INESSS
LE SAVOIR PREND FORME

JANVIER 2022

ÉTAT DES CONNAISSANCES

Panels des maladies musculaires par séquençage de nouvelle génération

Annexes complémentaires

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

Direction de l'évaluation des médicaments et des technologies à des fins de remboursement

Québec

Le présent document contient les annexes complémentaires au rapport intitulé *Panels multigéniques des maladies musculaires par séquençage de nouvelle génération*. Le contenu de cette publication a été rédigé et édité par l'INESSS.

Ces annexes et le rapport final sont accessibles en ligne dans la section *Publications* de notre site *Web*.

Renseignements
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Responsabilité

L'Institut rend accessibles les principales informations qui ont servi à la préparation du rapport *Panels des maladies musculaires par séquençage de nouvelle génération* aux lecteurs qui désirent plus de détails sur sa démarche scientifique.

Ce document n'a pas fait l'objet d'une révision linguistique. Il ne reflète pas forcément les opinions des autres personnes consultées aux fins du présent dossier.

TABLE DES MATIÈRES

LISTE DES TABLEAUX

ANNEXE A

Méthodologie

La démarche d'évaluation comprend une revue rapide structurée de la documentation scientifique et grise pour le volet clinique et économique, une analyse d'impact budgétaire, ainsi que des consultations auprès d'experts locaux. Les positions et constats de l'INESSS qui sont rapportés sont basés sur l'ensemble des données scientifiques extraites, des positions et lignes directrices émises par les principales sociétés savantes consultées, ainsi que sur les données contextuelles et les savoirs expérientiels recueillies.

Questions d'évaluation

1- Est-il cliniquement pertinent d'utiliser un panel de gènes et une approche par SNG pour effectuer le diagnostic des maladies musculaires?

2- Est-ce que l'approche par SNG pour effectuer le diagnostic des maladies musculaires est efficiente?

3- Quel serait l'impact budgétaire potentiellement associé au rapatriement des analyses moléculaires pour le diagnostic des maladies musculaires comparativement aux envois extérieurs?

4- Quels sont les enjeux cliniques, économiques et organisationnels potentiellement associés à l'utilisation clinique de ce panel multigénique effectué par SNG?

Stratégies de repérage de l'information scientifique et de la littérature grise

Les stratégies de recherche, qui incluent des mots-clés du vocabulaire libre et contrôlé (MeSH), ont été élaborées en collaboration avec un conseiller en information scientifique (Annexe B). Les documents publiés en français ou en anglais à partir de 2010 ont été considérés.

Les bases de données bibliographiques suivantes ont été interrogées : MEDLINE, Embase et EBM Reviews (Cochrane Database of Systematic Reviews, Health Technology Assessment et NHS Economic Evaluation Database).

La recherche d'information a été complétée par la consultation de sites Internet de sociétés savantes, d'organisations professionnelles, réglementaires et gouvernementales d'intérêt (Annexe C). Une recherche manuelle des références des publications consultées a également été effectuée.

Sélection des publications, extraction et synthèse des données publiées

Les devis d'études considérés étaient les rapports d'évaluation des technologies et des modes d'intervention en santé, les guides de bonne pratique et les revues systématiques avec ou sans méta-analyse. Les études ont été sélectionnées par la professionnelle scientifique responsable de l'évaluation en fonction des critères PICOTS (Population, Intervention, Comparateur, Résultat d'intérêt [de l'anglais *Outcome*], Temporalité et Milieu d'intervention [de l'anglais *Setting*]) établis. La sélection des publications (Annexe D) a été effectuée par la professionnelle responsable du rapport.

L'extraction de l'information pertinente, issue des publications sélectionnées, a été réalisée par la professionnelle responsable de l'évaluation, puis vérifiée par un professionnel associé. Les tableaux de synthèse des données extraites se trouvent à l'Annexe E.

Collecte et synthèse des données contextuelles et savoirs expérientiels

Des experts ont été consultés afin de recueillir l'information pertinente à l'évaluation. Lerecrutement a été effectué en collaboration avec les ordres et associations professionnels concernés de façon à représenter les différentes spécialités médicales et milieux de pratique engagés dans la prise en charge des patients concernées. Les données contextuelles et les savoirs expérientiels recueillis auprès des experts sont résumés sous forme de synthèse narrative en exposant les principaux constats dans la section *Considérations d'implantations* (section 7).

Validation et assurance qualité

Une validation du document a été effectuée par la coordination scientifique et la direction responsable de sa production. Une validation du gabarit utilisé et de la transparence des aspects méthodologiques a été réalisée en collaboration avec la Vice-présidence scientifique de l'INESSS par le Bureau – Méthodologie et éthique. Une validation finale du rapport a été effectuée par la Vice-présidence scientifique de l'INESSS. Le document n'a pas fait l'objet d'une lecture externe.

Prévention, déclaration et gestion des conflits d'intérêts et de rôles

Toutes les personnes qui ont collaboré à ces travaux ont déclaré les intérêts personnels qui pouvaient les placer dans une situation propice au développement de conflits d'intérêts, qu'ils soient commerciaux, financiers, relatifs à la carrière, relationnels ou autres. Elles ont également déclaré les différentes activités professionnelles ou les rôles qui pouvaient les placer dans une situation propice au développement de conflits de rôles. Une telle déclaration a été faite sur la base du formulaire standardisé applicable à l'INESSS. Les déclarations remplies ont fait l'objet d'une évaluation par l'INESSS, laquelle a permis de déterminer les modalités de gestion à appliquer selon les situations déclarées. Le cas échéant, les conflits d'intérêts et de rôles déclarés sont divulgués dans les pages liminaires du rapport.

ANNEXE B

Stratégies de recherche documentaire

Volet clinique

MEDLINE (Ovid) Date du repérage : janvier 2021 Limites : 2010- ; anglais, français	
1	exp High-Throughput Nucleotide Sequencing/
2	(deep sequencing* OR ((high-throughput OR high-through-put) ADJ (nucleotide sequence* OR nucleotide sequencing* OR rna sequencing* OR sequence analys* OR sequencing*)) OR ((illumina OR ion proton OR ion torrent) ADJ sequencing*) OR massive parallel sequencing* OR massively-parallel sequencing* OR mps OR next-gen sequence* OR next-gen sequencing* OR next-generation sequence* OR next-generation sequencing* OR ngs).ti,ab
3	1 OR 2
4	exp *Sequence Analysis, DNA/
5	((sequence* OR sequencing*) ADJ3 (dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna)).ti
6	((sequence* OR sequencing*) ADJ3 (analys* OR evaluation* OR technique* OR technolog*)).ti
7	4 OR 5 OR 6
8	exp *Genetic Testing/ OR *Molecular Diagnostic Techniques/
9	((dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna) ADJ3 (analys* OR data* OR diagnos* OR evaluation* OR expression profil* OR screen* OR technique* OR technolog* OR test OR testing OR tests)).ti
10	(((gene* OR multigene OR multi-gene) ADJ panel*) OR panel test*).ti,ab
11	8 OR 9 OR 10
12	3 OR 7 OR 11
13	exp *Muscular Diseases/di,ge OR exp *Neuromuscular Diseases/di,ge
14	(muscle disorder* OR muscular disease* OR muscular distroph* OR myastheni* OR myopath* OR (neuromuscular ADJ (disease* OR disorder*))).ti,ab
15	13 OR 14
16	12 AND 15
17	exp Guideline/ OR exp Guidelines as Topic/ OR Health Planning Guidelines/ OR exp Consensus/ OR exp Consensus Development Conference/ OR exp Critical Pathways/ OR Clinical Conference.pt OR exp Clinical Protocols/ OR (guideline* OR guide line* OR CPG OR CPGs OR guidance OR practical guide* OR consensus OR (clinical ADJ2 (path OR paths OR pathway* OR protocol*)) OR ((critical OR clinical) ADJ2 (path OR paths OR pathway*)) OR committee opinion* OR position statement* OR practice parameter* OR practice pathway* OR practice protocol* OR recommendation*).ti,ab,kw OR (position* OR statement*).ti
18	Meta-Analysis.pt OR Systematic Review/ OR exp Technology Assessment,Biomedical/ OR (meta-analy* OR metaanaly* OR met analy* OR metanaly* OR meta-review* OR metareview* OR meta regression* OR metaregression* OR meta synthesis OR metasynthesis OR overview of review* OR overviews of reviews OR (systematic* ADJ3 (review* OR overview* OR literature OR search* OR research*)) OR ((quantitative OR methodologic* OR integrativ*) ADJ (review* OR overview* OR synthes*)) OR umbrella review* OR HTA OR HTAs OR technology assessment* OR technology overview* OR technology appraisal* OR technology reassessment*).ti,ab,kw
19	17 OR 18
20	16 AND 19
21	(Case Reports OR Comment OR Editorial OR Letter).pt OR (case report* OR comment* OR reply OR replies OR editorial* OR letter*).ti
22	20 NOT 21
23	Animals/ NOT (Humans/ AND Animals/)
24	22 NOT 23

Embase (Ovid) Date du repérage : janvier 2021 Limites : 2010- ; anglais, français	
1	exp High Throughput Sequencing/
2	(deep sequencing* OR ((high-throughput OR high-through-put) ADJ (nucleotide sequence* OR nucleotide sequencing* OR rna sequencing* OR sequence analys* OR sequencing*)) OR ((illumina OR ion proton OR ion torrent) ADJ sequencing*) OR massive parallel sequencing* OR massively-parallel sequencing* OR mps OR next-gen sequence* OR next-gen sequencing* OR next-generation sequence* OR next-generation sequencing* OR ngs).ti,ab
3	1 OR 2
4	*DNA sequencing/ OR *Gene Sequence/
5	((sequence* OR sequencing*) ADJ3 (dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna)).ti
6	((sequence* OR sequencing*) ADJ3 (analys* OR evaluation* OR technique* OR technolog*)).ti
7	4 OR 5 OR 6
8	*Genetic Screening/ OR *Molecular Diagnosis/
9	((dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna) ADJ3 (analys* OR data* OR diagnos* OR evaluation* OR expression profil* OR screen* OR technique* OR technolog* OR test OR testing OR tests)).ti
10	(((gene* OR multigene OR multi-gene) ADJ panel*) OR panel test*).ti,ab
11	8 OR 9 OR 10
12	3 OR 7 OR 11
13	exp *Muscle Disease/di OR exp *Neuromuscular Disease/di
14	(muscle disorder* OR muscular disease* OR muscular distroph* OR myastheni* OR myopath* OR (neuromuscular ADJ (disease* OR disorder*))).ti,ab
15	13 OR 14
16	12 AND 15
17	Clinical Pathway/ OR Clinical Protocol/ OR Consensus/ OR Consensus Development/ OR Health Care Planning/ OR exp Practice Guideline/ OR (guideline* OR guide line* OR CPG OR CPGs OR guidance OR practical guide* OR consensus OR (clinical ADJ2 (path OR paths OR pathway* OR protocol*)) OR ((critical OR clinical) ADJ2 (path OR paths OR pathway*)) OR committee opinion* OR position statement* OR practice parameter* OR practice pathway* OR practice protocol* OR recommendation*).ti,ab,kw OR (position* OR statement*).ti
18	Biomedical Technology Assessment/ OR Meta Analysis/ OR Systematic Review/ OR (meta-analy* OR metaanaly* OR met analy* OR metanaly* OR meta-review* OR metareview* OR meta regression* OR metaregression* OR meta synthesis OR metasynthesis OR overview of review* OR overviews of reviews OR (systematic* ADJ3 (review* OR overview* OR literature OR search* OR research*)) OR ((quantitative OR methodologic* OR integrativ*) ADJ (review* OR overview* OR synthes*)) OR umbrella review* OR HTA OR HTAs OR technology assessment* OR technology overview* OR technology appraisal* OR technology reassessment*).ti,ab,kw
19	17 OR 18
20	16 AND 19
21	Case Report/ OR Editorial/ OR Letter/ OR (case report* OR comment* OR reply OR replies OR editorial* OR letter*).ti
22	20 NOT 21
23	Conference Abstract.pt
24	22 NOT 23
25	Nonhuman/ NOT (Human/ AND Nonhuman/)
26	24 NOT 25

EBM Reviews (Ovid) : Cochrane Database of Systematic Reviews; Health Technology Assessment; NHS Economic Evaluation Database Date du repérage : janvier 2021 Limites : 2010- ; anglais, français	
1	(deep sequencing* OR ((high-throughput OR high-through-put) ADJ (nucleotide sequence* OR nucleotide sequencing* OR rna sequencing* OR sequence analys* OR sequencing*)) OR ((illumina OR ion proton OR ion torrent) ADJ sequencing*) OR massive parallel sequencing* OR massively-parallel sequencing* OR mps OR next-gen sequence* OR next-gen sequencing* OR next-generation sequence* OR next-generation sequencing* OR ngs).ti,ab
2	((sequence* OR sequencing*) ADJ3 (dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna)).ti,ab
3	((sequence* OR sequencing*) ADJ3 (analys* OR evaluation* OR technique* OR technolog*)).ti,ab
4	((dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna) ADJ3 (analys* OR data* OR diagnos* OR evaluation* OR expression profil* OR screen* OR technique* OR technolog* OR test OR testing OR tests)).ti,ab
5	((sequence* OR sequencing*) ADJ3 (analys* OR evaluation* OR technique* OR technolog*)).ti,ab
6	1 OR 2 OR 3 OR 4 OR 5
7	(muscle disorder* OR muscular disease* OR muscular distroph* OR myastheni* OR myopath* OR (neuromuscular ADJ (disease* OR disorder*))).ti,ab
8	6 AND 7

