INESSS
LE SAVOIR PREND FORME

FÉVRIER 2022

ÉTAT DES CONNAISSANCES

Panel de la sclérose latérale amyotrophique avec ou sans démence frontotemporale par SNG

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 *Panel de la sclérose latérale amyotrophique avec ou sans démence frontotemporale par SNG*. 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 *Panel de la sclérose latérale amyotrophique avec ou sans démence frontotemporale par SNG* 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 basé 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 de la sclérose latérale amyotrophique (SLA) avec ou sans démence frontotemporale (DFT)?
2) Est-il économiquement pertinent d'utiliser un panel de gènes et une approche par SNG pour effectuer le diagnostic de la SLA/DFT?
3) Quel serait l'impact budgétaire potentiellement associé au rapatriement des analyses moléculaires pour le diagnostic de la SLA/DFT comparativement aux envois extérieurs?
4) Quels sont les enjeux cliniques, économiques, organisationnels, éthiques, sociaux et juridiques 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 pratique clinique et les revues systématiques avec ou sans méta-analyse. Les documents ont été sélectionnées par le professionnel scientifique responsable de l'évaluation en fonction des critères PICOTS [Population; Intervention; Comparateur; Résultat d'intérêt (de l'anglais *Outcome*); Temporalité; Milieu d'intervention (de l'anglais *Setting*)] préalablement établis.

La sélection des publications (Annexe D) et l'extraction de l'information pertinente (Annexe E) ont été réalisées par le professionnel responsable de l'évaluation.

Collecte des données contextuelles et des savoirs expérientiels

Des experts ont été consultés afin de recueillir l'information pertinente à l'évaluation. Le recrutement 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 6).

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 – Méthodologies 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.

ANNEXE B

Stratégie 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	Amyotrophic Lateral Sclerosis/di,ge
14	(als dementia OR amyotrophic lateral sclerosis OR charcot disease OR gehrig disease OR gehrigs disease OR gehrig's disease OR guam disease OR lou-gehrig disease OR lou-gehrig's disease OR lou-gehrigs disease).ti,ab
15	13 OR 14
16	ex Frontotemporal Dementia/di,ge
17	(disinhibition-dementia-parkinsonism-amyotrophy OR familial pick disease* OR familial picks disease* OR familial pick's disease* OR frontal dementia* OR frontotemporal dementia* OR frontotemporal lobar degeneration OR frontotemporal lobe dementia* OR hereditary dysphasic disinhibition dementia OR multiple system tauopathy OR pick complex OR pick's complex OR semantic dementia* OR ubiquitin-positive frontotemporal dementia* OR wilhelmsen-lynch disease*).ti,ab
18	16 OR 17
19	15 OR 18
20	12 AND 19
21	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
22	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
23	21 OR 22

24	20 AND 23
25	(Case Reports OR Comment OR Editorial OR Letter).pt OR (case report* OR comment* OR reply OR replies OR editorial* OR letter*).ti
26	24 NOT 25
27	Animals/ NOT (Humans/ AND Animals/)
28	26 NOT 27

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	Amyotrophic Lateral Sclerosis/di
14	(als dementia OR amyotrophic lateral sclerosis OR charcot disease OR gehrig disease OR gehrigs disease OR gehrig's disease OR guam disease OR lou-gehrig disease OR lou-gehrig's disease OR lou-gehrigs disease).ti,ab
15	13 OR 14
16	exp Frontotemporal Dementia/di
17	(disinhibition-dementia-parkinsonism-amyotrophy OR familial pick disease* OR familial picks disease* OR familial pick's disease* OR frontal dementia* OR frontotemporal dementia* OR frontotemporal lobar degeneration OR frontotemporal lobe dementia* OR hereditary dysphasic disinhibition dementia OR multiple system tauopathy OR pick complex OR pick's complex OR semantic dementia* OR ubiquitin-positive frontotemporal dementia* OR wilhelmsen-lynch disease*).ti,ab
18	16 OR 17
19	15 OR 18
20	12 AND 19
21	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
22	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

23	21 OR 22
24	20 AND 23
25	Case Report/ OR Editorial/ OR Letter/ OR (case report* OR comment* OR reply OR replies OR editorial* OR letter*).ti
26	24 NOT 25
27	Conference Abstract.pt
28	26 NOT 27
29	Nonhuman/ NOT (Human/ AND Nonhuman/)
30	28 NOT 29

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	(als dementia OR amyotrophic lateral sclerosis OR charcot disease OR gehrig disease OR gehrigs disease OR gehrig's disease OR guam disease OR lou-gehrig disease OR lou-gehrig's disease OR lou-gehrigs disease).ti,ab
8	(disinhibition-dementia-parkinsonism-amyotrophy OR familial pick disease* OR familial picks disease* OR familial pick's disease* OR frontal dementia* OR frontotemporal dementia* OR frontotemporal lobar degeneration OR frontotemporal lobe dementia* OR hereditary dysphasic disinhibition dementia OR multiple system tauopathy OR pick complex OR pick's complex OR semantic dementia* OR ubiquitin-positive frontotemporal dementia* OR wilhelmsen-lynch disease*).ti,ab
9	7 OR 8
10	6 AND 9

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	Amyotrophic Lateral Sclerosis/di,ge
14	(als dementia OR amyotrophic lateral sclerosis OR charcot disease OR gehrig disease OR gehrigs disease OR gehrig's disease OR guam disease OR lou-gehrig disease OR lou-gehrig's disease OR lou-gehrigs disease).ti,ab
15	13 OR 14
16	exp Frontotemporal Dementia/di,ge
17	(disinhibition-dementia-parkinsonism-amyotrophy OR familial pick disease* OR familial picks disease* OR familial pick's disease* OR frontal dementia* OR frontotemporal dementia* OR frontotemporal lobar degeneration OR frontotemporal lobe dementia* OR hereditary dysphasic disinhibition dementia OR multiple system tauopathy OR pick complex OR pick's complex OR semantic dementia* OR ubiquitin-positive frontotemporal dementia* OR wilhelmsen-lynch disease*).ti,ab
18	16 OR 17
19	15 OR 18
20	12 AND 19
21	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/
22	(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
23	21 OR 22
24	20 AND 23
25	(Case Reports OR Comment OR Editorial OR Letter).pt OR (case report* OR comment* OR reply OR replies OR editorial* OR letter*).ti
26	24 NOT 25

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	Amyotrophic Lateral Sclerosis/di
14	(als dementia OR amyotrophic lateral sclerosis OR charcot disease OR gehrig disease OR gehrigs disease OR gehrig's disease OR guam disease OR lou-gehrig disease OR lou-gehrig's disease OR lou-gehrigs disease).ti,ab
15	13 OR 14
16	exp Frontotemporal Dementia/di
17	(disinhibition-dementia-parkinsonism-amyotrophy OR familial pick disease* OR familial picks disease* OR familial pick's disease* OR frontal dementia* OR frontotemporal dementia* OR frontotemporal lobar degeneration OR frontotemporal lobe dementia* OR hereditary dysphasic disinhibition dementia OR multiple system tauopathy OR pick complex OR pick's complex OR semantic dementia* OR ubiquitin-positive frontotemporal dementia* OR wilhelmsen-lynch disease*).ti,ab
18	16 OR 17
19	15 OR 18
20	12 AND 19
21	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/
22	(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
23	21 OR 22
24	20 AND 23
25	Case Report/ OR Editorial/ OR Letter/ OR (case report* OR comment* OR reply OR replies OR editorial* OR letter*).ti
26	24 NOT 25
27	Conference Abstract.pt
28	26 NOT 27

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	(als dementia OR amyotrophic lateral sclerosis OR charcot disease OR gehrig disease OR gehrigs disease OR gehrig's disease OR guam disease OR lou-gehrig disease OR lou-gehrig's disease OR lou-gehrigs disease).ti,ab
8	(disinhibition-dementia-parkinsonism-amyotrophy OR familial pick disease* OR familial picks disease* OR familial pick's disease* OR frontal dementia* OR frontotemporal dementia* OR frontotemporal lobar degeneration OR frontotemporal lobe dementia* OR hereditary dysphasic disinhibition dementia OR multiple system tauopathy OR pick complex OR pick's complex OR semantic dementia* OR ubiquitin-positive frontotemporal dementia* OR wilhelmsen-lynch disease*).ti,ab
9	7 OR 8
10	6 AND 9
11	(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
12	10 AND 11

ANNEXE C

Recherche de la littérature grise

Date de consultation :

