# Annexes

# Annexes

## Table des matières

## Annexe I. Questionnaires sur les données médicales (Chapitre II, 2)

- Age au diagnostic
  ……...
- Nombre de copies SMN2 :
  ……
- Age aux premiers symptômes :
  ……
- Évaluation motrice à la dernière visite (Chop Intend, Hammersmith ou MFM)
  ……
- Nombre d'hospitalisation due à la maladie (en dehors des injections / traitements):
  ……
- Nombre de jours d'hospitalisation par an (en dehors des traitements) :
  ……
- Dans quel service ? (soins intensifs , pédiatrie…)
  ……
- Age au début du traitement :
  ……
- Traitement utilisé :
  ……
- Capacité motrice :
  - □ Marche
  - □ Marche avec aide
  - □ Debout
  - □ Assis autonome
  - □ Assis avec aide
- Nombre de consultation Kinésithérapeute par semaine :
  - Kiné motrice : ……../semaine
  - Kiné respiratoire : ……/semaine
- Ventilation. Mon enfant a besoin de ventilation :
  - □ non
  - □ …. heures / jour
  - □ toute la nuit
  - □ Trachéotomie
  - □ Ventilation non invasive (Masque)
- Alimentation. Mon enfant a besoin d'aide pour s'alimenter :
  - □ Non

- Complément alimentaire
- Sonde gastrique
- Gastrostomie

# Annexe II. Questionnaires sur les données socio-économiques (Chapitre II, 2)

| | Age |
|---|---|
| Mère | |
| Père | |

| | Profession | Quantité de travail (50 % - 80 % -100 %...) |
|---|---|---|
| Mère | | |
| Père | | |

Avez-vous dû ajuster votre vie professionnelle par rapport à la maladie de votre enfant ? Diminution de l'activité pour plus de présence auprès de lui / augmentation de l'activité pour appoint financier :
……
……
……

Quantité de jours de travail perdus à cause de la maladie en dehors d'une réduction du temps de travail : rester au domicile, hospitalisation, accompagnement examens…

| | Jours de travail perdus / par an |
|---|---|
| Mère | |
| Père | |

Votre enfant va-t-il à l'école ?.... Combien de jours par semaine ?....
Quantité de jours d'écoles perdus pour votre enfant à cause de la maladie : ……..

Couts additionnels :

| | Matériel adapté/ intervention : Cochez ou précisez | Coût total engagé | Quantité remboursement (sécurité sociale / mutuelle) | Financement annexe (association) | Coût restant |
|---|---|---|---|---|---|
| Lit | | | | | |
| Chaise | | | | | |
| Siège auto | | | | | |
| Voiture | | | | | |
| Poussette | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Ventilation | | | | | |
| Aspiration | | | | | |
| Matériel de propreté (couches si >6 ans) | | | | | |
| Aménagement du domicile | | | | | |
| Alimentation | | | | | |
| Kinésithérapie | | | | | |
| Traitements | | | | | |
| Soins | | | | | |
| Autres | | | | | |
| …… | | | | | |

Avez-vous des ressources financières annexes :

- ☐ Famille
- ☐ Association caritative
- ☐ Cagnotte de soutien (Facebook…)
- ☐ …

# Annexe III. EQ-5D (Chapitre II, 2)

**Questionnaire sur la santé**

**Version française pour la Belgique**

***(French version for Belgium)***

Pour chaque rubrique, veuillez cocher UNE case, celle qui décrit le mieux votre santé AUJOURD'HUI.

**MOBILITÉ**

Je n'ai aucun problème pour me déplacer à pied ❑
J'ai des problèmes légers pour me déplacer à pied ❑
J'ai des problèmes modérés pour me déplacer à pied ❑
J'ai des problèmes sévères pour me déplacer à pied ❑
Je suis incapable de me déplacer à pied ❑

**AUTONOMIE DE LA PERSONNE**

Je n'ai aucun problème pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes légers pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes modérés pour me laver ou m'habiller tout(e) seul(e) ❑
J'ai des problèmes sévères pour me laver ou m'habiller tout(e) seul(e) ❑
Je suis incapable de me laver ou de m'habiller tout(e) seul(e) ❑