Volet économique

MEDLINE (Ovid) **Date du repérage : mai 2021** **Limites : 2010- ; anglais, français**	
1	exp High-Throughput Nucleotide Sequencing/
2	(deep sequencing* OR ((high-throughput OR high-through-put) ADJ (nucleotide sequence* OR nucleotide sequencing* OR rna sequencing* OR sequence analys* OR sequencing*)) OR ((illumina OR ion proton OR ion torrent) ADJ sequencing*) OR massive parallel sequencing* OR massively-parallel sequencing* OR mps OR next-gen sequence* OR next-gen sequencing* OR next-generation sequence* OR next-generation sequencing* OR ngs).ti,ab
3	1 OR 2
4	exp *Sequence Analysis, DNA/
5	((sequence* OR sequencing*) ADJ3 (dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna)).ti
6	((sequence* OR sequencing*) ADJ3 (analys* OR evaluation* OR technique* OR technolog*)).ti
7	4 OR 5 OR 6
8	exp *Genetic Testing/ OR *Molecular Diagnostic Techniques/
9	((dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna) ADJ3 (analys* OR data* OR diagnos* OR evaluation* OR expression profil* OR screen* OR technique* OR technolog* OR test OR testing OR tests)).ti
10	(((gene* OR multigene OR multi-gene) ADJ panel*) OR panel test*).ti,ab
11	8 OR 9 OR 10
12	3 OR 7 OR 11
13	exp *Muscular Diseases/di,ge OR exp *Neuromuscular Diseases/di,ge
14	(muscle disorder* OR muscular disease* OR muscular distroph* OR myastheni* OR myopath* OR (neuromuscular ADJ (disease* OR disorder*))).ti,ab
15	13 OR 14
16	12 AND 15
17	Budgets/ OR exp "Costs and Cost Analysis"/ OR Decision Trees/ OR ec.fs. OR Economics, Medical/ OR Economics, Phamaceutical/ OR "Fees and Charges"/ OR Financial Management/ OR Financial Support/ OR Markov Chains/ OR exp Models, Statistical/ OR Monte Carlo Method/
18	(afford* OR budget* OR charge OR charges OR cheap* OR ((clinical OR critical OR patient) ADJ1 (path OR paths OR pathway*)) OR copayment* OR co-payment* OR cost* OR (decision ADJ2 (tree* OR analys* OR model*)) OR discount* OR economic* OR (expenditure* NOT energy) OR expens* OR ((federal* OR state* OR public* OR government*) ADJ2 funded) OR fee OR fees OR financ* OR income* OR ((increas* OR improv* OR more) ADJ1 access*) OR marginal analys* OR markov* OR monte carlo OR payment* OR pharmacoeconomic* OR price* OR pricing* OR reimburs* OR save money OR saves OR saving money OR savings OR sensitivity analys* OR (statistic* ADJ2 model*) OR (valu* ADJ2 money) OR "willingness to pay").tw,hw,sh
19	17 OR 18
20	16 AND 19
21	(Case Reports OR Comment OR Editorial OR Letter).pt OR (case report* OR comment* OR reply OR replies OR editorial* OR letter*).ti
22	20 NOT 21

Embase (Ovid) Date du repérage : mai 2021 Limites : 2010- ; anglais, français	
1	exp High Throughput Sequencing/
2	(deep sequencing* OR ((high-throughput OR high-through-put) ADJ (nucleotide sequence* OR nucleotide sequencing* OR rna sequencing* OR sequence analys* OR sequencing*)) OR ((illumina OR ion proton OR ion torrent) ADJ sequencing*) OR massive parallel sequencing* OR massively-parallel sequencing* OR mps OR next-gen sequence* OR next-gen sequencing* OR next-generation sequence* OR next-generation sequencing* OR ngs).ti,ab
3	1 OR 2
4	*DNA sequencing/ OR *Gene Sequence/
5	((sequence* OR sequencing*) ADJ3 (dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna)).ti
6	((sequence* OR sequencing*) ADJ3 (analys* OR evaluation* OR technique* OR technolog*)).ti
7	4 OR 5 OR 6
8	*Genetic Screening/ OR *Molecular Diagnosis/
9	((dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna) ADJ3 (analys* OR data* OR diagnos* OR evaluation* OR expression profil* OR screen* OR technique* OR technolog* OR test OR testing OR tests)).ti
10	(((gene* OR multigene OR multi-gene) ADJ panel*) OR panel test*).ti,ab
11	8 OR 9 OR 10
12	3 OR 7 OR 11
13	exp *Muscle Disease/di OR exp *Neuromuscular Disease/di
14	(muscle disorder* OR muscular disease* OR muscular distroph* OR myastheni* OR myopath* OR (neuromuscular ADJ (disease* OR disorder*))).ti,ab
15	13 OR 14
16	12 AND 15
17	exp Cost/ OR exp Decision Support System/ OR Economics/ OR exp Economic Aspect/ OR exp Economic Evaluation/ OR Economics, Medical/ OR Economics, Pharmaceutical/ OR exp Health Care Cost/ OR exp Health Economics/ OR exp Quality of Life/ OR exp Statistical Model/
18	(afford* OR budget* OR charge OR charges OR cheap* OR ((clinical OR critical OR patient) ADJ1 (path OR paths OR pathway*)) OR copayment* OR co-payment* OR cost* OR (decision ADJ2 (tree* OR analys* OR model*)) OR discount* OR economic* OR (expenditure* NOT energy) OR expens* OR ((federal* OR state* OR public* OR government*) ADJ2 funded) OR fee OR fees OR financ* OR income* OR ((increas* OR improv* OR more) ADJ1 access*) OR marginal analys* OR markov* OR monte carlo OR payment* OR pharmacoeconomic* OR price* OR pricing* OR reimburs* OR save money OR saves OR saving money OR savings OR sensitivity analys* OR (statistic* ADJ2 model*) OR (valu* ADJ2 money) OR "willingness to pay").tw,hw,sh
19	17 OR 18
20	16 AND 19
21	Case Report/ OR Editorial/ OR Letter/ OR (case report* OR comment* OR reply OR replies OR editorial* OR letter*).ti
22	20 NOT 21
23	Conference Abstract.pt
24	22 NOT 23

EBM Reviews (Ovid) : Cochrane Database of Systematic Reviews; Health Technology Assessment; NHS Economic Evaluation Database Date du repérage : mai 2021 Limites : 2010- ; anglais, français	
1	(deep sequencing* OR ((high-throughput OR high-through-put) ADJ (nucleotide sequence* OR nucleotide sequencing* OR rna sequencing* OR sequence analys* OR sequencing*)) OR ((illumina OR ion proton OR ion torrent) ADJ sequencing*) OR massive parallel sequencing* OR massively-parallel sequencing* OR mps OR next-gen sequence* OR next-gen sequencing* OR next-generation sequence* OR next-generation sequencing* OR ngs).ti,ab
2	((sequence* OR sequencing*) ADJ3 (dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna)).ti,ab
3	((sequence* OR sequencing*) ADJ3 (analys* OR evaluation* OR technique* OR technolog*)).ti,ab
4	((dna OR exome* OR gene* OR genetic* OR genome* OR genomic OR genotype* OR molecular OR multigene OR multi-gene OR multigenic OR multi-genic OR rna) ADJ3 (analys* OR data* OR diagnos* OR evaluation* OR expression profil* OR screen* OR technique* OR technolog* OR test OR testing OR tests)).ti,ab
5	((sequence* OR sequencing*) ADJ3 (analys* OR evaluation* OR technique* OR technolog*)).ti,ab
6	1 OR 2 OR 3 OR 4 OR 5
7	(muscle disorder* OR muscular disease* OR muscular distroph* OR myastheni* OR myopath* OR (neuromuscular ADJ (disease* OR disorder*))).ti,ab
8	6 AND 7
9	(afford* OR budget* OR charge OR charges OR cheap* OR ((clinical OR critical OR patient) ADJ1 (path OR paths OR pathway*)) OR copayment* OR co-payment* OR cost* OR (decision ADJ2 (tree* OR analys* OR model*)) OR discount* OR economic* OR (expenditure* NOT energy) OR expens* OR ((federal* OR state* OR public* OR government*) ADJ2 funded) OR fee OR fees OR financ* OR income* OR ((increas* OR improv* OR more) ADJ1 access*) OR marginal analys* OR markov* OR monte carlo OR payment* OR pharmacoeconomic* OR price* OR pricing* OR reimburs* OR save money OR saves OR saving money OR savings OR sensitivity analys* OR (statistic* ADJ2 model*) OR (valu* ADJ2 money) OR "willingness to pay").ti,ab,kw,sh
10	8 AND 9

ANNEXE C

Recherche de la littérature grise

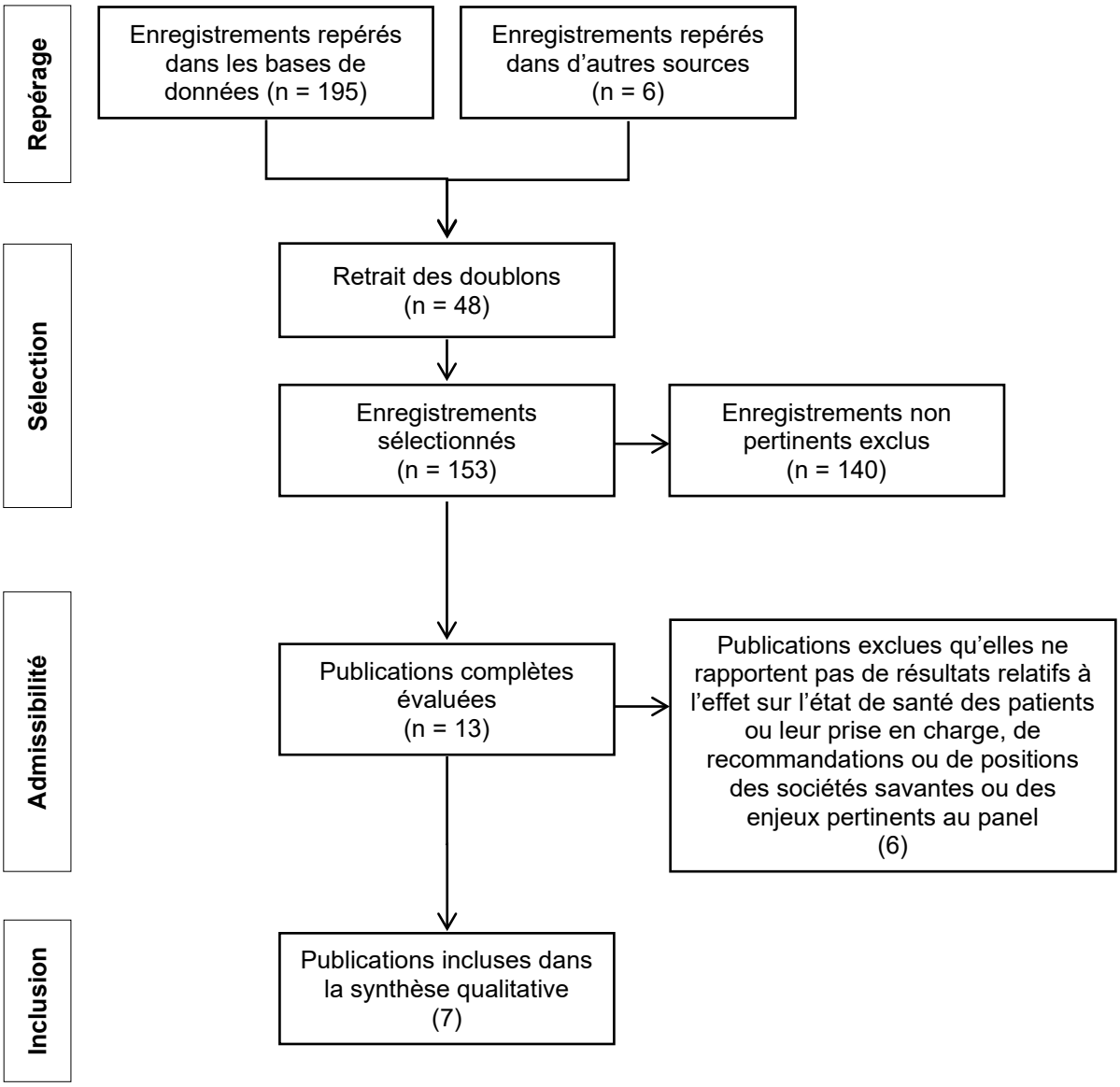
Liste de contrôle pour la recherche de la littérature grise **Sujet : Panels multigéniques des maladies musculaires** **Date : Recherches effectuées entre le 9 et le 22 décembre 2020**
Évaluation des technologies de santé – Guides de pratique
INESSS (Institut national d'excellence en santé et en services sociaux) www.inesss.qc.ca
INSPQ (Institut national de santé publique du Québec) www.inspq.qc.ca
ACMTS/CADTH (Canadian Agency for Drugs and Technologies in Health) www.cadth.ca
EMA (European Medicines Agency) www.ema.europa.eu
HAS (Haute Autorité de Santé, France) www.has-sante.fr
NICE (National Institute for Health and Care Excellence) www.nice.org.uk
EUnetHTA (European network for Health Technology Assessment) www.eunethta.eu
INAHTA (International Network of Agencies for Health Technology Assessment-Alberta) www.inahta.org
HTAi (Health Technology Assessment international-Alberta) www.htai.org
GIN (Guidelines International Network) www.g-i-n.net **et** https://guidelines.ebmportal.com/
SIGN (Scottish Intercollegiate Guidelines Network) www.sign.ac.uk
AHRQ (Agency for Healthcare Research and Quality) www.ahrq.gov
NHS (National Health Service) www.nhs.uk/pages/home.aspx
Infobanque AMC (Association médicale canadienne) www.cma.ca
MSAC (Medical Services Advisory Committee) www.msac.gov.au
CMQ (Collège des médecins du Québec) www.cmq.org
CRD (Centre for Reviews and Dissemination) www.york.ac.uk/crd/
CMS (Centers for Medicare & Medicaid Services) www.cms.gov
CFHI (Canadian Foundation for Healthcare Improvement) www.cfhi-fcass.ca
HQO (Health Quality Ontario) https://www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment
AHS (Alberta Health Services) www.albertahealthservices.ca
HTA Unit (Health Technology Assessment Unit - University of Calgary) http://vortal.htai.org
NIHR HTA programme (National Institute for Health Research, Health Technology Assessment programme) www.nihr.ac.uk
OAML (Ontario Association of Medical Laboratories) www.oaml.com
SBU (Swedish Agency for Health Technology assessment and assessment of social services) https://www.sbu.se/en/method/history-of-hta-in-sweden
NIPH (Norwegian Institute of Public Health) https://www.fhi.no/en
ZiN (Zorginstituut Nederland) https://english.zorginstituutnederland.nl
ICES (Institute for Clinical Evaluative Sciences, Canada) https://www.ices.on.ca/Publications
AIHTA (Austrian Institute for Health Technology Assessment, Autriche) https://aihta.at/page/homepage/en
KCE (Centre fédéral d'expertise des soins de santé, Belgique) https://kce.fgov.be/fr
CEDIT (Comité d'Évaluation et de Diffusion des Innovations Technologiques, France) http://cedit.aphp.fr
FIMEA (Finnish Medicines Agency) https://www.fimea.fi/web/en/frontpage
AVALIA-T (Galician Agency for Health Technology Assessment, Espagne) https://avalia-t.sergas.gal/Paxinas/web.aspx
HIQA (Health Information and Quality Authority, Irlande) https://www.hiqa.ie
HTRG (Health Technology Reference Group, Australie) https://www.coaghealthcouncil.gov.au/Health-Chief-Executives-Forum/Health-Technology-Reference-Group

