,262,109 | \$12,860,748    | -                         |
| Diagnostic yield of SGT (base case: 95%)                            |             |             |             |             |             |             |                 |                           |
| 90%   | \$1,889,031 | \$2,153,496 | \$2,299,933 | \$2,318,333 | \$2,225,599 | \$2,323,526 | \$13,209,918    | 3%                        |
| 80%   | \$1,988,895 | \$2,267,340 | \$2,421,519 | \$2,440,891 | \$2,343,255 | \$2,446,359 | \$13,908,258    | 8%                        |
| 70%   | \$2,088,758 | \$2,381,184 | \$2,543,105 | \$2,563,449 | \$2,460,911 | \$2,569,192 | \$14,606,599    | 14%                       |
| 60%   | \$2,188,621 | \$2,495,028 | \$2,664,690 | \$2,686,008 | \$2,578,567 | \$2,692,024 | \$15,304,940    | 19%                       |
| Proportion of biopsies offset (base case: 100%)                     |             |             |             |             |             |             |                 |                           |
| 90% of biopsies offset  | \$1,962,563 | \$2,237,322 | \$2,389,460 | \$2,408,576 | \$2,312,233 | \$2,413,971 | \$13,724,125    | 7%                        |
| 75% of biopsies offset  | \$2,147,759 | \$2,448,445 | \$2,614,940 | \$2,635,859 | \$2,530,425 | \$2,641,764 | \$15,019,192    | 17%                       |
| Test(s) used for reproductive partner testing (base case: SGT only) |             |             |             |             |             |             |                 |                           |
| SGT and gene sequencing (RCPA proposal)                             | \$1,853,055 | \$2,112,482 | \$2,256,131 | \$2,274,180 | \$2,183,213 | \$2,279,274 | \$12,958,335    | 0.8%                      |

Table incorporates post-MSAC Executive corrections to the analyses, and addition of the RCPA's post-PSD proposal.

## 12. Other relevant information

Nil.

## 13. 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 progressing this addition to Application 1585 to a successful outcome. Single gene testing in conjunction with gene panel testing, will ensure all NMD patients have equitable access to a test that may provide a definitive diagnosis and end their diagnostic odyssey.

Regarding reproductive partner testing – the same item number is going to be used on the proviso that underlying variation is the same type as that identified in one of the partners previously. For repeat disorders, the majority of cases would be covered. However, there is a small proportion of cases where sequence variation may also be relevant - i.e. CSNB, FXN etc. Disclaimers on test sensitivity would be on the reports for general scenarios. However, if there is a relevant FHx, comprehensive testing may be required i.e. the SGT + sequencing (through the GPT). A practice note is required to refer to the relevant partner testing for panel (sequencing) findings if there is a FHx and sequencing variation would also need to be excluded as a second tier if the SGT is NAD and the familial variation is unknown.

## 14. Further information on MSAC

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