**ACTIVITES COURANTES** *(exemples: travail, études, travaux ménagers, activités familiales ou loisirs)*

Je n'ai aucun problème pour accomplir mes activités courantes ❑
J'ai des problèmes légers pour accomplir mes activités courantes ❑
J'ai des problèmes modérés pour accomplir mes activités courantes ❑
J'ai des problèmes sévères pour accomplir mes activités courantes ❑
Je suis incapable d'accomplir mes activités courantes ❑

**DOULEURS / GÊNE**

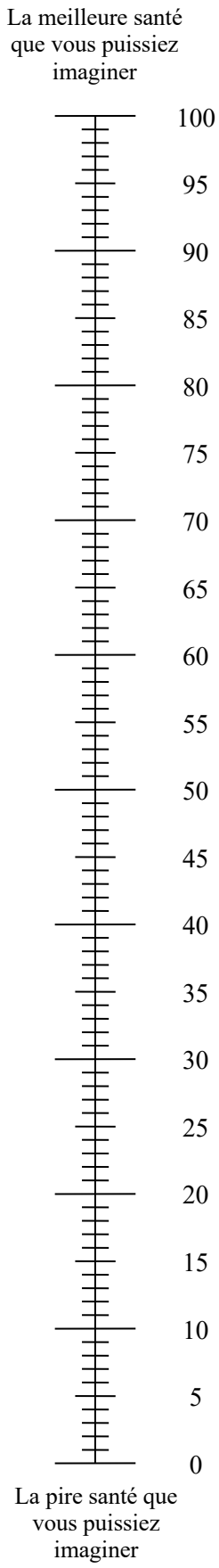
Je n'ai ni douleur ni gêne ❑
J'ai des douleurs ou une gêne légère(s) ❑
J'ai des douleurs ou une gêne modérée(s) ❑
J'ai des douleurs ou une gêne sévère(s) ❑
J'ai des douleurs ou une gêne extrême(s) ❑

**ANXIÉTÉ / DÉPRESSION**

Je ne suis ni anxieux(se), ni déprimé(e) ❑
Je suis légèrement anxieux(se) ou déprimé(e) ❑
Je suis modérément anxieux(se) ou déprimé(e) ❑
Je suis sévèrement anxieux(se) ou déprimé(e) ❑
Je suis extrêmement anxieux(se) ou déprimé(e) ❑

- Nous aimerions savoir dans quelle mesure votre santé est bonne ou mauvaise AUJOURD'HUI.
- Cette échelle est numérotée de 0 à 100.
- 100 correspond à la meilleure santé que vous puissiez imaginer.
  0 correspond à la pire santé que vous puissiez imaginer.
- Veuillez faire une croix (X) sur l'échelle afin d'indiquer votre état de santé AUJOURD'HUI.
- Maintenant, veuillez noter dans la case ci-dessous le chiffre que vous avez coché sur l'échelle.

VOTRE SANTÉ AUJOURD'HUI = ☐



# Annexe IV. HUI (Chapitre II, 2)



**HUI23P4Fr.15Q**
**HEALTH UTILITIES INDEX (HUI2/3)**
**QUESTIONNAIRE EN 15 POINTS POUR UNE ÉVALUATION AUTO-ADMINISTRÉE PAR PERSONNE INTERPOSÉE DE LA SITUATION DE SANTÉ SUR QUATRE SEMAINES**

**Mode d'emploi:** Veuillez noter que dans ce questionnaire, le terme de "sujet" se réfère à la personne à la place de qui vous répondez, par exemple un parent, votre fille, votre fils, votre mari, votre femme, votre ami(e) ou votre patient(e). Ce questionnaire a été conçu pour être utilisé par une grande varieté de personnes-substituts. Veuillez nous excuser d'avoir dû utiliser le terme de "sujet" dans les questions concernant la santé de votre parent, de votre ami(e), ou de votre patient(e).

Les questions suivantes portent sur différents aspects de la santé du sujet au cours des quatre dernières semaines. Avant de répondre à ces questions, veuillez bien réfléchir à la santé générale du sujet et à sa capacité à accomplir les tâches quotidiennes au cours des quatre dernières semaines. Afin de bien définir la période de quatre semaines, demandez-vous quelle était la date il y a quatre semaines et rappelez-vous les choses importantes que le sujet a vécues durant cette période. Dans vos réponses, veuillez vous concentrer sur ce que le sujet a été capable ou incapable de faire, ainsi que sur son état de santé général au cours des quatre dernières semaines.