Liste de contrôle pour la recherche de la littérature grise **Sujet : Panels multigéniques des maladies musculaires** **Date : Recherches effectuées entre le 9 et le 22 décembre 2020**
Évaluation des technologies de santé – Guides de pratique
HIS (Healthcare Improvement Scotland, Royaume-Uni) http://www.healthcareimprovementscotland.org
IQWiG (Institute for Quality and Efficiency in Health Care, Allemagne) https://www.iqwig.de/en/home.2724.html
Génétique
ACGS (Association for Clinical Genetic Science) www.acgs.uk.com
ACMG (American College of Medical Genetics and Genomics) www.acmg.net
CCMG (Canadian College of Medical Geneticists) www.ccmg-ccgm.org
Pathologie
CAP (College of American Pathologists) www.cap.org
AMP (Association for Molecular Pathology) www.amp.org

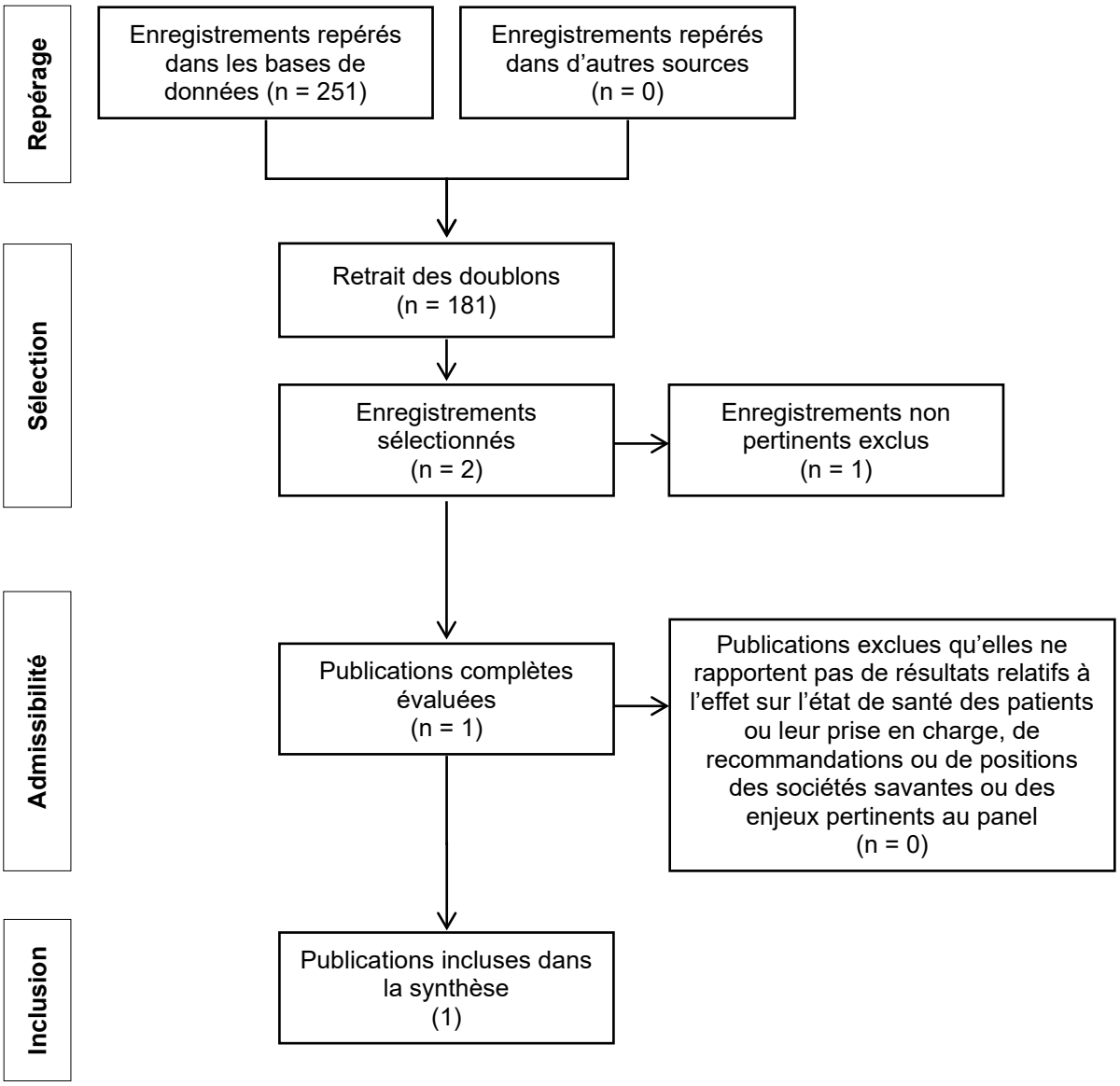
ANNEXE D

Diagrammes de flux de la sélection des publications

Volet clinique



Volet économique



ANNEXE E

Données extraites des publications sélectionnées – Volet clinique

Tableau E-1 Données extraites des documents publiés par des agences règlementaires, des autorités de santé et autres sociétés savantes

ORGANISATIONS, [AUTEUR, ANNÉE] HYPERLIEN	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
Medical Services Advisory Committee – Australian Government, Department of Health MSAC, 2021 Rapport d'ÉTS en cours (3 documents) http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1585-public	***Application 1585 - Genetic testing for the diagnosis of early-onset or familial neuromuscular disorders*** (Updated 14 May 2021) Évaluation en cours : Le MSAC se penche actuellement sur l'évaluation du test génétique pour le diagnostic des maladies neuromusculaires familiales ou d'apparition hâtive. Diagnostic genetic testing of affected individuals: Gene panel testing to identify pathogenic variants for inherited neuromuscular disorders, in patients where clinical criteria or a family history indicate genetic testing is warranted. The genes listed below may be considered "core genes" (currently tested in some Australian laboratories), that capture at least 90% of pathogenic variation. However, to increase the rate of capture, other genes may be added to these panels, depending on the patient and the laboratory conducting the test. Similarly, fewer genes on the panel would result in a reduced capture rate. Predictive genetic testing of family members: Detection of a clinically actionable pathogenic mutation, previously identified in a first-degree relative. Mutation-specific genetic testing is recommended for family members and appropriate relatives, following identification of causative mutation in an index case. Prenatal genetic testing: Prenatal genetic testing for a previously clarified familial neuromuscular disorder should be offered for any future pregnancies, after appropriate counselling. Muscular panel: ACADVL, ACTA1, ANO5, B3GALNT2, BICD2, CACNA1S, CAPN3, CAV3, CHRND, CHRNE, CHRNG, CLCN1, COL12A1,COL6A1, COL6A2, COL6A3, CPT2, DES, DMD, DNAJB6, DNM2, DOK7, DYNC1H1, DYSF, EMD, FKRP, FLNC, GAA, GMPPB,GNE, LAMA2, LMNA, LMNA, LPIN1, MAGEL2, MTM1, MYH2, MYH3, MYH7, MYOT, NALCN, NEB, PIEZO2, POLG,POMGNT1, POMT1, POMT2, PYGM, RAPSN, RRM2B, RYR1, SCN4A, SEPN1, SGCA, SGCB, SMCHD1, TNNI2, TPM2,TRIM32, TRPV4, TTN, VCP, ZC4H2 Neuropathy panel: AARS, ABCD1, ANO10, ARSA, ATL1, ATM, ATP1A3, BSCL2, CACNA1A, CACNA1G, CYP7B1, DCX,EIF2B5, FGF14, FIG4, GBA2, GCH1, GDAP1, GFAP, GJB1, HSPB1, IGHMBP2, KCNA1, KIF1A, KIF5A, LITAF, MFN2, MPZ,NIPA1, NOTCH3, PAFAH1B1, PLP1, PMP22, PRKCG, PRRT2, PRX, REEP1, REEP2, RYR1, SACS, SGCE, SH3TC2,SLC52A2, SOD1, SPAST, SPG11, SPG7, SPTLC2, TARDBP, THAP1, TOR1A, TRPV4, TTR, TUBB3, TUBB4A, WNK1

ORGANISATIONS, [AUTEUR, ANNÉE] HYPERLIEN	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
European Molecular Genetics Quality Network (EMGQN) Fratter *et al.*, 2020 Lignes directrices https://www.nature.com/articles/s41431-020-0643-7	***EMQN best practice guidelines for genetic testing in dystrophinopathies*** (18 May 2020) Résumé: These guidelines summarise current recommended technologies and methodologies for analysis of the DMD gene, including testing for deletions and duplications of one or more exons, small variant detection and RNA analysis. Genetic testing strategies for diagnosis, carrier testing and prenatal diagnosis (including non-invasive prenatal diagnosis) are then outlined. Guidelines for sequence variant annotation and interpretation are provided, followed by recommendations for reporting results of all categories of testing. Finally, atypical findings (such as non-contiguous deletions and dual DMD variants), implications for personalised medicine and clinical trials and incidental findings (identification of DMD gene variants in patients where a clinical diagnosis of dystrophinopathy has not been considered or suspected) are discussed. *Informations générales:* ▪ Dystrophinopathies are X-linked genetic diseases due to dystrophin (DMD, OMIM *300377, HGNC ID: 2928) gene variants. ▪ In all dystrophinopathy phenotypes, males have a hemizygous (or rarely mosaic) pathogenic DMD variant. Heterozygous females can be asymptomatic carriers, although in some cases they present symptoms ranging from adult-onset mild muscle weakness and/or dilated cardiomyopathy to rare instances of a DMD- or BMD-like phenotype. ▪ DMD is the largest human gene in terms of genomic length, spanning 2.2 Mb. *NGS:* ▪ Next generation sequencing (NGS) approaches are now routinely adopted to accurately detect single nucleotide variants (SNVs) (see below) and have emerged as a technology with the capability to detect accurately both SNVs and CNVs in a single assay. H.owever, CNV analysis via NGS is not yet routinely adopted in diagnostics. ▪ Both short read and long read whole-genome sequencing are beginning to be implemented by diagnostic laboratories and may prove to be the preferred methods for sensitive and specific detection of both CNVs and SNVs. ▪ Sanger sequencing is highly accurate but of course highly time consuming, therefore the new NGS approaches have led to a rapid change in sequencing strategies. ▪ NGS offers numerous technical advantages (improved cost-effectiveness, scalability, resolution) and can enhance the detection of low-level somatic mosaicism in patients or probands' mothers as compared to Sanger sequencing. ▪ However, while NGS has become more widely used to screen for unknown variants, Sanger sequencing remains the standard method used for known familial variant testing, validation of variants identified by NGS and prenatal diagnosis. ▪ Published guidelines on reporting of incidental findings from NGS panels, exome or genome sequencing should be referred to when considering reporting DMD variants identified by these methods. Genetic testing strategy: ▪ Molecular testing is usually now requested prior to a muscle biopsy, given the high frequency of deletions/duplications of one or more exons and new high-throughput NGS methods for DMD gene sequencing, but in some centres or in some cases a muscle biopsy may still be needed before any genetic testing is carried out. ▪ Genetic confirmation of a dystrophinopathy is achieved by demonstrating the presence of a clearly pathogenic variant in the DMD gene.