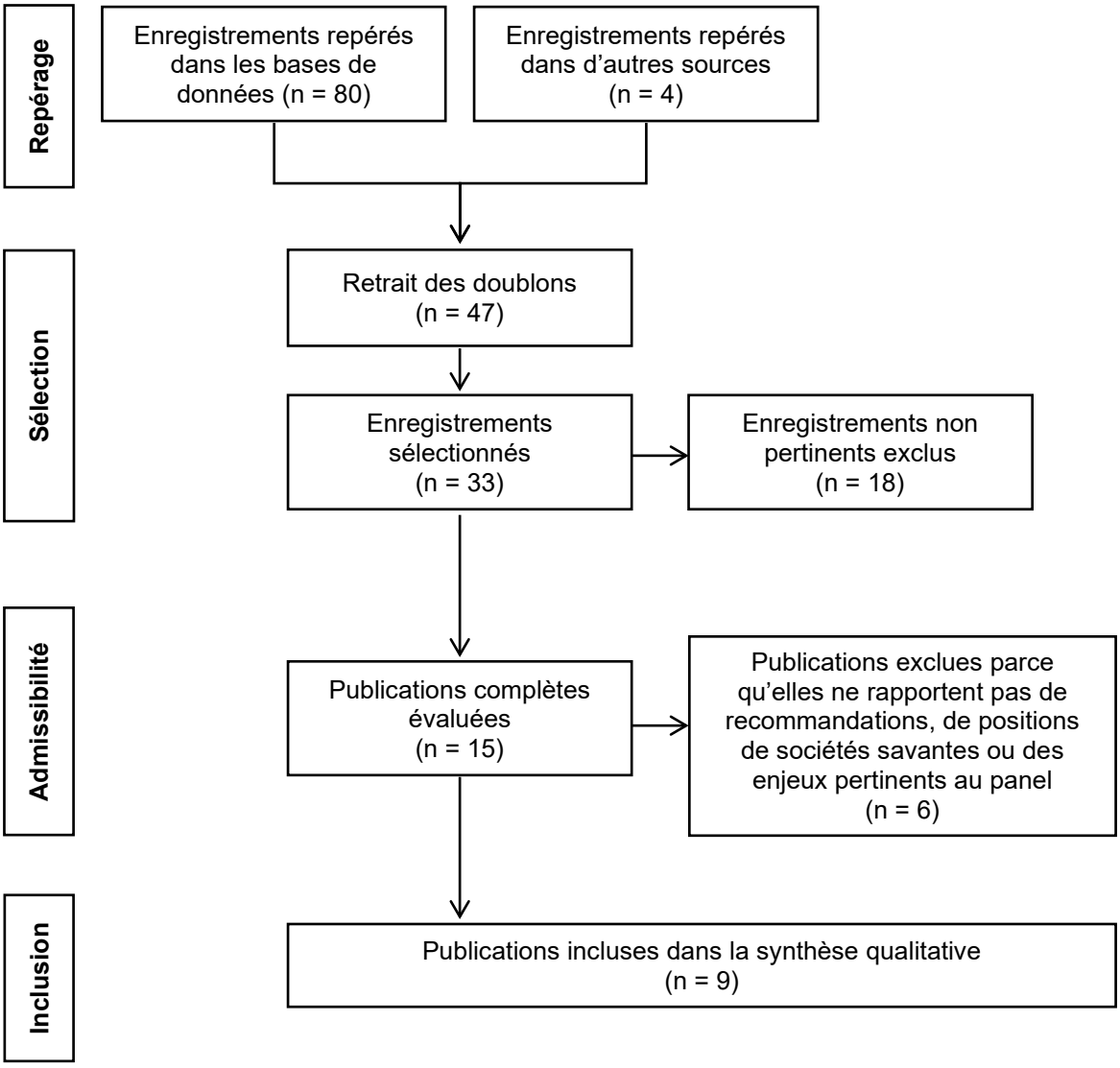
Liste de contrôle pour la recherche de la littérature grise **Sujet : Panels multigéniques de la sclérose amyotrophique avec ou sans démence frontotemporale** **Date de consultation : 10/12/2020, 14/12/2020, 21/12/2020, 22/12/2020, 17/03/2021**
Évaluation des technologies de santé – Guides de pratique
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 (Agence canadienne des médicaments et des technologies de la santé/Canadian Agency for Drugs and Technologies in Health) www.cadth.ca/fr
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
HTA Unit (Health Technology Assessment Unit - University of Calgary) https://vortal.htai.org/
G-I-N (Guidelines International Network) https://guidelines.ebmportal.com/
AHRQ (Agency for Healthcare Research and Quality) www.ahrq.gov
US Preventive Services Task Force www.uspreventiveservicestaskforce.org/uspstf/
NHS (National Health Service) www.nhs.uk/pages/home.aspx
SIGN (Scottish Intercollegiate Guidelines Network) www.sign.ac.uk
HIS (Healthcare Improvement Scotland, Royaume-Uni) www.healthcareimprovementscotland.org
NIHR HTA programme (National Institute for Health Research, Health Technology Assessment programme) www.nihr.ac.uk
CRD (Centre for Reviews and Dissemination) www.york.ac.uk/crd/
CEDIT (Comité d'Évaluation et de Diffusion des Innovations Technologiques, France) http://cedit.aphp.fr
Infobanque AMC (Association médicale canadienne) www.cma.ca
CMQ (Collège des médecins du Québec) www.cmq.org
CFHI (Canadian Foundation for Healthcare Improvement) www.cfhi-fcass.ca
HQO (Health Quality Ontario) www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment
ICES (Institute for Clinical Evaluative Sciences, Canada) www.ices.on.ca/Publications
OAML (Ontario Association of Medical Laboratories) www.oaml.com
AHS (Alberta Health Services) www.albertahealthservices.ca

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
FIMEA (Finnish Medicines Agency) https://www.fimea.fi/web/en/frontpage
KCE (Centre fédéral d'expertise des soins de santé, Belgique) https://kce.fgov.be/fr
ZiN (Zorginstituut Nederland) https://english.zorginstituutnederland.nl
IQWiG (Institute for Quality and Efficiency in Health Care, Allemagne) https://www.iqwig.de/en/home.2724.html
AIHTA (Austrian Institute for Health Technology Assessment, Autriche) https://aihta.at/page/homepage/en
HIQA (Health Information and Quality Authority, Irlande) https://www.hiqa.ie/
MSAC (Medical Services Advisory Committee) www.msac.gov.au
HTRG (Health Technology Reference Group, Australie) www.coaghealthcouncil.gov.au/Health-Chief-Executives-Forum/Health-Technology-Reference-Group
Pertinence des analyses biomédicales
Choosing Wisely Canada https://choosingwiselycanada.org/
Choosing Wisely www.choosingwisely.org/
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
NSGC (National Society of Genetic Counselors) www.nsgc.org
ANPGM (Association nationale des praticiens de génétique moléculaire) https://anpgm.fr/
Neurologie
EAN (European Academy of Neurology) www.ean.org/
EFNS (European Federation of the Neurological Societies) www.ean.org/
NIA (National Institute on Aging) www.nia.nih.gov/
Dementia Australia www.dementia.org.au/
Bases de données
Trip Database www.tripdatabase.com/
International HTA Database https://database.inahta.org