Vous aurez peut-être l'impression que quelques-unes de ces questions ne s'appliquent pas au sujet, mais il est important que nous posions les mêmes questions à tout le monde. De plus, certaines questions se ressemblent; veuillez nous pardonner ce chevauchement apparent, et répondez à chaque question séparément.

Veuillez lire attentivement chaque question et de prendre le temps de bien y répondre. Pour chaque question, veuillez choisir une seule réponse, celle qui décrit le mieux le niveau de capacité ou d'incapacité du sujet au cours des quatre dernières semaines. Veuillez indiquer votre choix en cochant la case (a, b, c,...) qui correspond à la réponse. Toute information que vous communiquez est confidentielle. Il n'y a ni bonne ni mauvaise réponse, seule importe votre opinion concernant les capacités du sujet et ses sentiments.

---

1. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux la capacité du sujet à voir assez suffisamment bien pour lire un article de journal?

   a. Capable de voir suffisamment bien sans lunettes ou des lentilles de contact.
   b. Capable de voir suffisamment bien avec des lunettes ou des lentilles de contact.
   c. Incapable de voir suffisamment bien, même avec des lunettes ou des lentilles de contact.
   d. Incapable de voir du tout.

2. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux la capacité du sujet à voir suffisamment bien pour reconnaître un ami de l'autre côté de la rue?

   a. Capable de voir suffisamment bien sans lunettes ou des lentilles de contact.
   b. Capable de voir suffisamment bien avec des lunettes ou des lentilles de contact.
   c. Incapable de voir suffisamment bien, même avec des lunettes ou des lentilles de contact.
   d. Incapable de voir du tout.

© Health Utilities Inc. (HUInc.) Dundas, ON, Canada 1999, 2000, 2001, 2014

3. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux la capacité du sujet à entendre ce qui était dit lors d'une conversation de groupe avec au moins trois autres personnes?

   a. Capable d'entendre ce qui était dit sans appareillage auditif.

   b. Capable d'entendre ce qui était dit avec un appareillage auditif.

   c. Incapable d'entendre ce qui était dit même avec un appareillage auditif.

   d. Incapable d'entendre ce qui était dit mais vous ne portiez pas d'appareillage auditif.

   e. Incapable d'entendre du tout.

4. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux la capacité du sujet à entendre ce qui était dit lors d'une conversation avec une autre personne dans une pièce calme?

   a. Capable d'entendre ce qui était dit sans appareillage auditif.

   b. Capable d'entendre ce qui était dit avec un appareillage auditif.

   c. Incapable d'entendre ce qui était dit même avec un appareillage auditif.

   d. Incapable d'entendre ce qui était dit mais vous ne portiez pas d'appareillage auditif.

   e. Incapable d'entendre du tout.

5. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux la capacité du sujet à se faire comprendre quand il/elle parlait dans sa propre langue avec des personnes qui ne le/la connaissaient pas?

   a. Capacité à prononcer permettant d'être entièrement compris.

   b. Capacité à prononcer permettant d'être partiellement compris.

   c. Incapable de vous faire comprendre.

   d. Pas du tout capable de parler.

6. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux la capacité du sujet à se faire comprendre quand il/elle parlait avec des personnes qui le/la connaissaient bien?

   a. Capacité à prononcer vous permettant d'être entièrement compris.

   b. Capacité à prononcer vous permettant d'être partiellement compris.

   c. Incapable de vous faire comprendre.

   d. Pas du tout capable de parler.

© Health Utilities Inc. (HUInc.) Dundas, ON, Canada 1999, 2000, 2001, 2014

7. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux l'état émotif du sujet?

   a. Heureux et intéressé par la vie.
   b. Relativement heureux.
   c. Relativement malheureux.
   d. Très malheureux.
   e. Tellement malheureux que la vie n'en vaut pas la peine.

8. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux les douleurs et malaises du sujet?

   a. Aucune douleur et gêne.
   b. Douleur ou gêne légère à modérée n'empêchant aucune activité.
   c. Douleur ou gêne modérée empêchant de réaliser des activités.
   d. Douleur ou gêne modérée à sévère empêchant de réaliser des activités.
   e. Douleur ou gêne sévère empêchant de réaliser la plupart des activités.

9. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux la capacité du sujet à marcher?
   **Remarque**: L'équipement pour la marche se réfère à des supports mécaniques tels qu'un appareil orthopédique, une canne, des béquilles ou un déambulateur.

   a. Capable de marcher sans aucune difficulté et sans équipement pour la marche.
   b. Capable de marcher, avec plus ou moins de difficultés parfois, mais vous n'avez besoin ni d'un équipement pour la marche ni de l'aide d'une autre personne.
   c. Capable de marcher seulement avec un équipement pour la marche mais sans l'aide d'une autre personne.
   d. Capable de marcher avec un équipement pour la marche sur de très courtes distances mais vous avez besoin d'un fauteuil roulant pour vous déplacer dans votre quartier.
   e. Incapable de marcher même sur de très courtes distances sans l'aide d'une autre personne et vous avez besoin d'un fauteuil roulant pour vous déplacer dans votre quartier.
   f. Pas du tout capable de marcher.

© Health Utilities Inc. (HUInc.) Dundas, ON, Canada 1999, 2000, 2001, 2014

10. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux la capacité du sujet à se servir de ses mains et de ses doigts?
    **Remarque**: Des outils spéciaux se réfèrent à des crochets pour boutonner les vêtements, à des appareils pour ouvrir les bocaux ou soulever des petits objets, ou autres appareils pour compenser la limitation de l'emploi des mains ou des doigts.

    a. Plein usage de vos deux mains et de vos dix doigts.
    b. Limité dans l'emploi de vos mains ou de vos doigts, mais vous n'avez pas besoin d'outils spéciaux ou de l'aide d'une autre personne.
    c. Limité dans l'emploi de vos mains ou de vos doigts mais autonome avec l'usage d'outils spéciaux (vous n'avez pas besoin de l'aide d'une autre personne).
    d. Limité dans l'emploi de vos mains ou de vos doigts et vous avez besoin de l'aide d'une autre personne pour quelques tâches (pour lesquelles vous n'êtes pas autonome même en utilisant des outils spéciaux).
    e. Limité dans l'emploi de vos mains ou de vos doigts et vous avez besoin de l'aide d'une autre personne pour la plupart des tâches (pour lesquelles vous n'êtes pas autonome même en utilisant des outils spéciaux).
    f. Limité dans l'emploi de vos mains ou de vos doigts et vous avez besoin de l'aide d'une autre personne pour toutes les tâches (vous n'êtes pas autonome même en utilisant des outils spéciaux).

11. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux la capacité du sujet à se souvenir des choses?

    a. Capable de vous souvenir de la plupart des choses.
    b. Parfois incapable de vous souvenir.
    c. Souvent incapable de vous souvenir.
    d. Incapable de vous souvenir de quoi que ce soit.

12. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux la capacité du sujet à penser et réfléchir sur des problèmes quotidiens?

    a. Capable de penser et réfléchir clairement.
    b. Capable de penser et réfléchir avec de petites difficultés.
    c. Capable de penser et réfléchir avec pas mal de difficultés.
    d. Capable de penser et réfléchir avec de très nombreuses difficultés.
    e. Incapable de penser et de réfléchir.

© Health Utilities Inc. (HUInc.) Dundas, ON, Canada 1999, 2000, 2001, 2014

13. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux la capacité du sujet à accomplir les activités élémentaires : manger, se laver, s'habiller et utiliser les toilettes??

    a. Capable de manger, de vous laver, de vous habiller et d'utiliser les toilettes normalement.
    b. Capable de manger, de vous laver, de vous habiller ou d'utiliser les toilettes de façon autonome mais avec difficulté.
    c. Capable de manger, de vous laver, de vous habiller ou d'utiliser les toilettes de façon autonome mais avec un équipement mécanique.
    d. Capable de manger, de vous laver, de vous habiller ou d'utiliser les toilettes mais avec l'aide d'une autre personne.