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	Enjeux : ▪ From the patients' and relatives' perspectives, the speed with which a diagnosis can be made is extremely important to minimise anxiety and to reduce the risk of recurrence of the disease in the family, as well as for variant-specific (personalised medicine) approved treatments and enrolment in clinical trials. Therefore, the above workflow should always be carried out in a timely manner. *Prenatal diagnosis, NIPD and PGT :* ▪ Invasive prenatal genetic testing for dystrophinopathies is preferentially performed on tissue (placental biopsy) from chorionic villus sampling (CVS) in early gestation (11–12 weeks). High DNA quality and yield is typically obtained from CVS, allowing a wide variety of possible testing methods (including NGS). ▪ High DNA quality and yield is typically obtained from CVS, allowing a wide variety of possible testing methods (including NGS); therefore, results can be obtained and reported rapidly (normally by 2–12 days from sampling). ▪ Testing of CVS or amniocentesis is carried out by standard procedures. ▪ It is important to confirm foetal sex by testing the CVS or amniocentesis material regardless of whether noninvasive foetal sexing was previously carried out. *Variant annotation and interpretation :* ▪ Fully characterised sequence variants should be described in accordance with the Human Genome Variation Society (HGVS) recommendations for description of sequence variants. ▪ Although HGVS variant description recommendations do not refer to the numbering of gene exons, as a variant should never formally be described in the context of exon or intron numbers, it is recommended that all whole-exon deletions/duplications be described with reference to specific exons (e.g. deletion of exons 2–6) in patient reports. ▪ Whole-exon deletions or duplications detected in patients with suspected dystrophinopathy can be considered pathogenic in the vast majority of cases. *Reporting results:* ▪ Reporting genome/gene variants is the crucial final step of genetic diagnosis, and the report represents a lifelong durable document for the patient and his/her relatives, that rarely needs to be revised or updated. The report should be comprehensible on its own, written in clear (though specific) language and provide a fully interpretative and authoritative answer to the clinical question, thus containing all necessary information for the reader. ▪ When reporting genetic testing of the DMD gene, an appropriate reference sequence accession number (including version where applicable) must be included (refer to variant annotation section above). ▪ If an NGS method is used, any exons/regions not covered should be outlined and the alternative/additional methods used (e.g. Sanger sequencing) to sequence the uncovered exons should be indicated.

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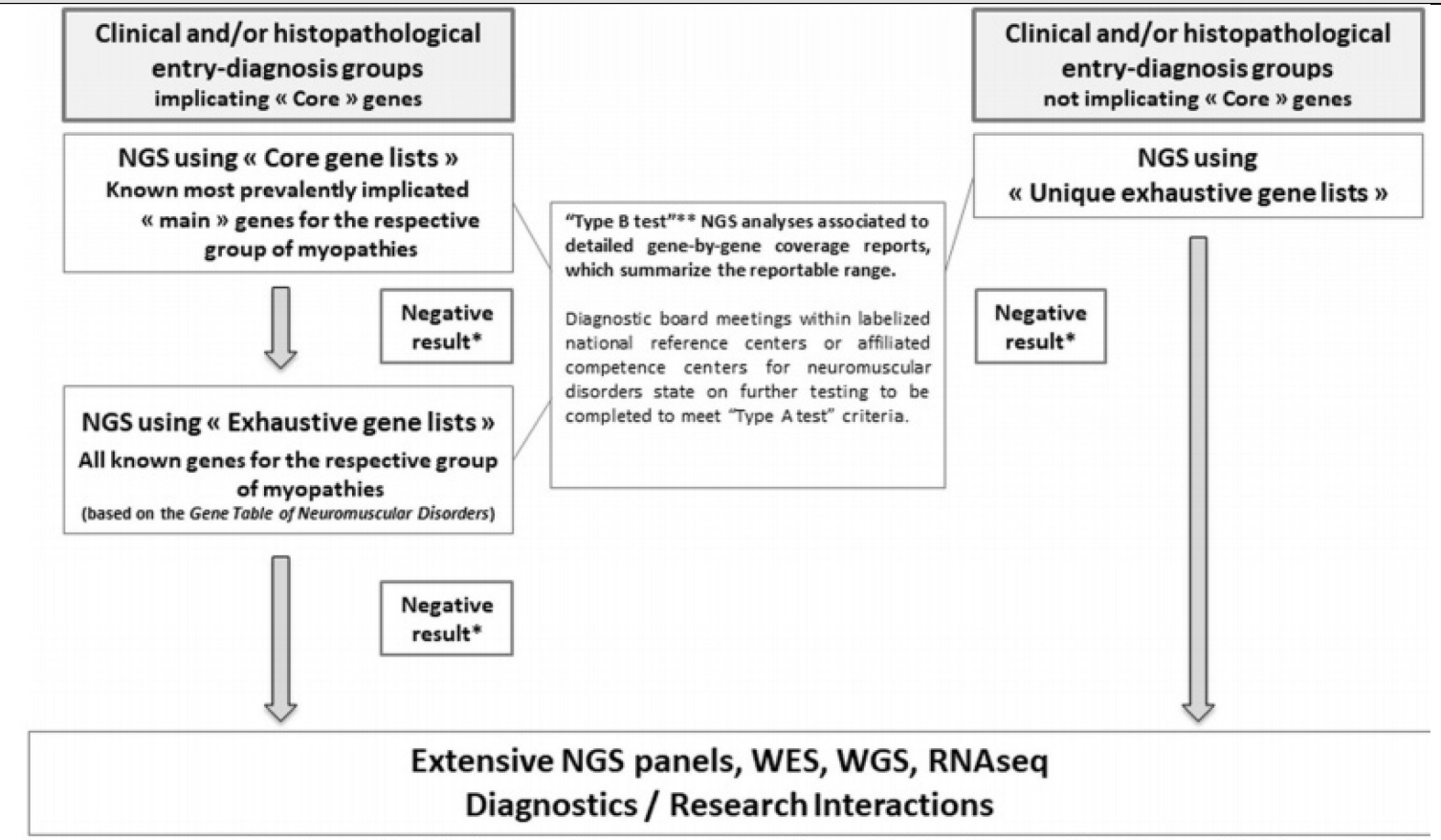
Filière Nationale des Maladies Rares Neuromusculaires (FILNEMUS) – France Krahn *et al.*, 2019 Consensus d'experts https://pubmed.ncbi.nlm.nih.gov/30552423/	***A National French consensus on gene lists for the diagnosis of myopathies using next-generation sequencing*** (Mars 2018) Filière Nationale des Maladies Rares Neuromusculaires (FILNEMUS) Abstract : Next-generation sequencing (NGS) gene-panel-based analyses constitute diagnosis strategies which are adapted to the genetic heterogeneity within the field of myopathies, including more than 200 implicated genes to date. Nonetheless, important interlaboratory diversity of gene panels exists at national and international levels, complicating the exchange of data and the visibility of the diagnostic offers available for referring neurologists. To address this issue, we here describe the initiative of the genetic diagnosis section of the French National Network for Rare Neuromuscular Diseases (Filière Nationale des Maladies Rares Neuromusculaires, FILNEMUS), which led to set up a consensual nationwide diagnostic strategy among the nine French genetic diagnosis laboratories using NGS for myopathies. The strategy is based on the determination of 13 clinical and/or histological entry-diagnosis groups, and consists for each group either in a successive NGS analysis of a "core gene list" followed in case of a negative result by the analysis of an "exhaustive gene list", or in the NGS analysis of a "unique exhaustive gene list". As for other monogenic diseases, the implementation of next generation sequencing (NGS) for diagnostic purposes allowed for an unprecedented increase in mutational screening capacities in the field of myopathies, through the simultaneous analysis of lists of genes (gene panels) related to specific disease groups. Such gene panels can be either physical enrichment panels (for example using sequence capture) or be used as in silico lists for filtering applied to whole-exome or whole-genome sequencing data. Consensual key points as the foundation for the nationwide standardization : ▪ giving a central importance to the clinical entry diagnosis; ▪ maintaining the existing nationwide distribution of expertise for specific groups of myopathies, ▪ while allowing for progressive extension of local expertise towards novel domains to favor local joint clinical-genetic board conclusions; ▪ taking into account the existing NGS platform capacities of the participating laboratories; ▪ and developing an efficient analysis turn-over time. The accurate initial determination of the patient's entry-diagnosis group is a key point in this strategy, to optimize genetic screening of the most relevant genes.

ORGANISATIONS, [AUTEUR, ANNÉE] HYPERLIEN	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT



« Core » genes: term used here for genes for which disease-causing sequence variants are frequently implicated in the considered phenotype/clinical entry-diagnosis group. Of note, several « Core » genes have not been included in one of the different « Core gene lists » (whose objective is a rapid first-instance screening), due to the complexity of their analysis, as in example due to the size of the coding region and large mutational spectrum in the case of the Titin gene.

* For autosomal recessive myopathies: in situations where only one disease-causing (or probably disease-causing) sequence variant is identified in a given gene, the search for an initially missed second disease-causing sequence variant in *trans* has to be initiated depending on the diagnostic orientation, in correlation with available clinical data.

** "The lab describes exactly which regions are sequenced at >99% reliable reference or variant calls, and fills some of the gaps with Sanger sequencing" (Matthijs et al., 2016)

Fig. 1 National French consensus strategy for genetic diagnosis of myopathies using NGS

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American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Kassardjian *et al.*, 2016 Consensus d'experts https://pubmed.ncbi.nlm.nih.gov/27554703/	***The utility of genetic testing in neuromuscular disease: A consensus statement from the AANEM on the clinical utility of genetic testing in diagnosis of neuromuscular disease*** (23 August 2016) Objectif: The aim of this consensus statement is to provide a recommendation from AANEM experts on the clinical utility of genetic testing. Methods: The AANEM Professional Practice Committee reached a consensus based on expert opinion on the utility of genetic testing in neuromuscular diseases. Results: Despite the costs of genetic testing, these tests can be both valuable and beneficial in the diagnosis and treatment of neuromuscular diseases in many situations. Conclusion: It is the position of the AANEM that genetic testing and arriving at a specific molecular diagnosis is critical for providing high-quality care to NM patients. ▪ There is a role for single gene testing in cases with characteristic phenotypes, in addition to larger gene panels or other techniques, such as whole exome sequencing. ▪ Testing should be ordered from accredited laboratories, such as those that have received Clinical Laboratory Improvement Amendments (CLIA) certification in the United States. ▪ It is the position of the AANEM that genetic testing plays a vital role in the diagnosis, appropriate investigation, and monitoring of NM diseases for several reasons. ▪ Genetic tests can: 1) be cost effective by avoiding potential harm; 2) help with disease management; 3) improve the psychological impact on patients and family members by confirming the diagnosis; 4) assist with family planning; 5) allow patients to participate in clinical trials and registries.
American Academy of Neurology et American Association of Neuromuscular & Electrodiagnostic Medicine (AAN-AANEM) Kang *et al.*, 2015 Lignes directrices https://pubmed.ncbi.nlm.nih.gov/25825463/	***Evidence-based guideline summary: Evaluation, diagnosis, and management of congenital muscular dystrophy*** (Mars 2015) Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine Les lignes directrices de l'AAN sont favorables à l'utilisation du SNG chez les individus atteints d'une dystrophie musculaire congénitale qui n'ont pas de mutation identifiée dans un des gènes couramment associés à cette maladie. Objective: To delineate optimal diagnostic and therapeutic approaches to congenital muscular dystrophy (CMD) through a systematic review and analysis of the currently available literature. Results: Genetic testing can confirm some subtype-specific diagnoses, but not all causative genes for CMD have been described. Recommendations: Accurate assessment of clinical presentations and genetic data will help in identifying the correct subtype-specific diagnosis in many cases. ***General recommendations*** R3. When genetic counselors are available to help families understand genetic test results and make family-planning decisions, physicians caring for patients with CMD might help families access such resources (Level B).