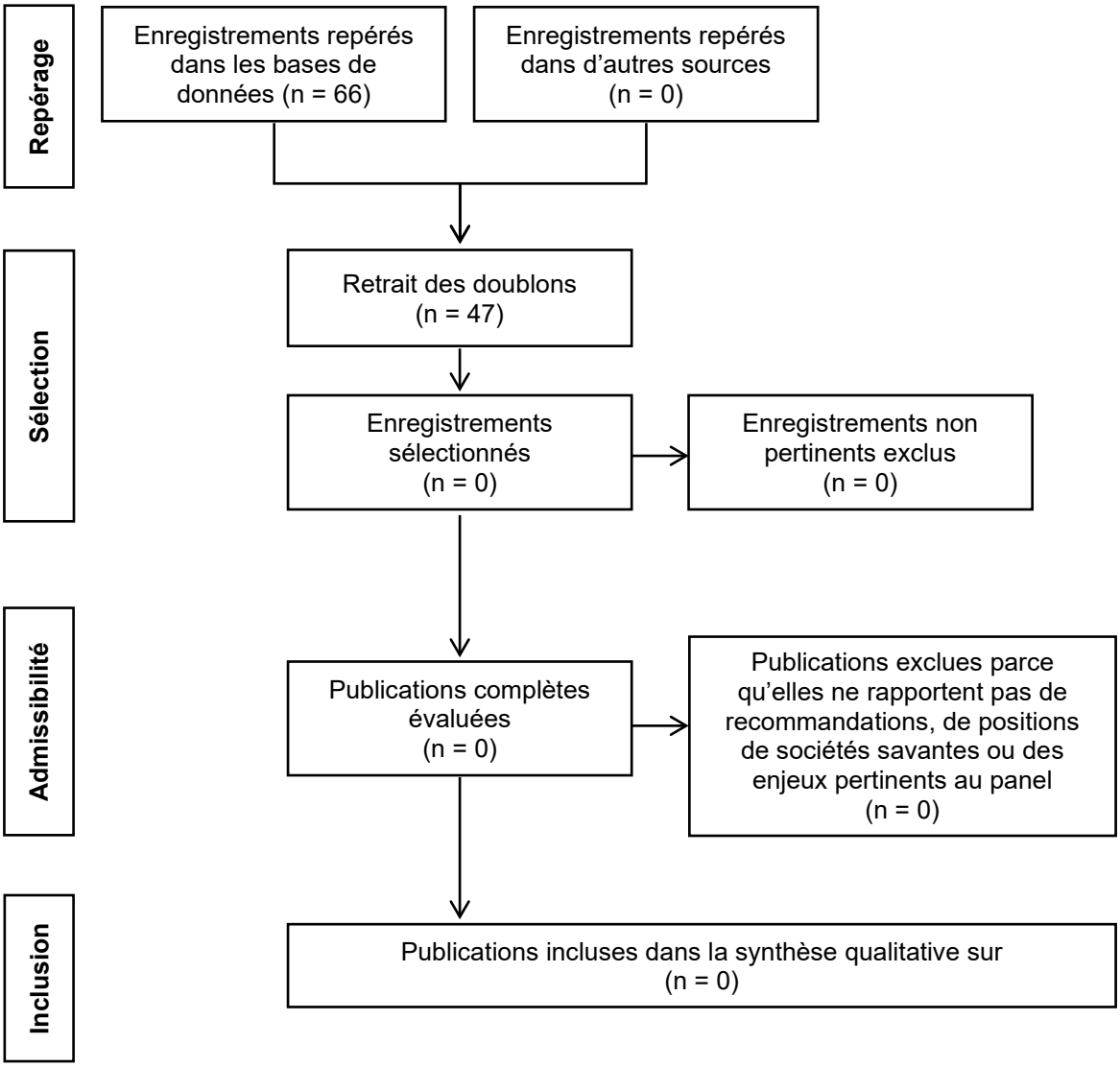
ANNEXE D

Diagrammes de flux de la sélection des publications

Volet clinique



Volet économique



ANNEXE E

Données extraites des documents sélectionnés

Tableau E-1 Données et informations extraites des études et rapports de synthèse retenues concernant l'utilité clinique

AUTEURS, ANNÉE TYPE DE DOCUMENT	DONNÉES ET INFORMATIONS EXTRAITES / NOTES DE LECTURE
Pecoraro *et al.*, 2020 Revue systématique	***The NGS technology for the identification of genes associated with the ALS. A systematic review*** ➢ *Background*: More than 30 causative genes have been identified in familial and sporadic amyotrophic lateral sclerosis (ALS). Despite documented advantages of NGS, its diagnostic reliability needs to be addressed in order to use this technology for specific routine diagnosis. ➢ *Objectifs* : a) conduct a structured systematic review of studies using the NGS to identify ALS-associated genes; b) assess the clinical and analytical validity of NGS technology to identify ALS-associated genes; c) evaluate the current literature to highlight the usefulness of NGS in the management of ALS patients. ➢ *Conclusion* : NGS seems to be a promising tool for the diagnosis of ALS in routine clinical practice. Its advantages are represented by an increased speed and a lowest sequencing cost, but patients' counselling could be problematic due to the discovery of frequent variants of unknown significance. ▪ Amyotrophic lateral sclerosis (ALS) is a progressive and devastating neurodegenerative disorder characterized by degeneration of motor neurons in the brain and spinal cord. It causes muscle weakness, disability and eventually death, with a median survival of three to five years. ▪ The annual incidence rates for ALS are 2-3 per 100 000 person-years in European and US populations, while prevalence rates range between 3 and 10 per 100 000. ▪ The lifetime risk is 1 in 300 for men and 1 in 400 for women with disease burden increasing with age. ▪ Most cases (90%) are classified as sporadic ALS (SALS), as they are not associated with a documented family history for the disease, while around 10% of cases are considered to be familial in nature (FALS). These familial cases of FALS are most commonly inherited with a Mendelian dominant pattern of disease within complete penetrance, although families with recessive and X-linked dominant inheritance have been reported. ▪ ALS and frontotemporal dementia (FTD): evidence from clinical, pathological and genetic studies has emphasized the multisystem nature of these diseases with overlapping symptoms and causes. ▪ Approximately 10%-15% of FTD patients display features of motor neuron disease, whereas half of ALS cases show cognitive and behavioural impairment *Evaluation of the clinical utility* ▪ In 13 studies,35-47 NGS allowed to identify already known mutations in 21 genes, and new or rare variants in 27 genes. ▪ Identified variants were nonsense or missense mutations leading to a frameshift mutation resulting in a truncated protein and a loss of protein function.

AUTEURS, ANNÉE TYPE DE DOCUMENT	DONNÉES ET INFORMATIONS EXTRAITES / NOTES DE LECTURE
	Discussion ▪ The NGS technology has brought to the detection of an over-growing number of variants of unknown significance, making genetic counselling and patients' management more complicated with further studies needed to verify genes role in ALS pathogenesis. ▪ In the worldwide, the origin of difference in ALS incidence is a matter of debate. Older age, male sex, family history of ALS have all been established as risk factors, but also environmental risk factors (such as exposure to heavy metals, pesticides, head trauma, electromagnetic field, high BMI and nutritional state, BMAA and even physical activity) and genetic factors (more than 20 different genes have been implicated in FALS and SALS, like SOD1, TARDBP, FUS, OPTN, VCP, UBQLN2, c9orf72, TBK1) contributing to the onset of the disease. ▪ The hexanucleotide repeat expansion (GGGGCC) in the first intron of the long gene c9orf72 is involved in the pathogenic mechanism of FALS, to a lesser extent of SALS, and frontotemporal dementia. ▪ The c9orf72 repeat expansion accounts for a significant percentage of familial and sporadic ALS in Caucasian populations but is rare in Asian cohorts. ▪ The most common genetic mutation in Caucasian population is c9orf72, accounting more than 40% of FALS (familial ALS) and 5%-20% of SALS (sporadic ALS), with particular high prevalence in Finland. In Asian population, this mutation occurs less frequently. The prevalence of c9orf72 in ALS cases is much lower in East (less than 4% in Japan) and South Asia (5.9% among FALS and 1.6% among SALS in Iran). ▪ In clinical practice, genetic testing is focused either on the research of mutations of SOD1, TARDBP, FUS genes or to establish the presence of a hexanucleotide repeat expansion in the c9orf72 gene. *Enjeux* ▪ Taken together, the potential to detect high number of mutations/variants without complete understanding of their pathological significance, the increasing information about the complexity of ALS genetics and the growing number of genetic test requests especially among at-risk subjects (relatives of an ALS patients), require a multidisciplinary team, including a neurologist, a geneticist and a genetic counsellor, with expertise in the field to give adequate information and support to the patient and his/her family, in an effort to translate the knowledge of ALS genetic architecture into clinically useful information. ▪ In fact, ALS heritability is characterized by oligogenic inheritance (a single mutation is likely not to be sufficient to cause disease despite significantly increasing risk), allelic heterogeneity, pleiotropy (especially for C9orf72, ATXN2, TBK1, FUS, C21orf2, NEK1, MATR3, CHCHD10, VCP, hn-RNPA1 and hnRNPA2B1) and age-dependent penetrance that make difficult the counselling of patients with genetic risk variants and their family members. ▪ On the other hand, if offering genetic testing to FALS patients is largely accepted by the clinical and scientific community, recent recommendations have suggested that genetic counselling should be offered routinely to all ALS patients. ▪ More debated is the approach to predictive testing, but the possibility of future drug therapy trials for at-risk mutation carriers should be taken into account. ▪ Moreover, genetic testing may directly benefit those undergoing it by empowering and helping them in life decisions, and lifestyle, health and procreation choices. ▪ Additionally, many individuals consider the anxiety of living with the unknown as worse than knowing whether or not to be at genetic risk. ▪ The main problem remains the interpretation of the results that derive from NGS, especially the evaluation of the possible pathogenicity of novel or rare variants that this technology allows to detect.
Zou *et al.*, 2017 Revue systématique avec méta-analyses	***Genetic epidemiology of amyotrophic lateral sclerosis: A systematic review and meta-analysis*** **Objectif :** to determine the mutation frequencies of the major ALS-related genes (C9orf72, SOD1, TARDBP and FUS) **Résultats** (111 études incluses dans la méta-analyse) **:**