14. Au cours des quatre dernières semaines, laquelles des réponses suivantes décrirait le mieux l'état émotif du sujet?

    a. Heureux et sans souci.
    b. Parfois inquiet, en colère, irritable, anxieux ou déprimé.
    c. Souvent inquiet, en colère, irritable, anxieux ou déprimé.
    d. Presque toujours inquiet, en colère, irritable, anxieux ou déprimé.
    e. Extrêmement inquiet, en colère, irritable, anxieux ou dépressif, nécessitant l'aide d'un professionnel de santé.

15. Au cours des quatre dernières semaines, laquelle des réponses suivantes décrirait le mieux l'intensité des douleurs ou des malaises du sujet?

    a. Aucune douleur et gêne.
    b. Douleur ou gêne occasionnelle. La gêne est soulagée par des médicaments vendus sans ordonnance, ou par la maîtrise de soi, sans perturbation des activités normales.
    c. Douleur ou gêne fréquente. La gêne est soulagée par des médicaments pris par voie orale, avec de temps en temps une perturbation des activités normales.
    d. Douleur ou gêne fréquente. La gêne requiert, pour être soulagée, des analgésiques puissants (oraux ou injectables) délivrés sur ordonnance. Perturbation fréquente des activités normales.
    e. Douleur ou gêne sévère. La douleur ne peut être soulagée par aucun médicament et perturbe constamment les activités normales.

© Health Utilities Inc. (HUInc.) Dundas, ON, Canada 1999, 2000, 2001, 2014

16. Au cours des quatre dernières semaines, diriez-vous que la santé du sujet a généralement été:

    a. Excellente?
    b. Très bonne?
    c. Bonne?
    d. Passable?
    e. Mauvaise?

17. Qui a fourni les informations nécessaires pour répondre aux questions de ce questionnaire? (Veuillez noter tout ce qui pourrait être pertinent.)

    a. La personne qui a rempli le questionnaire.
    b. Le sujet lui-même.
    c. D'autres personnes. Veuillez préciser le lien entre le sujet et chaque personne qui a fourni des informations.

       1._____

       2._____

       3._____

18. Qui a rempli ce questionnaire?

    a. Le mari ou la femme du sujet.
    b. Un parent du sujet.
    c. Un enfant du sujet.
    d. Un(e) ami(e) du sujet.
    e. Un(e) professionnel(le) de la santé.
    f. Le sujet lui-même ou elle-même.
    g. Une autre personne. Veuillez préciser son lien avec le sujet.

**MERCI.**

© Health Utilities Inc. (HUInc.) Dundas, ON, Canada 1999, 2000, 2001, 2014

## Annexe V. Exemple de questionnaires PedsQL
## Impact Familial / Core (pediatric) / Neuromusculaire (NMM) (Chapitre II, 2)

Exemple avec les questionnaires 2-4 ans.

N° du participant : _____

Date : _____

# PedsQL™

## Module Impact Familial

Version 2.0 - French (France)

**RAPPORT PARENTS**

**INSTRUCTIONS**

Les familles ont quelquefois des inquiétudes ou des difficultés en raison de la santé de leurs enfants. Sur la page suivante, vous trouverez une liste de choses qui peuvent représenter un problème pour **vous**. Veuillez indiquer si ces choses ont été **un problème** pour **vous** au cours du **MOIS DERNIER,** en entourant :

**0** si ce n'est **jamais** un problème
**1** si ce n'est **presque jamais** un problème
**2** si c'est **parfois** un problème
**3** si c'est **souvent** un problème
**4** si c'est **presque toujours** un problème

Il n'y a pas de réponses justes ou fausses.
Si vous ne comprenez pas une question, n'hésitez pas à demander de l'aide.

*Conformément aux dispositions de la loi relative à l'informatique aux fichiers et aux libertés, vous disposez d'un droit d'accès et de rectification aux données collectées dans ce questionnaire. Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel. Enfin, vous pouvez accéder à l'ensemble de vos données médicales en application des dispositions de l'article L. 1111-7 du code de la santé publique. Ces droits s'exercent auprès du médecin qui vous suit dans le cadre de la recherche et qui connaît votre identité.*


Reproduction interdite sans autorisation

Copyright © 1998 JW Varni, Ph.D.
Tous droits réservés.