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	Genetic testing Targeted genetic testing often identifies causative mutations in the classic CMD subtypes. Genetic diagnoses are beneficial to the patient, as they often enable physicians to provide more accurate prognoses and facilitate genetic counseling and family-planning discussions and may enable patients to become more aware of future clinical trials for which they may be eligible. R1. When available and feasible, physicians might order targeted genetic testing for specific CMD subtypes that have well-characterized molecular causes (Level C). R2. In individuals with CMD who either do not have a mutation identified in one of the commonly associated genes or have a phenotype whose genetic origins have not been well characterized, physicians might order whole-exome or whole genome sequencing when those technologies become more accessible and affordable for routine clinical use (Level C). Our systematic review indicates that many patients with CMD do not have mutations in one of the currently known genes. The cost of next-generation sequencing (whole-exome and whole-genome sequencing) is dropping rapidly, to the point where these technologies are now readily available to many researchers who seek novel causative disease genes.
The International Standard of Care Committee for Congenital Myopathies North *et al.*, 2014 Consensus d'experts https://pubmed.ncbi.nlm.nih.gov/24456932/	***Approach to the diagnosis of congenital myopathies*** (February 2014) ➢ In this overview, we will provide an approach to the diagnosis of congenital myopathies and a guide to identifying the genetic basis for an individual patient based on clinical clues, muscle imaging (MRI) and histological features on muscle biopsy. ➢ It is acknowledged that the increasing use of exome, targeted sub-exomic and whole genome sequencing as a diagnostic tool in clinical practise is likely to reduce the need for muscle biopsy as a first line investigation. *Genetic testing for congenital myopathies* ▪ Molecular testing for congenital myopathies is in rapid evolution with recent advances in sequencing technology likely to have considerable impact on the method of genetic testing for these diseases. ▪ The Leiden Open Variation database is an open access resource that provides a list of DNA sequence variants in specific genes and associated phenotypes to assist in the identification of which variants are pathogenic: http://www.lovd.nl/ ▪ An up-to-date internet resource Genetests: www.genetests.org ▪ Proceeding directly to genetic analysis in congenital myopathies has usually not been practical for multiple reasons. ▪ Nevertheless, going straight to specific genetic testing has been used in the following circumstances: o To exclude an alternative diagnosis o Where the muscle biopsy may not be helpful but the clinical phenotype may be characteristic o In the rare case where there is a severely ill neonate in whom a congenital myopathy is a possibility and the decision to withdraw care is being considered ▪ In general, genetic testing should be prioritised based on a combination of information gained from clinical presentation and examination, family history, muscle biopsy ± muscle MRI.

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	Interpreting genetic testing ▪ Genetic testing for many congenital myopathies is relatively new. Therefore, many tests may result in variants of uncertain significance. ▪ If clinicians have any questions about the interpretation of genetic results or the inheritance pattern, or if the results are incongruous with the disease presentation or family history, they should seek advice from the laboratory or a specialist neuromuscular service.
European Federation of the Neurological Societies (EFNS) Burgunder *et al.*, 2011 Lignes directrices https://pubmed.ncbi.nlm.nih.gov/20500522/	***EFNS guidelines for the molecular diagnosis of neurogenetic disorders: Motoneuron, peripheral nerve and muscle disorders*** (26 Mars 2010) Objectives: These EFNS guidelines on the molecular diagnosis of motoneuron disorders, neuropathies and myopathies are designed to summarize the possibilities and limitations of molecular genetic techniques and to provide diagnostic criteria for deciding when a molecular diagnostic work-up is indicated. Conclusion: These guidelines are provisional and the future availability of molecular genetic epidemiological data about the neurogenetic disorders under discussion in this article will allow improved recommendation with an increased level of evidence. Congenital myopathies : ▪ This is a large group of rare diseases having as common clinical denominator congenital floppiness, muscle, weakness, slimness, frequent skeletal dysmorphism. ▪ The diagnosis is based on specific morphological abnormalities found in the muscle biopsy. Recommendations : ▪ In patients with certain distinctive phenotypes, and a suggestive family history, a molecular diagnosis can be made without additional investigations. In such cases, an analysis of the respective gene should be performed without a muscle biopsy (level B). ▪ In limb-girdle dystrophies, in congenital dystrophies and in congenital myopathies, a biopsy is needed to collect data on the morphological and molecular phenotype through microscopical and protein expression analysis. This data will then guide the choice of the appropriate gene testing (level B).

ANNEXE F

Description sommaire de l’étude économique répertoriée

La population visée par l’étude de Schofield [2017] est la population pédiatrique australienne atteinte de dystrophies musculaires congénitales (DMC) et des myopathies congénitales (non dystrophiques), dont la myopathie némaline (MN) est un sous-type.

L’analyse de l’efficience repose sur la comparaison entre le rendement diagnostique avec le SNG, par rapport au bilan diagnostique traditionnel. Ce bilan comprend une biopsie musculaire, des analyses histologiques et biochimiques des spécimens musculaires le tout suivi du séquençage Sanger des gènes candidats. Ici le SNG prend deux formes un panel génétique neuromusculaire et le séquençage de l’exome. Dans le cadre de la présente évaluation, seul le panel génétique neuromusculaire s’avère pertinent.

L'analyse économique a été réalisée selon la perspective du payeur de soins et l’horizon temporel couvre la période allant de l'orientation des patients suspectés d’avoir un diagnostic de DMC ou de NM jusqu'au diagnostic génétique.

Modèle économique

Une analyse de coût par diagnostic a été effectuée sur la base d’un arbre de décision comparant l’algorithme de prise en charge du diagnostic traditionnelle avec un algorithme de prise en charge de diagnostics utilisant le SNG (panel génétique ciblé).

Intrants cliniques

Les résultats cliniques proviennent d’une cohorte de 56 patients recensés sur une période de 15 ans dans un centre neuromusculaire pédiatrique

Intrants économiques

Les données sur les coûts reflètent les coûts, en 2016, facturés à l'hôpital pour tous les examens diagnostiques et les tests de dépistage.

Résultats

Les résultats sont interprétés en coût moyen par diagnostic. Selon les auteurs, le SNG serait efficient par rapport aux soins usuels puisque son coût par diagnostic serait de 210 000 $/23 plutôt que 570 000 $/23 pour les soins usuels. Il en ressort également que le panel ciblé serait plus efficient que le séquençage de l’exome, puisque son coût par diagnostic est estimé à 335 000 $/38. Les analyses de sensibilité probabiliste démontrent que les résultats sont robustes.

Analyse critique de la littérature et transposabilité des résultats

En se référant aux différents critères de la grille CHEERS [Husereau *et al.*, 2013], quant aux éléments à rapporter dans une étude économique afin de s'assurer de sa validité, l'article ici étudié correspond au standard de bonne pratique. Toutefois, il est important de noter que l'étude économique repose sur une seule étude clinique avec un faible nombre de participants. Ce qui peut toutefois se justifier par le fait que les pathologies étudiées sont rares. De plus, l'étude clinique comporte un biais de recrutement, puisque les personnes recrutées étaient majoritairement des patients avec une atteinte à la naissance ou à moins de 2 ans, de myopathie congénitale et de dystrophie musculaire congénitale.

Les résultats de cette étude ne peuvent être transposés en contexte québécois. Tout d'abord la population visée par l'article est une population pédiatrique et celle visée par la présente évaluation porte à la fois sur la population pédiatrique et adulte. De plus, même pour la population pédiatrique, il existe une disparité qui s'explique par le fait que la majorité des demandes au Québec proviennent des cliniques externes et de ce fait les diagnostics sont plus hétérogènes que dans l'étude de l'Australie où tous les patients avaient essentiellement des diagnostics de myopathie congénitale et dystrophie musculaire congénitale.

Selon les experts consultés, ces patients sont plus susceptibles d'être hospitalisés pour l'investigation, ce qui augmente les coûts des procédures reliées à l'investigation pour les soins usuels en Australie par rapport à la situation au Québec. Toujours selon les experts, l'hétérogénéité des diagnostics aurait aussi comme conséquence que plus de biopsies musculaires post panel pourraient être effectué au Québec comparativement à l'Australie. Chez la population adulte, selon les experts consultés, les soins usuels comprennent moins de biopsies que chez la population pédiatrique, les soins usuels correspondent davantage à des panels sériques d'auto-anticorps.

Étant donné que les patients suivis en consultations externes au Québec sont plus hétérogènes que dans l'étude de l'Australie, le rendement diagnostic chez la population pédiatrique devrait être plus faible que ceux de l'article. Il avoisinerait plutôt les 22 %, tel qu'estimé dans l'étude de Thuriot [2020]. Comme le rendement diagnostic est plus faible en général chez l'adulte il faudrait s'attendre plutôt à un rendement de 13 % [Thuriot *et al.*, 2020]. Globalement, par rapport aux résultats énoncés dans l'article de Schofield [2017], le SNG pour le panel musculaire en comparaison aux soins usuels serait assurément moins efficient au Québec. Comme les résultats de l'article ne peuvent être transposés en contexte québécois, l'INESSS ne peut statuer sur l'efficience de la technologie SNG pour le panel musculaire.

ANNEXE G

Consultations effectuées par le demandeur

Les spécialistes et experts locaux consultés par le demandeur pour l'élaboration des panels et de l'algorithme clinique sont les suivants :

- **Dr Nicolas Chrestian**, neurologue pour enfants, CHU de Québec – Université Laval
- **Dr Benjamin Ellezam**, pathologiste, CHU Ste-Justine
- **Dr Sali Farhan**, généticienne moléculaire, CUSM
- **Dre Emilie Lareau-Trudel**, neurologue, CIUSSS de l'Estrie – CHUS
- **Dre Sandrine Larue**, neurologue, CHUM
- **Dre Emmanuelle Lemyre**, généticienne, CHU Ste-Justine
- **Dre Amélie Nadeau**, neurologue pour enfants, CIUSSS de l'Estrie – CHUS
- **Dre Erin O'ferall**, neurologue, CUSM
- **Dr Maxime Richer**, pathologie, CIUSSS de l'Estrie – CHUS

ANNEXE H

Conception du panel global et des sous-panels panels musculaires – Rationnel de décision

Sources consultées pour déterminer la pertinence clinique des gènes

- PanelApp[1] (*Green gene only*) :
  - Limb girdle muscular dystrophy v2.12
  - Congenital myopathy v2.8
  - Congenital myaesthenic syndrome v2.7
  - Congenital muscular dystrophy v2.4
  - Rhabdomyolysis and metabolic muscle disorders v1.43
  - Distal myopathies v1.26
- Thuriot F. *et al.*, Molecular diagnosis of muscular diseases in outpatient clinics: A Canadian perspective. Neurol Genet. 2020 Apr;6(2). [Thuriot *et al.*, 2020]. Disponible à : https://pubmed.ncbi.nlm.nih.gov/32337335/
- Winder T. *et al.*, Clinical utility of multigene analysis in over 25,000 patients with neuromuscular disorders. Neurol Genet. 2020 Apr;6(2). [Winder *et al.*, 2020]. Disponible à : https://pubmed.ncbi.nlm.nih.gov/32337338/

La liste a aussi été bonifiée de certains gènes de la littérature.

Protocole et révision des gènes

Le demandeur a pris la décision de réviser plus en détails certains gènes *« green »* après avoir relevé certaines erreurs potentielles sur la liste initiale. Le demandeur propose de procédé de la façon suivante :

1) Si PanelApp « *green* » + ClinGen « *moderate* » ou « *definitive* » = inclusion au panel sans autre révision;
2) Si PanelApp « *green* » + Thuriot *et al.* [2020] (CHUS/SGM) **ET** Winder *et al.* [2020] (Invitae) rapportent des diagnostics, acceptation sans plus de révision;
3) Autres cas PanelApp « green » = révision supplémentaire de la littérature.

[1] Genomics England PanelApp, disponible à : https://panelapp.genomicsengland.co.uk/.

Certains gènes ont été exclus :

- Si la condition reliée est causée par une répétition de trinucléotides, sauf pour la DMOP qui a été conservée (nombre faible de répétitions et détection fiable + potentiel de détecter des cas atypiques non-suspectés cliniquement et envoyés pour PCR);
- Gène mitochondrial (nucléaire), car analysé par autre panel plus complet offert dans le RQDM;
- La cause de la faiblesse est une amyotrophie spinale ou une neuropathie (sauf si composante mixte de myopathie);
- Le gène cause une arthrogrypose et donc il serait préférable d'inclure le gène dans un autre panel plus complet qui couvre également les causes d'arthrogrypose d'origine centrale.

Aucun gène n'a été exclus à cause d'une couverture incomplète. Toutefois, le gène *SELENON* et le gène *TPM3* demande un séquençage de type Sanger pour chacun un exon.

Organisation des sous-panels (ou panels restreints)

Les différents sous-panels (rhabdomyolyse, dystrophies musculaires, myopathies congénitales, myasthénies congénitales) qui pourront être prescrits en plus du panel musculaire global ont été établis à partir de PanelApp. Les modifications suivantes ont été effectuées :

- **Rhabdomyolyse :** Seulement l'indication de rhabdomyolyse du panel « *rhabdomyolysis and metabolic myopathies* » (PanelApp) a été conservée. Toutefois, si une myopathie dite « métabolique » ne se présente pas par une rhabdomyolyse, le gène est gardé dans le panel global.
- **Dystrophies musculaires :** Compte tenu que plusieurs des dystrophies musculaires congénitales donnent un spectre de sévérité allant de manifestations à la naissance à des formes de dystrophies des ceintures plus légères, il a été décidé de regrouper les panels de dystrophies musculaires des ceintures et dystrophies musculaires congénitales. À noter que le panel de « *Limb-girdle muscular dystrophies dystrophies* » (PanelApp) contient à la base des gènes causant des faiblesses des ceintures qui ne sont pas des dystrophies.
- Certains gènes sont inclus dans le panel global seulement (myopathies distales, formes rares de myopathies métaboliques sans rhabdomyolyse, etc).