AUTEURS, ANNÉE TYPE DE DOCUMENT	DONNÉES ET INFORMATIONS EXTRAITES / NOTES DE LECTURE
	Overall pooled mutation frequencies of these major ALS-related genes were 47.7% in familial amyotrophic lateral sclerosis (FALS) and 5.2% in sporadic ALS (SALS). A significant difference was identified regarding the frequencies of mutations in major ALS genes between European and Asian patients. Mutations les plus fréquentes dans les populations européennes : ▪ C9orf72 repeat expansions : FALS 33.7%, SALS 5.1% ▪ SOD1 : FALS 14.8%, SALS 1.2% ▪ TARDBP : FALS 4.2%, SALS 0.8% ▪ FUS : FALS 2.8%, SALS 0.3%) Mutations les plus fréquentes dans la population asiatique : ▪ SOD1 : FALS 30.0%, SALS 1.5% ▪ FUS :FALS 6.4%, SALS 0.9% ▪ C9orf72 : FALS 2.3%, SALS 0.3% ▪ TARDBP : FALS 1.5%, SALS 0.2% **Conclusions des auteurs** These findings demonstrated that the genetic architecture of ALS in Asian populations is distinct from that in European populations, which need to be given appropriate consideration when performing genetic testing of patients with ALS.
Klepek *et al.*, 2019 Étude qualitative (sondage : perspective des patients et cliniciens)	***Lack of consensus in ALS genetic testing practices and divergent views between ALS clinicians and patients*** ➢ *Objectifs* : o With the goal of characterising clinician practices, perceived challenges, and attitudes towards ALS genetic testing, we surveyed NEALS Consortium. o In addition, we compared clinician attitudes towards genetic testing to attitudes of persons with ALS. ➢ *Method :* o The survey was emailed to 255 members of the NEALS; 80 responded (participant response rate = 31.4%). o Data from a 9-item Likert scale assessing clinician attitudes towards ALS genetic testing found that respondents overall had positive perceptions of genetic testing and its value for ALS patients, families, research, and clinicians. ➢ *Conclusion :* Clinicians valued the scientific potential of testing, but were less likely to say they would have testing themselves, or to see the value in testing for family members. People with ALS were more likely to see value of testing for themselves and for family members, and less likely to strongly value the scientific potential of testing. *Discussion* ▪ Results from this survey support findings of previous studies indicating that a growing proportion of clinicians are offering ALS genetic testing in their practices. ▪ Clinicians who worked in a clinic also staffed by a genetic counsellor were not more likely to offer testing to patients with sALS. ▪ Clinicians valued the scientific and research potential of genetic testing, but were less likely to say they would have testing themselves, or to see the value in testing for family members. People with ALS were more likely to see the value of genetic testing for themselves and for family members, and less likely to strongly value the scientific potential of testing. ▪ Clinicians should be aware that their own attitudes and motivations might be different than those of their patients, as this can influence the way in which genetic testing is introduced and discussed. ▪ In addition to the complexities surrounding the offer of testing, challenges also exist with clinician interpretation of ALS genetic test results. Evidence suggests that many neurologists have a need for support in understanding genetic testing results

AUTEURS, ANNÉE TYPE DE DOCUMENT	DONNÉES ET INFORMATIONS EXTRAITES / NOTES DE LECTURE
	Conclusion Most academic ALS clinicians offer genetic testing in their clinics; however, there are ongoing inconsistencies in practice that have significant implications for the care of the 'typical' ALS patient. Both ALS clinicians and persons with ALS perceive genetic testing positively.
Roggenbuck et Fong, 2020 Revue narrative	***Genetic testing for amyotrophic lateral sclerosis and frontotemporal dementia: Impact on clinical management*** ▪ C9orf72 is the most common known genetic cause of ALS, FTD, and ALS-FTD in persons of European descent. ▪ Most pathogenic variants in ALS and FTD genes are dominantly transmitted with variable and age-related penetrance. ▪ Symptoms, age of onset, and disease progression show significant intrafamilial and interfamilial variability. ▪ Genetic cause is more likely to be identified in patients with familial disease, but can also be found in sporadic cases. ▪ ALS and FTD are adult-onset neurodegenerative disorders that share important clinical and pathologic features. ALS is characterized by loss of upper and lower motor neurons, progressive paralysis, and death within an average of 2 to 5 years after symptom onset. ▪ FTD have overlapping features and are delineated by the behavior or language deficits that are the first persistent and predominant symptom in the course of illness. ▪ Approximately 10% of ALS cases and 40% of FTD cases are familial; a genetic cause may be identified in up to 70% of familial ALS cases and 10% of sporadic ALS cases, whereas a genetic cause may be identified in about 10% of familial FTD cases and 5% to 6% of sporadic FTD cases. ▪ More than 30 genes have been identified that are implicated in ALS, FTD, or both. ▪ The utility of genetic testing as part of clinical management is valued by patients. ▪ Evidence suggests that there is a growing consensus to offer genetic testing to patients with familial disease, but there is no consistent approach to the offer of testing to the typical patient, who has apparently sporadic disease. ▪ The testing approach outlined here may be most applicable to patients of European ancestry. The variable ethnogeographic incidence of specific pathogenic variants (eg, the C9orf72 expansion) may warrant population-specific testing approaches. For example, studies in Asian populations indicate that pathogenic variants in SOD1 and FUS are more frequent causes of ALS than C9orf72. ▪ Nonetheless, current understanding of the familial clustering and genetic basis of ALS and FTD is primarily derived from the study of Caucasian individuals and could reflect medical referral biases, differential access to health care, as well as sociocultural differences on what constitutes normal behavior in instances of possible FTD. ▪ Variants of uncertain significance (VUS) are frequently identified in multigene panel testing, including ALS and FTD panels. ▪ False positive or negative results could have profound implications for patients and family members. ▪ Genetic testing has the potential to empower persons and families affected by ALS and FTD. Many affected persons wish to know why they developed their condition, irrespective of their family history, and understanding the cause can bring a sense of accommodation and closure. ▪ A genetic diagnosis also has significant implications for family members, enabling specific risk assessment and providing the opportunity to undergo presymptomatic testing. ▪ At-risk individuals may wish to learn their genetic status to plan many aspects of their lives, including education, career, finances, insurance, disease surveillance, reproduction, and research participation. ▪ The limitations of genetic testing should be emphasized, including the following: (a) a negative result does not exclude a genetic basis or contribution to the condition; (b) the test may be uninformative if a variant of uncertain significance is identified; and (c) positive results do not uniformly allow prediction of penetrance or disease course.

AUTEURS, ANNÉE TYPE DE DOCUMENT	DONNÉES ET INFORMATIONS EXTRAITES / NOTES DE LECTURE
Crook *et al.*, 2017 Revue narrative	***Predictive genetic testing for amyotrophic lateral sclerosis and frontotemporal dementia: Genetic counselling considerations*** ➢ *Objectif :* We review the uptake of genetic counselling, predictive and reproductive testing, and the factors that impact the decision to undergo testing, for consideration in clinical practice. ➢ *Results* : Factors impacting the decision to undergo testing are complex due to the nature of these diseases, absence of available preventative medical treatment and variable age of onset in mutation carriers. ▪ Approximately 60–70% of FALS cases and 40–50% of familial FTD cases are explained by causal variants (mutations) in known ALS or FTD genes. ▪ Tableau 1 - Currently known causal genes in FTD, ALS and FTDALS *Predictive genetic counselling process* ▪ Effective genetic counselling providers are equipped with competences and skills that allow them to conduct the counselling process comprehensively and safely. ▪ In this process, the various medical, psychological, social, familial and reproductive factors that influence and impact pre-test decision-making are raised, with the aim to help individuals make an informed decision about genetic testing, while minimising adverse outcomes (such as possible psychological, ethics and legal implications). ▪ An evaluation of evidence for the gene variant's pathogenicity and efficacy of the testing methods employed are important aspects to consider in the genetic counselling process. ▪ ALS and FTD are similar as mostly adult-onset, neurodegenerative, and progressive diseases with no currently available effective therapies to stop or slow progression, that may result in a loss of the ability to communicate and care for oneself, change of personality, and can be a heavy burden on families due to increased care needs and premature death. ▪ It is possible that additional issues may arise in predictive testing for FTD/ALS genes because the causal mutations vary between families (genetic heterogeneity), ▪ The causal ALS/FTD mutations can display greater clinical heterogeneity with variable penetrance, age of onset, disease progression, phenotype and prognosis, and the possibility of oligogenic inheritance. ▪ Patients with newly diagnosed ALS may express a wish to die, have depression, cognitive or behavioural impairment at the new diagnosis stage, and therefore a psychiatric/psychological assessment could be useful for pre-symptomatic individuals, some of whom may already have sub-clinical symptoms ▪ Families with a known causal gene mutation may have access to reproductive options to prevent passing the mutation on to future children, and this is a key reason individuals have undergone predictive genetic testing previously. ▪ Options include choosing not to have children, use of a donor sperm, egg, or embryo via in vitro fertilisation (IVF), adoption prenatal diagnosis (PND, with subsequent termination of pregnancy should the gene mutation be identified) and pre-implantation genetic diagnosis (PGD, via IVF). Importantly, not all options are accessible everywhere due to differences in legislation, regulation, and technical infrastructure between countries, as well as personal, social, financial, or ethics reasons.
Siddique et Siddique, 2019 Revue narrative (GeneReviews)	***Amyotrophic lateral sclerosis overview. Synonym: Lou Gehrig Disease*** ▪ Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disease involving both the brain and spinal cord. ▪ The diagnosis of ALS requires characteristic clinical features and specific findings on electrodiagnostic testing, as well as exclusion of other health conditions with related manifestations (see Differential Diagnosis of ALS). The most commonly employed consensus criteria for its diagnosis are the revised Escorial criteria. ▪ ALS/FTD: evidence of progressive deterioration of behavior and/or cognition by observation or history AND the presence of three behavioral/cognitive symptoms from Raskovsky criteria (2011) OR the presence of at least two behavioral/cognitive symptoms together with loss of insight and/or psychotic symptoms OR the presence of language impairment meeting criteria for semantic dementia / semantic variant of primary progressive aphasia (PPA) or non fluent PPA.