PedsQL 2

Au cours du **MOIS DERNIER**, en raison de la santé de votre enfant, les choses suivantes ont-elles représenté un problème pour **vous** ?

| **LA SANTE PHYSIQUE** ***(problèmes avec…)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Je me sens fatigué(e) pendant la journée | 0 | 1 | 2 | 3 | 4 |
| 2. Je me sens fatigué(e) au réveil le matin | 0 | 1 | 2 | 3 | 4 |
| 3. Je me sens trop fatigué(e) pour faire les choses que j'aime faire | 0 | 1 | 2 | 3 | 4 |
| 4. J'ai mal à la tête | 0 | 1 | 2 | 3 | 4 |
| 5. Je me sens physiquement faible | 0 | 1 | 2 | 3 | 4 |
| 6. J'ai l'estomac noué | 0 | 1 | 2 | 3 | 4 |

| **L'ETAT EMOTIONNEL** ***(problèmes avec…)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Je me sens anxieux(se) | 0 | 1 | 2 | 3 | 4 |
| 2. Je me sens triste | 0 | 1 | 2 | 3 | 4 |
| 3. Je me sens en colère ou énervé(e) | 0 | 1 | 2 | 3 | 4 |
| 4. Je me sens frustré(e) | 0 | 1 | 2 | 3 | 4 |
| 5. Je me sens impuissant(e) ou désespéré(e) | 0 | 1 | 2 | 3 | 4 |

| **LES RELATIONS AVEC LES AUTRES** ***(problèmes avec…)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Je me sens isolé(e) | 0 | 1 | 2 | 3 | 4 |
| 2. J'ai du mal à trouver du soutien | 0 | 1 | 2 | 3 | 4 |
| 3. C'est dur de trouver du temps pour mener des activités avec d'autres personnes | 0 | 1 | 2 | 3 | 4 |
| 4. Je n'ai pas assez d'énergie pour mener des activités avec d'autres personnes | 0 | 1 | 2 | 3 | 4 |

| **LA FONCTION COGNITIVE** ***(problèmes avec…)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. J'ai du mal à rester concentré(e) | 0 | 1 | 2 | 3 | 4 |
| 2. J'ai du mal à me souvenir de ce qu'on me dit | 0 | 1 | 2 | 3 | 4 |
| 3. J'ai du mal à retenir les choses que je viens d'entendre | 0 | 1 | 2 | 3 | 4 |
| 4. J'ai du mal à réfléchir vite | 0 | 1 | 2 | 3 | 4 |
| 5. J'ai du mal à me souvenir de ce à quoi j'étais en train de penser | 0 | 1 | 2 | 3 | 4 |

| **LA COMMUNICATION** ***(problèmes avec…)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. J'ai l'impression que les autres ne comprennent pas ma situation familiale | 0 | 1 | 2 | 3 | 4 |
| 2. J'ai du mal à parler de la santé de mon enfant avec les autres | 0 | 1 | 2 | 3 | 4 |
| 3. J'ai du mal à dire aux médecins et aux infirmières comment je me sens | 0 | 1 | 2 | 3 | 4 |

PedsQL 2.0 - Parent Family Impact 06/04 Reproduction interdite sans autorisation Copyright © 1998 JW Varni, Ph.D. Tous droits réservés.

PedsQL-2.0-Family Impact Module - France/French - Version of 04 Apr 14 - Mapi.
ID7822 / PedsQL_2.0-FIM_AU2.0_fra-FR.doc

PedsQL 3

*Au cours du **MOIS DERNIER**, en raison de la santé de votre enfant, les choses suivantes ont-elles représenté un problème pour **vous** ?*

| **L'INQUIETUDE** ***(problèmes avec...)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Je m'inquiète de savoir si le traitement médical de mon enfant agit ou non | 0 | 1 | 2 | 3 | 4 |
| 2. Je m'inquiète des effets secondaires des médicaments/du traitement médical de mon enfant | 0 | 1 | 2 | 3 | 4 |
| 3. Je m'inquiète de savoir comment les autres vont réagir par rapport à l'état de santé de mon enfant | 0 | 1 | 2 | 3 | 4 |
| 4. Je m'inquiète de savoir combien la maladie de mon enfant affecte les autres membres de la famille | 0 | 1 | 2 | 3 | 4 |
| 5. Je m'inquiète pour l'avenir de mon enfant | 0 | 1 | 2 | 3 | 4 |

**INSTRUCTIONS**

Voici une liste de choses qui peuvent représenter un problème pour **votre famille**. Veuillez indiquer si ces choses ont été **un problème** pour **votre famille** au cours du **MOIS DERNIER**.