Liste des gènes sélectionnés

La liste de gènes du sous-panels des rhabdomyolyses (Tableau H-1), des dystrophies musculaires (Tableau H-2), des myopathies congénitales (Tableau H-3), des myasthénies congénitales (Tableau H-4), des hyperthermies malignes (Tableau H-5), des gènes additionnels inclus dans le panel global (Tableau H-6) et de ceux ayant été considérés sans être retenus (Tableau H-7), ainsi que les principales évidences associées à chaque gène, sont présentés dans les tableaux suivants. Au besoin, des informations supplémentaires peuvent être obtenues sur demande auprès de l'INESSS ou du demandeur.

Tableau H-1 Gènes inclus dans le panel des rhabdomyolyse (n = 25) et niveaux d'évidence associés

Entity Name	Rhab	DM	Myo	Myas	HT	PanelApp	Clingen	Évidences génétiques (PMID)	Données expérimentales (PMID)	Dx yield [Thuriot, 2020]	Dx Yield [Winder, 2020]	% pt with VUS	Couverture moyenne exome	% > 20X
ANO5	1	1				Green	Definitive			13	22	2,08	174,46	100,00
CAV3	1	1				Green	N/A			5	6	0,28	276,36	100,00
DMD	1	1				Green	N/A			33	635	3,20	256,66	99,99
DYSF	1	1				Green	Definitive			12	43	5,15	192,91	100,00
FKRP	1	1				Green	Definitive			15	36	1,02	164,42	99,99
FKTN	1	1				Green	Definitive			N/A	0	0,89	206,85	100,00
PFKM	1	1				Green	N/A	22133655; 8037209; 24427140	22133655; 24427140	1	N/A	N/A	166,76	100,00
PHKA1	1	1				Green	N/A	7874115; 12825073; 9731190	12825073; 9731190	N/A	N/A	N/A	247,40	100,00
PYGM	1	1				Green	N/A			17	N/A	N/A	220,23	100,00
RYR1	1	1	1		1	Green	N/A			21	83	10,85	199,67	98,56
ACADVL	1					Green	Definitive			N/A	N/A	N/A	229,51	100,00
CACNA1S	1		1		1	Green	N/A			N/A	62	3,56	179,52	100,00
CPT2	1					Green	Definitive			N/A	5	1,30	153,46	100,00
ENO3	1					Green	N/A	11506403; 25267339; 31741825	11506403; 25267339; 31741825	N/A	N/A	N/A	188,47	100,00
ETFA	1					Green	Definitive			N/A	N/A	N/A	169,11	100,00
ETFB	1					Green	Moderate			N/A	N/A	N/A	210,88	100,00
ETFDH	1					Green	Definitive			N/A	N/A	N/A	196,41	100,00
HADHA	1					Green	Definitive	27117294		N/A	N/A	N/A	195,41	100,00
HADHB	1					Green	Definitive	27117294		N/A	N/A	N/A	189,63	100,00
LDHA	1					Green	N/A	3383424; 7449146; 7944300; 29198466	3383424	N/A	N/A	N/A	187,82	100,00
LPIN1	1					Green	Definitive			N/A	N/A	N/A	219,24	99,97
PGAM2	1					Green	N/A	6262916; 7603528; 8761269; 27612597	6262916; 27612597	N/A	N/A	N/A	283,31	100,00
PGK1	1					Green	N/A	6830158; 10809925; 30111548	6830158; 10809925; 30111548	N/A	N/A	N/A	248,95	100,00
PGM1	1					Green	N/A	24499211; 28190645	24499211; 28190645	N/A	N/A	N/A	162,42	99,94
SIL1	1					Green	N/A			N/A	N/A	N/A	193,37	100,00

Abréviations : DM : dystrophies musculaires; HM : hyperthermies malignes; Myas : myasthénies congénitales; Myo : myopathies congénitales; N/A : non applicable; PMID : numéro d'identification de la publication sur PubMed (*PubMed Identifier*); pt : patients; Rhab : rhabdomyolyses; VUS : variant de signification incertaine (*Variant of Uncertain Significance*)

Tableau H-2 Gènes inclus dans le panel des dystrophies musculaires (n = 71) et niveaux d'évidence associés

Entity Name	Rhab	DM	Myo	Myas	HT	PanelApp	Clingen	Évidences génétiques (PMID)	Données expérimentales (PMID)	Dx yield [Thuriot, 2020]	Dx Yield [Winder, 2020]	% pt with VUS	Couverture moyenne exome	% > 20X
ANO5	1	1				Green	Definitive			13	22	2,08	174,46	100,00
B3GALNT2		1				Green	N/A			N/A	0	1,12	193,77	99,83
B4GAT1		1				Green	N/A			N/A	0	0,42	234,59	100,00
BAG3		1				Green	Definitive			1	4	1,12	226,15	100,00
BVES[1]		1				Red	N/A	31119192; 26642364; 32528171	26642364	N/A	N/A	N/A	174,57	100,00
CAPN3		1				Green	N/A			20	57	2,20	225,81	100,00
CASQ1[2]		1	1			Amber	N/A	28895244; 30258016	19237502	N/A	N/A	N/A	147,24	100,00
CAV3	1	1				Green	N/A			5	6	0,28	276,36	100,00
CHKB		1				Green	N/A			N/A	1	0,61	240,52	100,00
COL6A1		1	1			Green	N/A			3	40	3,20	241,14	100,00
COL6A2		1	1			Green	N/A			6	23	3,92	232,55	100,00
COL6A3		1	1			Green	N/A			1	16	7,58	218,42	100,00
CRYAB		1				Green	N/A			N/A	2	0,40	215,34	100,00
DAG1		1				Green	N/A			N/A	0	1,60	218,47	100,00
DES		1				Green	Moderate			1	7	1,17	190,05	100,00
DMD	1	1				Green	N/A			33	635	3,20	256,66	99,99
DNAJB6		1				Green	N/A			N/A	2	0,47	200,17	100,00
DOK7		1	1	1		Green	N/A			3	16	2,82	213,39	100,00
DPM3[3]		1				Amber	N/A	28803818; 31266720	28803818; 31266720	N/A	0	0,18	239,43	100,00
DYSF	1	1				Green	Definitive			12	43	5,15	192,91	100,00
EMD		1				Green	N/A			4	11	0,39	274,47	100,00
FHL1		1				Green	N/A			1	3	0,30	289,17	100,00
FKRP	1	1				Green	Definitive			15	36	1,02	164,42	99,99
FKTN	1	1				Green	Definitive			N/A	0	0,89	206,85	100,00
FLNC		1				Green	Definitive			5	8	5,83	243,39	100,00
GAA		1				Green	Definitive			11	16	2,97	232,28	100,00
GMPPB		1		1		Green	N/A			5	7	0,53	213,76	100,00
GNE		1				Green	Limited			2	8	1,43	166,90	100,00
HNRNPDL		1				Green	N/A			N/A	N/A	N/A	177,39	100,00
INPP5K		1				Green	N/A			N/A	N/A	N/A	243,67	100,00
ISPD		1				Green	N/A			N/A	1	0,89	N/A	N/A
ITGA7		1				Green	N/A	9590299	16476707; 9354797	N/A	2	2,56	161,92	100,00
LAMA2		1				Green	N/A			5	48	6,70	190,99	100,00
LAMP2		1				Green	Definitive			1	1	0,28	227,41	100,00

Entity Name	Rhab	DM	Myo	Myas	HT	PanelApp	Clingen	Évidences génétiques (PMID)	Données expérimentales (PMID)	Dx yield [Thuriot, 2020]	Dx Yield [Winder, 2020]	% pt with VUS	Couverture moyenne exome	% > 20X
LARGE1		1				Green	N/A			N/A	0	1,47	243,44	100,00
LMNA		1	1			Green	Limited			4	67	0,73	198,28	100,00
MTM1		1	1			Green	Definitive			1	14	0,26	242,03	100,00
MYH7		1	1			Green	Limited			8	23	2,67	288,59	100,00
MYOT		1				Green	N/A			6	16	0,57	185,56	100,00
ORAI1		1	1			Green	Definitive			N/A	N/A	N/A	226,59	99,11
PABPN1[4]		1				Red	N/A			2	N/A	N/A	193,50	96,24
PFKM	1	1				Green	N/A	22133655; 8037209; 24427140	22133655; 24427140	1	N/A	N/A	166,76	100,00
PHKA1	1	1				Green	N/A	7874115; 12825073; 9731190	12825073; 9731190	N/A	N/A	N/A	247,40	100,00
PLEC		1		1		Green	N/A			1	0	17,94	236,19	100,00
POGLUT1[5]		1				Amber	N/A	31897643; 32528171	31897643	N/A	N/A	N/A	195,47	100,00
POMGNT1		1				Green	Definitive			1	2	1,29	137,63	100,00
POMGNT2		1				Green	Definitive			N/A	0	1,83	227,38	100,00
POMK		1				Green	N/A	29910097	24925318	N/A	0	0,77	220,47	100,00
POMT1		1				Green	N/A			1	1	1,34	215,77	100,00
POMT2		1				Green	N/A			N/A	2	1,60	215,99	99,96
POPDC3[6]		1				-	N/A	31610034	31610034	N/A	N/A	N/A	167,87	100,00
PYGM	1	1				Green	N/A			17	N/A	N/A	220,23	100,00
RXYLT1		1				Green	N/A			N/A	0	0,16	121,93	99,86
RYR1	1	1	1		1	Green	N/A			21	83	10,85	199,67	98,56
*SELENON**		1	1			Green	N/A			1	24	1,35	151,61	84,13
SGCA		1				Green	Definitive			6	32	0,72	211,50	100,00
SGCB		1				Green	Definitive			N/A	9	0,99	180,74	100,00
SGCD		1				Green	Definitive			N/A	0	0,46	216,80	100,00
SGCG		1				Green	Definitive			2	9	0,68	202,58	100,00
STIM1		1	1			Green	N/A			N/A	3	1,16	212,78	100,00
SYNE1		1				Green	N/A			N/A	N/A	N/A	205,60	100,00
SYNE2		1				Green	N/A			N/A	N/A	N/A	198,25	100,00
TCAP		1				Green	N/A			N/A	1	0,75	193,52	100,00
TMEM43[7]		1				Red	Definitive	21391237; 30311943	21391237	N/A	0	5,53	280,45	99,97
TNPO3		1				Green	N/A			N/A	0	0,63	201,65	100,00
TOR1AIP1[8]		1				Amber	N/A	24856141; 27342937	24055652	N/A	0	1,28	138,31	99,66
TRAPPC11		1				Green	N/A			2	1	1,77	207,15	100,00

Entity Name	Rhab	DM	Myo	Myas	HT	PanelApp	Clingen	Évidences génétiques (PMID)	Données expérimentales (PMID)	Dx yield [Thuriot, 2020]	Dx Yield [Winder, 2020]	% pt with VUS	Couverture moyenne exome	% > 20X
TRIM32		1				Green	N/A			N/A	5	1,32	197,81	100,00
TTN		1	1			Green	N/A			N/A	72	3,88	153,54	100,00
VCP		1				Green	N/A			7	20	0,44	187,61	100,00
VMA21		1	1			Green	N/A			N/A	2	0,12	251,98	100,00

Abréviations : DM : dystrophies musculaires; HM : hyperthermies malignes; Myas : myasthénies congénitales; Myo : myopathies congénitales; N/A : non applicable; PMID : numéro d'identification de la publication sur PubMed (*PubMed Identifier*); pt : patients; Rhab : rhabdomyolyses; VUS : variant de signification incertaine (*Variant of Uncertain Significance*)

* L'exon du gène *SELENON* pour lequel la couverture est insuffisante sera effectué par séquençage de type Sanger.

Notes complémentaires sur le niveau d'évidence de certains gènes :

[1] *BVES* : Muscular dystrophy, limb-girdle, type 2X, 616812; PanelApp: mixed review. Newer one are "green".

[2] *CASQ*1 : Myopathy, vacuolar, with CASQ1 aggregates; main reason for "amber" is only one missense variants seems to have been reported in this gene (p.Asp244Gly), a founder mutation in Italy. However, it is noteworthy that other mutations have been reported (PMID: 28895244, but also Italy).

[3] *DPM3* : Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 15; pure myopathic presentation reported (PMID: 28803818).

[4] *PABPN1* : Oculopharyngeal muscular dystrophy; short (GCG)n repeats expansion are detectable by NGS. 2 dx in [Thuriot *et al.*, 2020]; PanelApp red for congenital muscular dystrophy. Not graded for muscular dystrophy. Only analyse exon 1 GCN repeat. Offer testing for clinical suspicion by PCR.

[5] *POGLUT1* : Muscular dystrophy, limb-girdle, autosomal recessive 21; several families added since PanelApp evaluation (PMID: 31897643).

[6] *POPDC3* : Muscular dystrophy, limb-girdle, autosomal recessive 26; a single paper, 5 patients from 3 families. Nevertheless, sufficient evidence from this paper to include in panel. Not graded in PanelApp.