AUTEURS, ANNÉE TYPE DE DOCUMENT	DONNÉES ET INFORMATIONS EXTRAITES / NOTES DE LECTURE
	▪ The gold standard for neuropsychological evaluation is a neuropsychological examination administered by a neuropsychologist that includes an interview and a series of standardized tests that assess intelligence, executive function (including planning, abstraction, and conceptualization), attention, memory, language, perception, sensorimotor functions, motivation, mood state and emotion, quality of life, and personality style. ▪ Genetic counseling for individuals with amyotrophic lateral sclerosis (ALS) and their families is reviewed for the following clinical contexts: o Genetic ALS. ALS resulting from a pathogenic variant in a known ALS gene regardless of family history (see Tables 2a and 2b) o ALS of unknown cause. The cause may be unknown because molecular genetic testing either has not been performed or did not identify a genetic cause (see Tables 2a and 2b). ALS of unknown cause can either be "familial" (i.e., occur in families with two or more close relatives with ALS) or can occur in a simplex case (i.e., a single occurrence in family). ▪ Genetic ALS can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. Determination of the mode of inheritance is based on family history and molecular genetic testing. ▪ In a family with an established diagnosis of ALS, it is appropriate to consider testing of symptomatic individuals regardless of age. **Related genetic counseling issues** ▪ Predictive testing (i.e., testing of asymptomatic at-risk individuals) : o Predictive testing for at-risk relatives is possible once the ALS-related pathogenic variant(s) have been identified in an affected family member. o Potential consequences of such testing (including, but not limited to, socioeconomic changes, the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing. ▪ Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals age <18 years): o For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause. o For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.
Olney *et al.*, 2017 Revue narrative	***Frontotemporal dementia*** ▪ The incidence of FTD is estimated to be 1.61 to 4.1 cases per one hundred thousand people annually. ▪ Frontotemporal dementia frequently has a strong genetic component contributing to its pathogenesis. Over half of FTD cases are sporadic, but up to 40% of cases have a family history of dementia, psychiatric disease or motor symptoms, with at least 10% of cases having an autosomal dominant pattern. ▪ Of the clinical syndromes, FTD-MND is the most heritable and svPPA is the least heritable. ▪ The three most common genes associated with FTD are C9ORF72, MAPT and GRN. Other less common genes associated with FTD include: VCP, CHMP2B, TARDBP, FUS, EXT2, TBK1 and SQSTM1. ▪ There are currently no FDA approved treatments for FTD, but off-label pharmacological and behavioral modification techniques can be used to manage symptoms in FTD.

AUTEURS, ANNÉE TYPE DE DOCUMENT	DONNÉES ET INFORMATIONS EXTRAITES / NOTES DE LECTURE
	▪ There are also important non-pharmacological therapies to treat FTD symptoms. FTD symptoms can improve with caregiver education about behavioral, environmental and physical techniques to minimize or redirect unwanted behaviors (Merrilees, 2007). Benefits from physical exercise have been shown to delay cognitive decline and should be recommended to all FTD patients that can safely tolerate it ▪ Although there are no FDA-approved treatments for FTD, this is a hopeful time for FTD treatments to come to fruition. There are currently active clinical trials targeting specific FTD mechanisms and pathology.

Tableau E-2 Positions ou orientations d'organisations d'intérêt relatives à l'utilisation du séquençage de nouvelle génération dans le diagnostic de la sclérose latérale amyotrophique avec ou sans démence frontotemporale

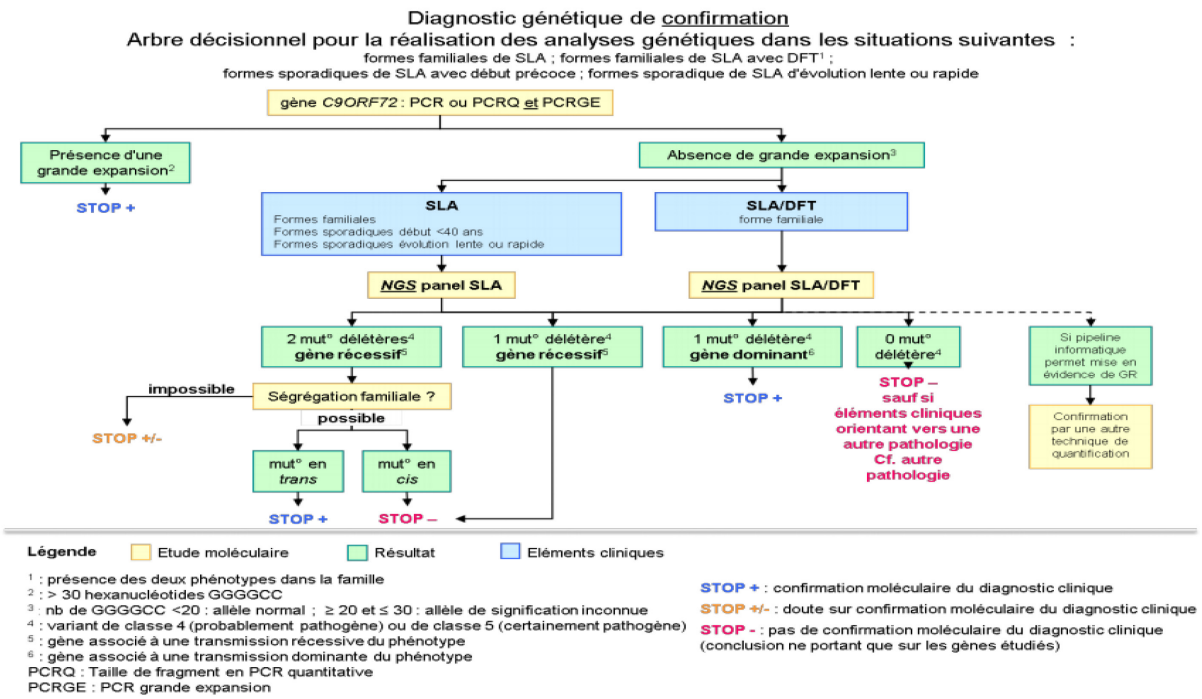
ORGANISATION [AUTEURS, ANNÉE] TYPE DE DOCUMENT	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
Association nationale des praticiens de génétique moléculaire – ANPGM France [ANPGM, 2018]	***Arbre décisionnel pour le diagnostic moléculaire de la sclérose latérale amyotrophique*** (Approuvé le 25 juin 2018) L'ANPGM a proposé des algorithmes décisionnels pour le diagnostic moléculaire de la SLA/DFT. Les groupes de clientèle visée par les analyses génétiques (dont l'analyse d'un gène ou des panels de gènes par SNG) sont : ▪ le proposant, soit le patient avec des formes familiales de SLA/DFT ou formes sporadiques d'évolution lente ou rapide ou sans particularité clinique; ▪ l'apparenté non atteint et majeur souhaitant connaître son statut (diagnostic pré-symptomatique); ▪ en contexte de diagnostic prénatal. La personne à risque de la maladie, notamment l'apparenté non atteint, doit être préparée à l'annonce d'un résultat qui peut bouleverser ses perspectives d'avenir. Cette préparation et la réflexion associée doivent se faire dans le cadre d'une consultation pluridisciplinaire (généticien, psychologue, psychiatre, assistante sociale) et suivant un plan de prise en charge. L'ANPGM présente les Corrélations génotype/phénotype des 27 principaux gènes responsables de SLA familiales, lesquels sont visées par les analyses moléculaires. **A. Proposant** 1. Recherche d'amplification de répétition par PCR ADN simplex fluorescente et analyse sur séquenceur automatique : o Etude du gène *C9ORF72* (2 PCR, voir chapitre V.A.) : **N354** + **N903** 2. Recherche de mutations ponctuelles par séquençage haut débit (NGS) : o Core panel SLA : **N351** o Core panel SLA/DFT : **N351** o Si plus de gènes étudiés, la cotation peut passer à : **N352** 3. Recherche de réarrangement de grande taille : a. Par séquençage haut débit (NGS) > 20 kb et < 100 kb : o Si le pipeline informatique le permet (même analyse que point VIII.A.2) o Pas de cotation supplémentaire b. Par recherche de réarrangements génomiques ciblés : o MLPA (ou autre technique de quantification) : **N318**

VI. Arbres décisionnels pour la prise en charge en diagnostic d'un échantillon, selon les différents contextes cliniques

A. Proposant

1. Formes familiales de SLA ; formes familiales de SLA/DFT* ; formes sporadiques de SLA avec début précoce ; formes sporadique de SLA d'évolution lente ou rapide

*présence de SLA et/ou DFT dans la famille



B. Apparenté non atteint

Selon le gène et la nature de la mutation :

- soit étude du gène *C9ORF72* : **N354** + **N903**
- soit recherche de mutation ponctuelle par séquençage Sanger : **N353**
- soit recherche de réarrangements génomiques ciblés : **N318**

C. Diagnostic prénatal

4083 quelle que soit la(les) techniques utilisées

4082 si contrôle des parents sur nouveau prélèvement à l'occasion du DPN

ORGANISATION [AUTEURS, ANNÉE] TYPE DE DOCUMENT	*TITRE DU DOCUMENT* (DATE DE PUBLICATION) RECOMMANDATIONS, POSITIONS ET AUTRES INFORMATIONS D'INTÉRÊT
Haute Autorité de Santé – HAS France [HAS, 2015]	***Protocole national de diagnostic et de soins (PNDS) pour la sclérose latérale amyotrophique (ALD9). Guide – Affection de longue durée*** (18 Novembre 2015) L'analyse génétique (type non précisé) devrait être réalisée sous les conditions suivantes : ▪ en présence d'une forme familiale (au moins deux cas familiaux dans la généalogie quel que soit le degré de la parenté) ou s'il existe un antécédent familial de démence, plus spécifiquement de démence fronto-temporale (même s'il s'agit du premier cas de SLA dans cette famille); ▪ l'analyse se fait dans un contexte de génétique clinique sans omettre d'expliquer au patient et à sa famille les implications de la découverte éventuelle d'une mutation (conseil génétique).
European Federation of Neurological Societies – EFNS [Sorbi *et al.*, 2012]	***EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia*** (24 Avril 2012) L'analyse génétique (type non précisé) peut être réalisée chez les adultes pré-symptomatiques lorsqu'il y a un antécédent familial clair et lorsqu'il y a une mutation connue chez un individu affecté afin d'assurer qu'un résultat négatif est cliniquement significatif. **Recommendations :** ▪ No studies have addressed the value of genetic counselling for patients with dementia or their families when autosomal-dominant disease is suspected. Because the genetics of dementing illnesses is a very young field, expertise in genetic counselling for the dementias of the elderly is likely to be found only in specialized dementia research centres. ▪ Pre-symptomatic testing may be performed in adults where there is a clear family history, and when there is a known mutation in an affected individual to ensure that a negative result is clinically significant. ▪ Genetic testing is indicated if the patient has a combination of characteristic clinical and neuroimaging features or a positive family history, particularly if there is no history of hypertension (class IV evidence). ▪ Genetic testing is more debatable if a patient without a family history has only migraine with aura and a few hypersignals on T2-weighted imaging (class IV evidence).

ANNEXE F

Conception du panel virtuel de 22 gènes – Rationnel de décision[1]

Sources consultées pour déterminer la pertinence clinique des gènes

La liste des gènes est basée sur :

- PanelApp[2] (*Green gene only*): *Amyotrophic lateral sclerosis/motor neuron disease, version 1.29* (34 gènes, dont 22 "*green*").
- Brown and Al-Chalabi. *Amyotrophic Lateral Sclerosis*. N Engl J Med 2017;377(2):162-172. [Brown et Al-Chalabi, 2017].

Par ailleurs, la liste a été bonifiée de certains gènes de la littérature (voir tableau F-1 pour les références spécifiques à chacun des gènes sélectionnés).

Protocole de sélection et de révision des gènes

Selon le demandeur, la liste des gènes a été établie par deux évaluateurs conformément, en grande partie, au document du RQDM intitulé *Niveau d'évidence minimal pour déterminer les gènes à inclure dans une analyse*. Les évaluateurs ont pris la décision de réviser plus en détails certains gènes classés « *Green* » selon PanelApp après avoir relevé certaines erreurs potentielles. En résumé, les évaluateurs ont procédé de la façon suivante :

1) Si PanelApp « *Green* » + Brown and Al-Chalabi rapportent des diagnostics pour le gène = acceptation avec un examen plus approfondi tenant compte des données supplémentaires relatives aux :
    a) preuves génétiques;
    b) preuves expérimentales; et
    c) toute preuve contraire aux points a) et b) précédemment mentionnés (c.-à-d., données contradictoires).
2) Autres cas PanelApp « *Green* » = révision supplémentaire de la littérature

Certains gènes ont été exclus :

- En cas d'échec des critères ci-dessus;
- Étaient rouges (*Red*) sur le PanelApp;
- Étaient verts (*Green*) sur la PanelApp mais ne disposaient pas : a) de preuves génétiques et/ou; b) de preuves expérimentales pour soutenir leur implication dans la SLA.

Liste des gènes sélectionnés

Au total, 37 gènes ont été considérés desquels 22 ont été inclus (tableau F-1) et 15 ont été exclus (tableau F-2) du panel virtuel pour le diagnostic moléculaire de la SLA/DFT. Ces gènes et les principales évidences associées sont présentés dans les tableaux suivants.

[1] Informations issues des documents de validation transmis à l'INESSS par le demandeur en date du 22 avril 2021.
[2] Genomics England PanelApp, disponible à : https://panelapp.genomicsengland.co.uk/.

Tableau F-1 Gènes inclus (n = 22) dans le panel virtuel de la SLA/DFT et principales évidences associées

Gène	Panel App[2]	Clin Gen[3]	Évidences génétiques (PMID)	Données expérimentales (PMID)	Étude(s) contradictoire(s) (PMID)	Any pathogenic variants in ClinVar?	gnomAD pLI	gnomAD missense constraint Z score	Comments
ALS2	Green	N/A	23881933	25474699		Yes	0	1,9	Important to report biallelic variants otherwise may get many het VUS
ANG	Green	N/A	28700839; 26255299; 20577002	25372031; 17886298	26753798; 25907842	Yes	0,29	0,08	Not a major cause of disease
CHMP2B	Green	N/A	20352044	s. o.	s. o.	Yes	0	0,34	Primarily a frontotemporal dementia (FTD) gene though can be mutated in cases of ALS and FTD
DCTN1	Green	N/A	25109764	26954557	s. o.	Yes	0,08	0,89	Primarily a distal hereditary motor neuropathy gene
DNAJC7	N/A	N/A	31768050; 33062890	31768050		No	0,99	2,51	Recent discovery in 2019; coding variants in patients with ALS
FIG4	Green	N/A	19118816	s. o.	s. o.	Yes	0	1,88	Primarily a Charcot-Marie-Tooth disease gene
FUS	Green	N/A	28700839; multiple papers	Multiple papers	s. o.	Yes	1	2,21	Can also be mutated in essential tremor
GRN	Red	N/A				Yes	0,07	0,28	Primarily an FTD gene though can be mutated in cases of ALS and
HNRNPA1	Green	N/A	23455423; 27694260	s. o.	23827524; 24119545; 24612671	Yes	1	2,82	Very rare, more evidence is needed; monoallelic mutations also cause a multisystem proteinopathy manifesting as as frontotemporal lobar degeneration and/or amyotrophic lateral sclerosis and/or Paget disease of bone, and/or inclusion body myositis
KIF5A	N/A	N/A	29566793; 29342275			Yes	1	3,6	N terminal associated with HSP; C terminal seems to harbour ALS mutations
MATR3	N/A	N/A	24686783			Yes	1	2,73	Overlaps with distal myopathy
OPTN	Green	N/A	20428114; 25943890; 31838784	25859013	s. o.	Yes	0	0,62	Variants may also cause glaucoma
PFN1	Green	N/A	22801503; 24309268	22801503	s. o.	Yes	0,73	1,95	A select few variants have a higher OR in ALS cases than controls; though still limited evidence for coding variants as causal of ALS; not always segregating with disease
SETX	Green	N/A	15106121; 21438761	s. o.	23129421	Yes	0,95	-0,11	Still limited evidence; primarily driven by frameshift; initially described in juvenile ALS; can cause autosomal recessive spinocerebellar ataxia
SOD1	Green	N/A	Many papers; well established gene	s. o.	s. o.	Yes	0,18	0,84	Well established ALS gene; primarily driven by missense variation
SQSTM1	N/A	N/A	23303844; 24042580			Yes	0	-0,94	Overlaps with FTD; neurodegeneration with ataxia, dystonia, and gaze palsy, childhood-onset; seems to be extremely rare
TARDBP	Green	N/A	18372902; 23881933; 22539580	19959528	s. o.	Yes	0,99	3,71	Overlaps with FTD; well established ALS gene; C terminus particularly mutated in ALS
TBK1	Green	N/A	25700176; 25803835; 26350399	25803835	s. o.	Yes	0,08	1,93	Overlaps with FTD
TUBA4A	N/A	N/A	25374358	25374358		Yes	0,16	3,3	Overlaps with FTD; very rare; evidence is still limited
UBQLN2	Green	N/A	21857683; 24771548	s. o.	s. o.	Yes	0,85	1,5	Overlaps with FTD
VAPB	Green	N/A	15372378	15372378	s. o.	Yes	0,58	1,25	Overlaps with late-onset SMA; very rare
VCP	Green	N/A	25457024; 23881933	25492614	25618255	Yes	1	5,41	Can overlap with FTD; CMT; Paget disease; very rare proportion of ALS