[7] *TMEM43* : Emery-Dreifuss muscular dystrophy 7, AD 614302; ClinGen definitive is for ARVD. Only 5 patients reported with EDMD: 2 father-son duo + one isolated case; "red" for congenital muscular dystrophy in PanelApp. Not graded for limb-girdle muscular dystrophy.

[8] *TOR1AIP1* : Muscular dystrophy, autosomal recessive, with rigid spine and distal joint contractures (OMIM:617072).

Tableau H-3 Gènes inclus dans le panel des myopathies congénitales (n = 48) et niveaux d'évidence associés

Entity Name	Rhab	DM	Myo	Myas	HT	PanelApp	Clingen	Évidences génétiques (PMID)	Données expérimentales (PMID)	Dx yield [Thuriot, 2020]	Dx Yield [Winder, 2020]	% pt with VUS	Couverture moyenne exome	% > 20X
ACTA1			1			Green	N/A			3	20	0,54	214,47	100,00
ACTN2			1			Green	N/A			N/A	0	2,96	234,13	100,00
ADSSL1			1			Green	N/A			N/A	N/A	N/A	N/A	N/A
ATP2A1			1			Green	N/A	32040565	2943216; 2966306	N/A	1	1,56	162,35	98,84
BIN1			1			Green	Definitive			N/A	0	1,09	181,93	100,00
CACNA1S	1		1		1	Green	N/A			N/A	62	3,56	179,52	100,00
CASQ1 [1]		1	1			Amber	N/A	28895244; 30258016	19237502	N/A	N/A	N/A	147,24	100,00
CCDC78			1			Green	Limited			2	0	1,96	227,83	100,00
CFL2			1			Green	Definitive			N/A	0	0,12	138,62	100,00
COL12A1			1			Green	N/A			1	3	6,51	184,07	100,00
COL6A1		1	1			Green	N/A			3	40	3,20	241,14	100,00
COL6A2		1	1			Green	N/A			6	23	3,92	232,55	100,00
COL6A3		1	1			Green	N/A			1	16	7,58	218,42	100,00
DNM2			1			Green	Definitive			4	24	0,87	209,28	100,00
DOK7		1	1	1		Green	N/A			3	16	2,82	213,39	100,00
FKBP14			1			Green	N/A			N/A	1	0,13	220,86	100,00
KBTBD13			1			Green	Moderate			N/A	0	1,38	179,68	100,00
KLHL40			1			Green	Definitive			N/A	2	1,60	209,55	100,00
KLHL41			1			Green	Moderate			1	0	0,46	155,98	100,00
LMNA		1	1			Green	Limited			4	67	0,73	198,28	100,00
LMOD3			1			Green	Definitive			N/A	0	1,12	189,02	100,00
MAP3K20			1			Green	Moderate			N/A	N/A	N/A	152,50	100,00
MEGF10			1			Green	Definitive			N/A	0	2,10	192,43	100,00
MTM1		1	1			Green	Definitive			1	14	0,26	242,03	100,00
MYBPC1			1			Green	N/A	31025394; 31264822	31025394; 31264822	N/A	N/A	N/A	145,74	100,00
MYH2			1			Green	Definitive			N/A	0	3,37	281,06	100,00
MYH7		1	1			Green	Limited			8	23	2,67	288,59	100,00
MYMK			1			Green	N/A	28681861; 29560417; 30065953	28681861	N/A	N/A	N/A	191,42	100,00
MYO18B			1			Green	Limited	25748484; 32637634	27879346	N/A	N/A	N/A	241,43	100,00
MYPN			1			Green	Limited	28017374; 31133047; 28220527	28017374	N/A	0	2,29	185,28	100,00
NEB			1			Green	Definitive			4	14	14,05	184,81	99,93
ORAI1		1	1			Green	Definitive			N/A	N/A	N/A	226,59	99,11

Entity Name	Rhab	DM	Myo	Myas	HT	PanelApp	Clingen	Évidences génétiques (PMID)	Données expérimentales (PMID)	Dx yield [Thuriot, 2020]	Dx Yield [Winder, 2020]	% pt with VUS	Couverture moyenne exome	% > 20X
PAX7			1			Green	N/A	31092906	21828093	N/A	N/A	N/A	167,38	100,00
PNPLA2 [2]			1			Red	N/A	17657808; 21544567		3	3	1,66	205,85	100,00
PYROXD1			1			Green	Definitive			N/A	N/A	N/A	178,13	100,00
RBCK1			1			Green	N/A	23798481; 23889995		N/A	N/A	N/A	238,69	100,00
RYR1	1	1	1		1	Green	N/A			21	83	10,85	199,67	98,56
SCN4A			1	1		Green	N/A	28003497; 30283817; 28330959		N/A	112	3,79	233,40	100,00
*SELENON**		1	1			Green	N/A			1	24	1,35	151,61	84,13
SPEG			1			Green	Definitive			N/A	N/A	N/A	182,93	100,00
STAC3			1		1	Green	Definitive			N/A	1	0,69	127,79	100,00
STIM1		1	1			Green	N/A			N/A	3	1,16	212,78	100,00
TNNT1			1			Green	N/A	29931346; 31970803; 26296490		N/A	2	0,63	255,62	100,00
TPM2			1			Green	N/A			N/A	5	0,25	233,92	100,00
*TPM3**			1			Green	N/A			N/A	6	0,21	112,35	84,23
TRIP4			1			Green	N/A	31794073; 27008887	27008887	N/A	N/A	N/A	216,56	100,00
TTN		1	1			Green	N/A			N/A	72	3,88	153,54	100,00
VMA21		1	1			Green	N/A			N/A	2	0,12	251,98	100,00

Abréviations : DM : dystrophies musculaires; HM : hyperthermies malignes; Myas : myasthénies congénitales; Myo : myopathies congénitales; N/A : non applicable; PMID : numéro d'identification de la publication sur PubMed (*PubMed Identifier*); pt : patients; Rhab : rhabdomyolyses; VUS : variant de signification incertaine (*Variant of Uncertain Significance*)

* Le séquençage d'un exon du gène *SELENON* et d'un exon du gène *TMP3*, pour lequel la couverture est insuffisante, sera effectué par séquençage de type Sanger.

Notes complémentaires sur le niveau d'évidence de certains gènes :

[1] *CASQ1* : Myopathy, vacuolar, with CASQ1 aggregates; main reason for "amber" is only one missense variants seems to have been reported in this gene (p.Asp244Gly), a founder mutation in Italy. However, it is noteworthy that other mutations have been reported (PMID: 28895244, but also Italy).

[2] *PNPLA2* : Neutral Lipid Storage Disease with Myopathy; Neutral lipid storage disease with myopathy, 610717; Dx made by [Thuriot *et al.*, 2020] and Invitae labs [Winder *et al.*, 2020].

Tableau H-4 Gènes inclus dans le panel des myasthénies congénitales (n = 22) et niveaux d'évidence associés

Entity Name	Rhab	DM	Myo	Myas	HT	PanelApp	Clingen	Évidences génétiques (PMID)	Données expérimentales (PMID)	Dx yield [Thuriot, 2020]	Dx Yield [Winder, 2020]	% pt with VUS	Couverture moyenne exome	% > 20X
DOK7		1	1	1		Green	N/A			3	16	2,82	213,39	100,00
SCN4A			1	1		Green	N/A	28003497; 30283817; 28330959		N/A	112	3,79	233,40	100,00
GMPPB		1		1		Green	N/A			5	7	0,53	213,76	100,00
PLEC		1		1		Green	N/A			1	0	17,94	236,19	100,00
AGRN				1		Green	N/A	See 32221959 for recent review of published cases	11323662	N/A	0	7,21	223,75	100,00
CHAT				1		Green	N/A			N/A	0	2,41	175,36	100,00
CHRNA1				1		Green	N/A		29054425; 20157724 (see OMIM for other publications)	N/A	5	1,15	163,44	100,00
CHRNB1				1		Green	N/A			1	1	0,80	225,28	100,00
CHRND				1		Green	N/A	11435464; 18398509; 12499478		N/A	0	1,99	232,84	100,00
CHRNE				1		Green	N/A			5	20	1,78	192,00	100,00
COL13A1				1		Green	N/A	31081514; 31018245; 26626625	26626625; 20844119; 11583983	N/A	N/A	N/A	162,14	100,00
COLQ				1		Green	N/A			1	5	1,10	253,68	100,00
DPAGT1				1		Green	N/A	22742743; 24759841; 23278575	23278575	N/A	0	0,43	181,32	100,00
GFPT1				1		Green	N/A	21310273; 30635494	21310273	N/A	4	0,41	174,13	99,39
LRP4				1		Green	N/A	26052878; 24234652	25319686	N/A	N/A	N/A	199,85	100,00
MUSK				1		Green	N/A	27588369 for a recent review of reported cases	8653786; 11323662	N/A	0	1,71	200,52	100,00
RAPSN				1		Green	N/A			1	8	0,89	211,06	100,00
SLC18A3				1		Green	N/A	27590285; 29130637	31531871	N/A	N/A	N/A	232,68	100,00
SLC25A1				1		Green	N/A	26870663; 31527857	26870663	N/A	N/A	N/A	154,19	97,10
SLC5A7				1		Green	N/A	27569547; 33250374	15173594	N/A	0	0,53	153,13	100,00
SYT2				1		Green	N/A	32776697; 32250532; 25192047	25192047	N/A	N/A	N/A	177,40	100,00
VAMP1				1		Green	N/A	28253535; 32616363; 28168212	28253535; 28168212	N/A	0	0,09	267,80	100,00

Abréviations : DM : dystrophies musculaires; HM : hyperthermies malignes; Myas : myasthénies congénitales; Myo : myopathies congénitales; N/A : non applicable; PMID : numéro d'identification de la publication sur PubMed (*PubMed Identifier*); pt : patients; Rhab : rhabdomyolyses; VUS : variant de signification incertaine (*Variant of Uncertain Significance*)

Tableau H-5 Gènes inclus dans le panel des hyperthermies malignes (n = 3) et niveaux d'évidence associés

Entity Name	Rhab	DM	Myo	Myas	HT	PanelApp	Clingen	Évidences génétiques (PMID)	Données expérimentales (PMID)	Dx yield [Thuriot, 2020]	Dx Yield [Winder, 2020]	% pt with VUS	Couverture moyenne exome	% > 20X
RYR1	1	1	1		1	Green	N/A			21	83	10,85	199,67	98,56
CACNA1S	1		1		1	Green	N/A			N/A	62	3,56	179,52	100,00
STAC3			1		1	Green	Definitive			N/A	1	0,69	127,79	100,00

Abréviations : DM : dystrophies musculaires; HM : hyperthermies malignes; Myas : myasthénies congénitales; Myo : myopathies congénitales; N/A : non applicable; PMID : numéro d'identification de la publication sur PubMed (*PubMed Identifier*); pt : patients; Rhab : rhabdomyolyses; VUS : variant de signification incertaine (*Variant of Uncertain Significance*)

Tableau H-6 Gènes additionnels (n = 8) inclus dans le panel global* et niveaux d'évidence associés

Entity Name	Rhab	DM	Myo	Myas	HT	PanelApp	Clingen	Évidences génétiques (PMID)	Données expérimentales (PMID)	Dx yield [Thuriot, 2020]	Dx Yield [Winder, 2020]	% pt with VUS	Couverture moyenne exome	% > 20X
AGL						Green	N/A			N/A	0	4,37	110,07	99,83
GBE1						Green	N/A	30569318; 15452297; 7683169	30569318	N/A	N/A	N/A	168,11	100,00
GYG1						Green	N/A	25272951; 26652229; 29264399	25272951; 29264399	N/A	N/A	N/A	198,69	100,00
HSPB8						Green	N/A	28501893; 31403083	28780615	N/A	0	0,27	225,98	99,97
LDB3						Green	Disputed	15668942; 27546599; 32419263; 23263837	12499364; 11696561	N/A	9	1,69	185,65	100,00
MATR3						Green	N/A	19344878; 25154462	29763601	N/A	0	0,59	170,84	100,00
MYH14 [1]						Red	Moderate	21480433; 27875632	21480433	N/A	N/A	N/A	222,27	100,00
TIA1						Green	N/A	23401021; 23348830	23401021	N/A	1	0,31	152,92	100,00

Abréviations : DM : dystrophies musculaires; HM : hyperthermies malignes; Myas : myasthénies congénitales; Myo : myopathies congénitales; N/A : non applicable; PMID : numéro d'identification de la publication sur PubMed (*PubMed Identifier*); pt : patients; Rhab : rhabdomyolyses; VUS : variant de signification incertaine (*Variant of Uncertain Significance*)

* Le panel global comporte un total de 145 gènes. Toutefois, seuls les gènes n'ayant pas été présentés dans les tableaux précédents sont inclus dans le Tableau H-6.

Notes complémentaires sur le niveau d'évidence de certains gènes :

[1] *MYH14* : Peripheral neuropathy, myopathy, hoarseness, and hearing loss; progressive distal weakness as the initial presentation reported (PMID: 21480433; PMID: 27875632). Biopsie has shown muscle phenotype (PMID: 21480433). 1 dx in PMID: 32337335 in the context of exome sequencing of muscular disease.