Abréviations : AD : transmission autosomique dominante; AR : transmission autosomique récessive; N/A : non applicable (ou non disponible); PMID : numéro d'identification de la publication sur PubMed (de l'anglais *PubMed Identifier).*

Tableau F-2 Gènes considérés sans être sélectionnés (n = 15) et principales raisons de l'exclusion

Gène	Panel App[2]	Clin Gen[3]	Évidences génétiques (PMID)	Données expérimentales (PMID)	Étude(s) contradictoire(s) (PMID)	Any pathogenic variants in ClinVar?	gnomAD pLI	gnomAD missense constraint Z score	Comments
C21orf2	N/A	N/A	27455348	s. o.	s. o.	No	0	-0,16	Identified via GWAS though insufficient evidence of coding variants in patients
CHCHD10	Red	N/A	s. o.	s. o.	s. o.	Yes	0	0,82	Insufficient evidence of disease association
DAO	N/A	N/A	s. o.	s. o.	s. o.	No	0	0,11	Insufficient evidence of coding variants in patients
ERBB4	Red	N/A	24119685	s. o.	s. o.	Yes	1	2,01	Insufficient/limited evidence that this is a ALS/MND gene
MOBP	N/A	N/A	27455348	s. o.	s. o.	No	0,55	0,97	Identified via GWAS though insufficient evidence of coding variants in patients
NEFH	Amber	N/A	s. o.	s. o.	s. o.	No	0	0,52	A select few pathogenic mutations in CMT; may modify disease
NEK1	N/A	N/A	27455347; 26945885	s. o.	s. o.	Yes/No	0	1,07	A very polymorphic gene; coding mutations are not necessarily causal of ALS
SCFD1	N/A	N/A	27455348; 29260601	s. o.	s. o.	No	1	2,05	Insufficient evidence of coding variants in patients
SIGMAR1	Green	N/A	21842496	s. o.	26088964; 22739338	Yes	0,17	1,46	Very limited evidence for now; also reported in distal hereditary motor neuropathy
SLC52A1	Red	N/A	s. o.	s. o.	s. o.	No	0	0,05	No pathogenic variants causing ALS; insufficient evidence of
SLC52A2	Green	N/A	s. o.	s. o.	s. o.	No	0	-0,85	No pathogenic variants causing ALS; insufficient evidence of
SLC52A3	Green	N/A	s. o.	s. o.	s. o.	No	0,02	1,25	No pathogenic variants causing ALS; insufficient evidence of
TAF15	N/A	N/A	s. o.	s. o.	s. o.	No	0,17	1,22	Insufficient evidence of coding variants in patients
UNC13A	Red	N/A	32627229	s. o.	s. o.	No	1	5,63	GWAS finding; coding variants not causative of ALS; associated SNPs modulating disease duration
VEGFA	Red	N/A	s. o.	s. o.	s. o.	No	0	0,47	No evidence of ALS association; may modify disease

Abréviations : AD : transmission autosomique dominante; AR : transmission autosomique récessive; N/A : non applicable (ou non disponible); PMID : numéro d'identification de la publication sur PubMed (de l'anglais *PubMed Identifier*).

ANNEXE G

Association entre les gènes et les phénotypes

Tableau G-1 Gènes les plus couramment impliqués dans la SLA et caractéristiques cliniques associées

Gene	% of:		MOI	Associated Phenotype(s)				Onset/Penetrance	Other Clinical Features / Comments
	ALS w/ family history	Simplex ALS		ALS	ALS/ FTD	FTD	Other		
C9orf72 (*C9orf72*-ALS/FTD)	39%-45%	3%-7%	AD	+	+	+	• PLS • PSP • Psychiatric symptoms • Parkinsonism • Chorea	• 50% are symptomatic by age 58 yrs. • ~100% by 80 yrs	Assoc w/bvFTD
SOD1 (OMIM 105400)	15%-20%	3%	AD AR	+				• 50% symptomatic by age 46 yrs [1] • 90% by 70 yrs	1 report of cognitive involvement (assoc w/Ile113Thr variant) [2]
FUS (OMIM 608030)	~4%-8%	Very rare	AD	+	+	+	Parkinsonism	• Earlier average onset than *SOD1*-ALS & *C9orf72*-ALS • 50%-70% symptomatic by age 51 • >90% by 71 yrs	• ALS occurs w/or w/out mild cognitive impairment. • 1/3 of affected individuals have bulbar onset. • More common in Asian cohorts
TARDBP (*TDP-43*) (*TARDBP*-ALS)	1%-4%	Yes	AD	+	+	+		Mean onset age 53.5 ±12 yrs	

Source : Tableau tiré de la revue publiée par Siddique et Siddique [2019].

Abréviations : AD = autosomal dominant; ALS = amyotrophic lateral sclerosis; AR = autosomal recessive; bvFTD = behavioral variant of FTD; FTD = frontotemporal dementia; LMN = lower motor neuron; MOI = mode of inheritance; PLS = primary lateral sclerosis; PSP = progressive supranuclear palsy; UMN = upper motor neuron.

Notes :

[1] *SOD1* variants other than p.Ala4Val may have a wide range of disease duration within the same family.

[2] Katz *et al.*, 2012.

Tableau G-2 Gènes moins couramment identifiés dans la SLA et caractéristiques cliniques associées

Gene [1]	MOI	Associated Phenotype(s)				Other Clinical Features / Comments
		ALS	ALS/ FTD	FTD	Other	
ALS2 (*ALS2*-ALS) [2]	AR	+			PLS	• ALS is UMN-predominant. • Onset from infancy to mid-childhood • Long course: bedridden by age 12-50 • Not observed in adult-onset ALS • Reported in both familial & simplex ALS
ANG (OMIM 611895)	? AD [3]	+		+	Parkinson disease	• Phenotype is primarily ALS (may present as FTD or parkinsonism). • To date, primarily limited to families of European ancestry [4] • Reported in both familial & simplex ALS
ANXA11 (OMIM 617839)	AD	+				Reported in both familial & simplex ALS
CFAP410 (*C21orf2*) [5]	AD [3]	+		+		Reported in both familial & simplex ALS
CHCHD10 (See *CHCHD10* Disorders.)	AD	+		+		• Cerebellar ataxia or myopathy • Reported in familial ALS only
CHMP2B (OMIM 614696)	AD	+		+		• ALS is more often LMN-predominant. • Reported in familial ALS only
DAO (OMIM 124050)	AD	+				Reported in familial ALS only
DCTN1 [6] (OMIM 601143)	AD [3]	+	+			Reported in familial ALS only
ERBB4 (OMIM 615515)	AD	+				Reported in both familial & simplex ALS
FIG4 [7] (OMIM 612577)	AD	+				• Normal NCVs; limited LMN involvement on EMG • Reported in both familial & simplex ALS
HNRNPA1 [8] (OMIM 615426)	AD [3]	+				Reported in both familial & simplex ALS
MATR3 (OMIM 606070)	AD	+	+		PLS	Reported in familial ALS only [9]
MOBP [10]	See footnote 3.	+				Reported in both familial & simplex ALS
NEK1 (OMIM 617892)	AD [3]	+				• ALS occurs w/or w/out cognitive impairment. • Reported in both familial & simplex ALS

Gene [1]	MOI	Associated Phenotype(s)				Other Clinical Features / Comments
		ALS	ALS/ FTD	FTD	Other	
OPTN [11] (OMIM 613435)	AR AD	+	+			• ALS is characterized by slow progression & extended duration. • Reported in both familial & simplex ALS
PFN1 (OMIM 614808)	AD	+				Features of Miller-Dieker syndrome noted in a few affected individuals
SCFD1 [10]	See footnote 3.	+				Reported in both familial & simplex ALS
SETX (OMIM 602433) [12]	AD	+				• 1st decade to adult onset; most commonly in adolescence (juvenile ALS) • Also referred to as distal hereditary motor neuropathy • No bulbar involvement • Reported in familial ALS only
SPG11 (*spatacsin*) [13] (OMIM 602099)	AR	+				• Juvenile ALS w/onset in 1st or 2nd decade; very slowly progressive • Multiple ethnicities; often consanguineous parents • Cognitive impairment not reported • Thin corpus callosum not reported • Reported in familial ALS only
SQSTM1 (OMIM 616437)	AD	+	+	+	Paget disease	• *SQSTM1* pathogenic variant has been identified in individuals w/*SOD1*-ALS, *FUS*-ALS, Lewy body dementia, & Alzheimer dementia. • Reported in both familial & simplex ALS (*SQSTM1* pathogenic variant identified in ≤4% of simplex ALS)
TAF15 [14]	See footnote 3.	+				Reported in familial ALS only
TBK1 (OMIM 616439)	AD	+	+			• ALS occurs w/or w/out mild cognitive impairment. • *TBK1* pathogenic variants identified in a few individuals w/*OPTN*-ALS & *FUS*-ALS. • Reported in both familial & simplex ALS
TUBA4A (OMIM 616208)	AD	+	+	+		Reported in both familial & simplex ALS
UBQLN2 (OMIM 300857)	XL	+	+	+	PLS; spastic paraparesis	• Onset from childhood to late adulthood • Reported in familial ALS only