Tableau H-7 Gènes considérés sans être sélectionnés (n = 48) et principales raisons de l'exclusion

Entity Name	Notes
ACAD9	Green and definitive but multi-system presentation. Better evaluated by another panel.; Mitochondrial
ACADM	Green and definitive. However it is MCAD deficiency - to be evaluated by another panel.; rhabdomyolysis not a frequent presentation
ALDOA	Rare. Few patients reported (5 in 2014). All reported patients have hemolytic anemia except 1 report of isolated rhabdomyolysis (PMID: 25392908).
ALG14	Myasthenic syndrome reported in a single paper, 2 sisters (PMID: 23404334). Other patients reported with neromuscular involvement also presented neurodegeneration and died in the first year of live (5 patients, a single paper:PubMed: 28733338). Insufficient genetic evidence for pure myasthenic syndome and to include in panel.
ALG2	Reported in 3 families (2 of them from Saudi arabia with same mutation). Just enough evidence for inclusion. However, very limited and if we include ALG2 we should also include ALG14.; reconsider on next evaluation.
AMPD1	panelapp=red
AR_CAG	triplet repeats
CHRNG	No pure myopathy presentation as far as I can see. Will be better evaluated by another panel.; fœtal subunit and thus phenotype is multiple pterigium/Escobar. Better included in an arthrogryposis panel ythat include both central and peripheral causes.
CNBP	triplet repeats
DMPK_CTG	triplet repeats
DOLK	CDG. No pure myopathic presentation reported in the litterature. Better evaluated via another panel.; CDG1M. Agree with comment and can be screened by biochemical testing.
DPM2	CDG. No pure myopathic presentation reported in the litterature. Better evaluated via another panel; Agree with comment and can be screened by biochemical testing.
ECEL1	Although muscle weakness has been described (PMID: 30131190), the main feature is distal arthrogryposis. This condition will be better evaluated in a different panel.; Better included in an arthrogryposis panel that include both central and peripheral causes.
EPG5	VICI syndrome, no pure myopathy presentation (OMIM; PMID: 26917586). This condition will be better evaluated in a different panel.; multisystemic condition with allosal agenesis, cataracts, cardiomyopathy, hypopigmentation and combined immunodeficiency. Profound developmental delay.
FXR1	A single paper (PMID: 30770808), 2 families, 4 patients. Insufficient to include in panel. Neonatal presentation will be evaluated by another panel.
GYS1	Seems to be extremely rare
HSPB1	Classical presentation is neuropathy. Two papers describe a myopathic presentation (PMID: 27830184; PMID: 28702508). 4 patients from the same family in the 1st paper, a single case in the second paper. Evidence from litterature is borderline for inclusion but Invitae has 30 dx (phenotype unknown however) and low rate of VUS. We could consider inclusion.; supporting functional evidence but not 3 independant families. To be reviewed in futur.
ISCA-37408-Loss	large deletion
ISCA-37420-Loss	large deletion
ISCA-37429-Loss	large deletion
ISCU	mitochondrial. Analyzed in comprehensive panel.
LIMS2	Found only 2 patients reported, no animal model. Too preliminary for inclusion.
MICU1	41 patients reported so far (PMID: 32395406). Does not present as pure myopathy as far as I can see. This condition will be better evaluated by another panel.; mitochondrial
MSTO1	Mitochondrial DNA depletion. Full genotype-phenotype spectrum remains to be explored but so far, published patients have cerebellar ataxia in addition to muscle phenotype. Probably better evaluater by another panel
MYH3	Patients essentially presenting with arthrogryposis/contractures. No pure myopathy as far as I can see. Will be better evaluated by another panel.; arthrogrposis panel with both central and peripheral causes
MYH8	No pure myopathy presentation as far as I can see. Will be better evaluated by another panel.; arthrogryposis panel with both central and peripheral causes.

Entity Name	Notes
MYL1	Nothing new since Clingen evaluation. I come to the same conclusion, insufficient evidence to include in panel at this time.
MYO9A	A single paper, 3 patients from 2 families (PMID: 27259756). 1 paper report a case with distal arthrogryposis w/o muscle weakness (PMID: 26752647). I agree with Clingen, evidence too limited thus far to include in panel.
PHKB	Reports of myopathic presentation not found in the littérature. See PMID: 9215682; no rhabod found. Find transient mild muscle symptoms in a review paper citing old literature (17689125)
PIEZO2	Syndromic presentation (PMID: 30941898). Will be better evaluated by other panel.; arthrogryposis panel with both central and peripheral causes
POLG	mitochondrial
POLG2	mitochondrial
PRKAG2	Cardiomyopathy gene. I did not find evidence of pure skeletal muscle myopathy. No dx at invitae: has been removed quickly (only 778 pt)?
RRM2B	mitochondrial
RYR3	Insufficient evidence. A single paper reporting a single patient: PMID: 29498452
SLC22A5	Pure myopathy rare/unseen. To evaluate by other means; can be scrteend by biochemicala genetics testing. Can present with hypotonia and cardiomyopathy. One case of rhabdo: 29895548 . Review paper cited by panelapp (25929793): no mention of SLC22A5 or OCTN2. Agree to no include in the muscle panels.
SLC25A20	Clingen definitive is for CATD. Not considered by panelapp for rhabdo.; can be identified with biochemical genetics testing. Multisystemic presention. Panelapp considred for super panel hypotonic infant
SLC25A4	mitochondrial
SMCHD1	The diagnosis of FSHD2 is established in a proband by identification of hypomethylation of the D4Z4 repeat array in the subtelomeric region of chromosome 4q35 on a chromosome 4 permissive haplotype. Hypomethylation of the D4Z4 repeat array can be due to a heterozygous pathogenic variant in SMCHD1 or DNMT3B. A Southern blot-based method has been developed that measures the total D4Z4 methylation at chromosomes 4q and 10q by using methylation-sensitive restriction enzyme (FseI) in the promoter region of DUX4 (Lemmers et al 2012, PMID: 23143600). Upon clinical suspicion, better use methylation study or methyl-sensitive restriction enzyme while testing for FSHD1. To be considered to be added, but not at first round.
SQSTM1	SQSTM1 mutations are associated with several disorders - see OMIM. The expression of a distal myopathy phenotype apparently requires the presence of an additionnal variant (digenic inheritance), notably in TIA1 (PMID: 29599744; PMID: 29457785). Only report when TIA1 mutation also present?; unusual mechanism. TIA1 mutation reported also in other patient with phenotype more typical of SQSTM1 (frontemporal dementia -+/- ALS). Propose to wait for additional functional evidence.
SUCLA2	mitochondrial
SUN1	A single patient reported thus far. See PMID: 31840275 for a recent review. Too preliminary for inclusion
TK2	mitochondrial
TNNI2	Arthrogryposis presentation. No evidence of pure myopathic presentation. ;arthrogryposis panel with central and peripheric causes
TNNT3	Presentation is arthrogryposis. I found only one evidence of myopathic presentation+ arthro (PMID: 29266598).
TSEN54	wrong classification in panel app - a reviewer correctly indicated than rhabdo is not a common feature. Remove.
TSFM	panelapp reviewer classify as red: rhabdo not a common feature and mitochondrial
TYMP	mitochondrial

RÉFÉRENCES

Burgunder JM, Schols L, Baets J, Andersen P, Gasser T, Szolnoki Z, et al. EFNS guidelines for the molecular diagnosis of neurogenetic disorders: Motoneuron, peripheral nerve and muscle disorders. Eur J Neurol 2011;18(2):207-17.

Fratter C, Dalgleish R, Allen SK, Santos R, Abbs S, Tuffery-Giraud S, Ferlini A. EMQN best practice guidelines for genetic testing in dystrophinopathies. Eur J Hum Genet 2020;28(9):1141-59.

Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and elaboration: A report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health 2013;16(2):231-50.

Kang PB, Morrison L, Iannaccone ST, Graham RJ, Bönnemann CG, Rutkowski A, et al. Evidence-based guideline summary: Evaluation, diagnosis, and management of congenital muscular dystrophy. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology 2015;84(13):1369-78.

Kassardjian CD, Amato AA, Boon AJ, Childers MK, Klein CJ, Committee APP. The utility of genetic testing in neuromuscular disease: A consensus statement from the AANEM on the clinical utility of genetic testing in diagnosis of neuromuscular disease. Muscle Nerve 2016;54(6):1007-9.

Krahn M, Biancalana V, Cerino M, Perrin A, Michel-Calemard L, Nectoux J, et al. A National French consensus on gene lists for the diagnosis of myopathies using next-generation sequencing. Eur J Hum Genet 2019;27(3):349-52.

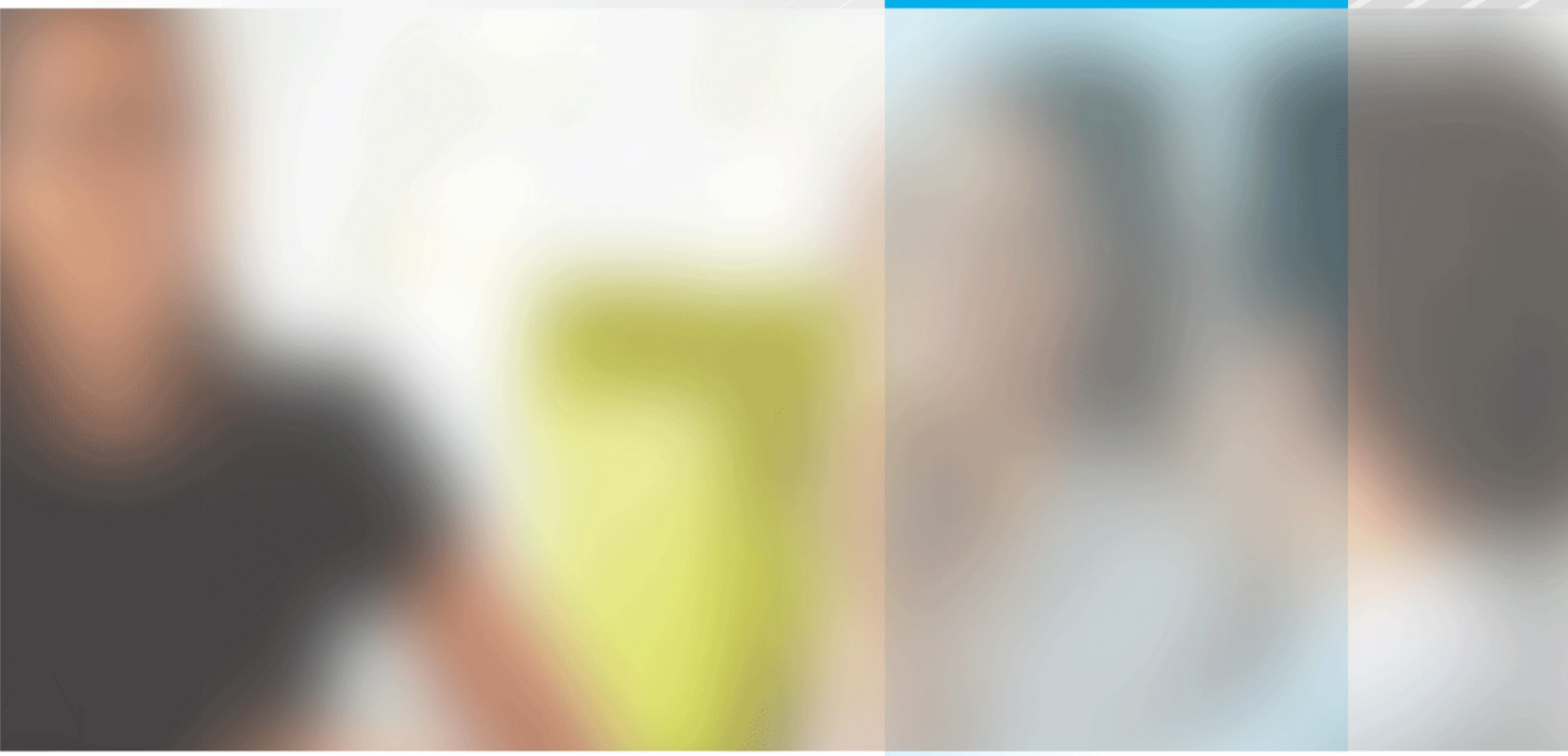
Medical Services Advisory Committee (MSAC). 1585 - Genetic testing for the diagnosis of early-onset or familial neuromuscular disorders [site Web]. Canberra, Australie : Australian Government, Department of Health; 2021. Disponible à : http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1585-public (consulté le 4 août 2021).

North KN, Wang CH, Clarke N, Jungbluth H, Vainzof M, Dowling JJ, et al. Approach to the diagnosis of congenital myopathies. Neuromuscul Disord 2014;24(2):97-116.

Schofield D, Alam K, Douglas L, Shrestha R, MacArthur DG, Davis M, et al. Cost-effectiveness of massively parallel sequencing for diagnosis of paediatric muscle diseases. NPJ Genom Med 2017;2:4.

Thuriot F, Gravel E, Buote C, Doyon M, Lapointe E, Marcoux L, et al. Molecular diagnosis of muscular diseases in outpatient clinics: A Canadian perspective. Neurol Genet 2020;6(2):e408.

Winder TL, Tan CA, Klemm S, White H, Westbrook JM, Wang JZ, et al. Clinical utility of multigene analysis in over 25,000 patients with neuromuscular disorders. Neurol Genet 2020;6(2):e412.



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