Gene [1]	MOI	Associated Phenotype(s)				Other Clinical Features / Comments
		ALS	ALS/ FTD	FTD	Other	
UNC13A [14]	See footnote 3.	+				Reported in familial ALS only
VAPB [15, 16] (OMIM 608627)	AD	+				• ALS occurs w/or w/out postural tremor. • To date, reported primarily in Brazilians [16] & Japanese • Reported in familial ALS only
VCP [17] (OMIM 613954)	AD	+	+		Paget disease	• ALS occurs w/or w/o mild cognitive impairment. • Clinical course may be rapid. • May include parkinsonism • Reported in familial ALS only

Source : Tableau tiré de la revue publiée par Siddique et Siddique [2019].

Abréviations : AD = autosomal dominant; ALS = amyotrophic lateral sclerosis; AR = autosomal recessive; EMG = electromyography; FTD = frontotemporal dementia; LMN = lower motor neuron; MOI = mode of inheritance; NCV = nerve conduction velocity; PLS = primary lateral sclerosis; UMN = upper motor neuron; XLD = X-linked.

Notes :

[1] Genes are listed alphabetically.

[2] ALS2: long protein transcript results in primary lateral sclerosis, short transcript produces ALS.

[3] Susceptibility gene (i.e., a genetic variant that increases a person's predisposition for developing a given disorder)

[4] Ryan *et al*., 2019

[5] Chia *et al*., 2018

[6] DCTN1 allelic disorders: distal hereditary motor neuronopathy with vocal cord paresis and Perry syndrome

[7] FIG4 allelic disorder: Charcot-Marie Tooth (CMT) hereditary neuropathy

[8] HNRNPA1 allelic disorder: inclusion body myopathy with Paget disease of bone and/or frontotemporal dementia

[9] Amyotrophic lateral sclerosis 21 (formerly MPD2)

[10] Van Rheenen *et al.*, 2016

[11] OPTN allelic disorder: primary open angle glaucoma

[12] SETX allelic disorder: ataxia with oculomotor apraxia type 2

[13] SPG11 allelic disorders: spastic paraplegia 11 (with mild intellectual disability and thin corpus callosum) and CMT

[14] Brown et Al-Chalabi [2017]

[15] VAPB allelic disorder: adult-onset spinal muscular atrophy, Finkel type

[16] VAPB founder variant p.Pro56Ser identified identifiedidentified identified in individuals of Portuguese/Brazilian & African/Brazilian descent

[17] VCP allelic disorder: inclusion body myopathy, Paget disease, and frontotemporal dementia (IBMPFD)

ANNEXE H

Diagnostics différentiels de la sclérose latérale amyotrophique et gènes associés

Tableau H-1 Troubles monogéniques d'intérêt dans le diagnostic différentiel de la SLA

Gene [1]	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/ALS	Distinguishing from ALS
AR	Spinal and bulbar muscular atrophy	XL	LMN signs: weakness, atrophy, fasciculations	• No UMN involvement • Proximal weakness • Sensory involvement • Slowly progressive • Males only affected • May have gynecomastia, testicular atrophy, & ↓ fertility
BSCL2	*BSCL2*-related neurologic disorders [2]	AD	UMN & LMN involvement	• Slowly progressive • Abnormal vibration sense • *Pes cavus*
GBE1	Adult polyglucosan body disease	AR	UMN & LMN involvement, cognitive impairment	• Slowly progressive • Distal sensory loss • Early neurogenic bladder • Cerebellar dysfunction
HEXA	Chronic and adult-onset hexosaminidase A deficiency	AR	LMN > UMN involvement, possible cognitive impairment	• Spinocerebellar degeneration • Dystonia • Slowly progressive
SMN1	Spinal muscular atrophy IV	AR	Proximal > distal muscle weakness & atrophy	• Onset typically in 2nd-3rd decade • No UMN involvement • Symmetric weakness & atrophy

Source : Tableau tiré de la revue publiée par Siddique et Siddique [2019].

Abréviations : AD = autosomal dominant; AR = autosomal recessive; LMN = lower motor neuron; MOI = mode of inheritance; UMN = upper motor neuron; XL = X-linked

Notes :

[1] Genes are in alphabetic order.

[2] The spectrum of *BSCL2*-related neurologic disorders includes Silver syndrome and variants of Charcot-Marie-Tooth neuropathy type 2, distal hereditary motor neuropathy (dHMN) type V, and spastic paraplegia 17.

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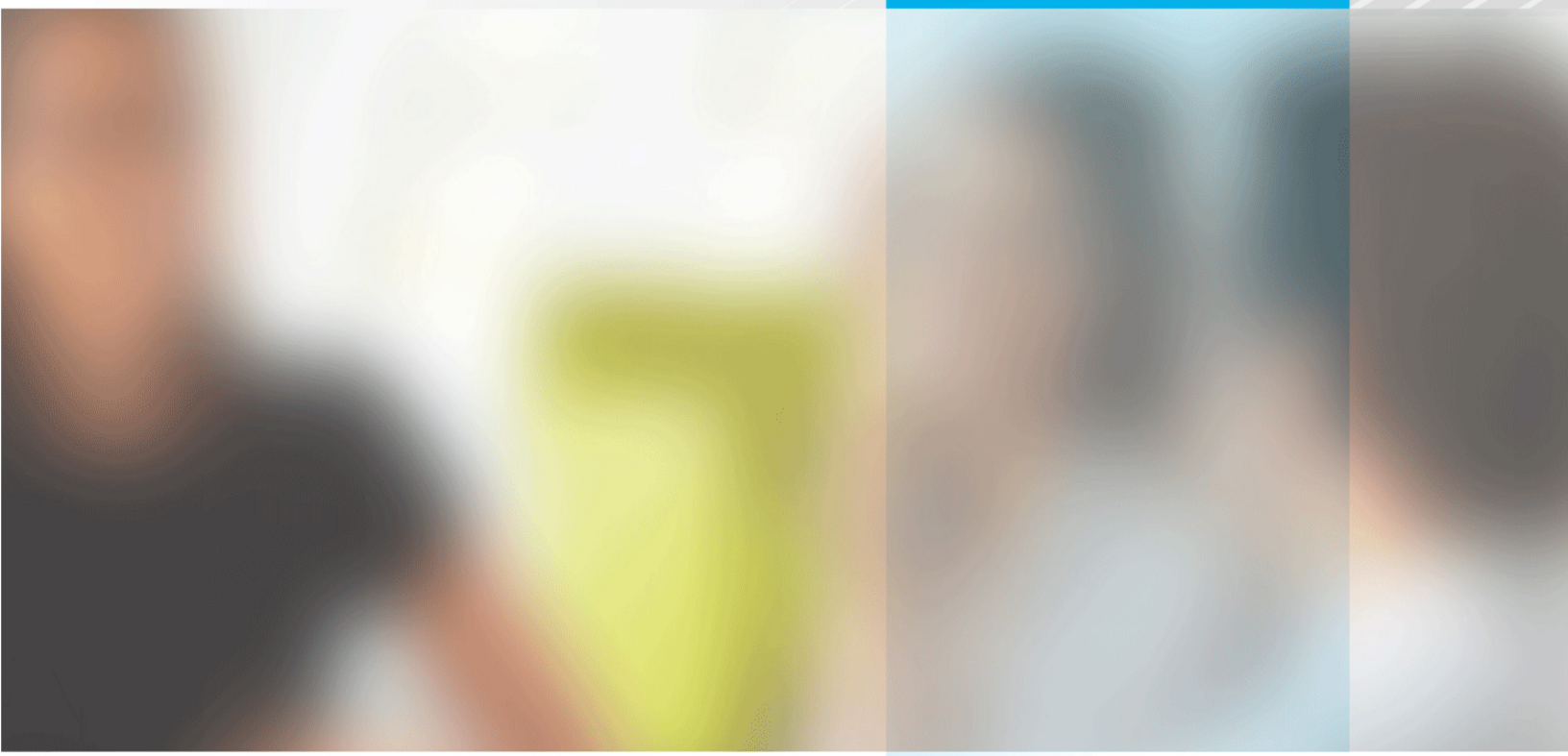

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