*Au cours du **MOIS DERNIER**, en raison de la santé de votre enfant, les choses suivantes ont-elles représenté un problème pour **votre famille** ?*

| **LES ACTIVITES JOURNALIERES** ***(problèmes avec...)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Les activités familiales nécessitent plus de temps et d'efforts | 0 | 1 | 2 | 3 | 4 |
| 2. Il est difficile de trouver du temps pour finir les tâches ménagères | 0 | 1 | 2 | 3 | 4 |
| 3. La fatigue nous empêche de finir les tâches ménagères | 0 | 1 | 2 | 3 | 4 |

| **LES RELATIONS FAMILIALES** ***(problèmes avec...)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Il y a un manque de communication entre les membres de la famille | 0 | 1 | 2 | 3 | 4 |
| 2. Il y a des conflits entre les membres de la famille | 0 | 1 | 2 | 3 | 4 |
| 3. Il est difficile de prendre des décisions ensemble en tant que famille | 0 | 1 | 2 | 3 | 4 |
| 4. Il est difficile de résoudre les problèmes familiaux ensemble | 0 | 1 | 2 | 3 | 4 |
| 5. Il y a du stress et des tensions entre les membres de la famille | 0 | 1 | 2 | 3 | 4 |


Reproduction interdite sans autorisation

Copyright © 1998 JW Varni, Ph.D.
Tous droits réservés.

N° du participant :_____

Date :_____

# PedsQL™

## Questionnaire sur la qualité de vie en pédiatrie

Version 4.0 - French (Belgium)

**RAPPORT PARENTS** pour les **TRÈS JEUNES ENFANTS** (**2 à 4** ans)

**INSTRUCTIONS**

À la page suivante, vous trouverez une liste de choses qui peuvent représenter un problème pour **votre enfant**. Veuillez indiquer **dans quelle mesure ces choses ont été un problème** pour **votre enfant** au cours du **MOIS DERNIER** en entourant :

**0** si ce n'est **jamais** un problème
**1** si ce n'est **presque jamais** un problème
**2** si c'est **parfois** un problème
**3** si c'est **souvent** un problème
**4** si c'est **presque toujours** un problème

Il n'y a pas de bonnes ou de mauvaises réponses.
Si vous ne comprenez pas une question, n'hésitez pas à demander de l'aide.

 Ne peut être reproduit sans autorisation

Copyright © 1998 JW Varni, Ph.D.
Tous droits réservés

PedsQL-4.0-Core-PT - Belgium/French - Version of 23 Oct 15 - Mapi.
ID044480 / PedsQL-4.0-Core-PT_AU4.0_fra-BE.doc

PedsQL 2

*Au cours du **MOIS DERNIER**, les choses suivantes ont-elles représenté un **problème** pour votre enfant ?*

| **CAPACITÉ PHYSIQUE** ***(problèmes avec…)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Marcher | 0 | 1 | 2 | 3 | 4 |
| 2. Courir | 0 | 1 | 2 | 3 | 4 |
| 3. Participer à des jeux actifs ou faire de l'exercice | 0 | 1 | 2 | 3 | 4 |
| 4. Soulever un objet lourd | 0 | 1 | 2 | 3 | 4 |
| 5. Prendre un bain/une douche | 0 | 1 | 2 | 3 | 4 |
| 6. Aider à ramasser ses jouets | 0 | 1 | 2 | 3 | 4 |
| 7. Ressentir des douleurs | 0 | 1 | 2 | 3 | 4 |
| 8. Manquer d'énergie | 0 | 1 | 2 | 3 | 4 |

| **ÉTAT ÉMOTIONNEL** ***(problèmes avec…)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Avoir peur | 0 | 1 | 2 | 3 | 4 |
| 2. Se sentir triste | 0 | 1 | 2 | 3 | 4 |
| 3. Être en colère | 0 | 1 | 2 | 3 | 4 |
| 4. Avoir du mal à dormir | 0 | 1 | 2 | 3 | 4 |
| 5. S'inquiéter | 0 | 1 | 2 | 3 | 4 |

| **RELATIONS AVEC LES AUTRES** ***(problèmes avec…)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Jouer avec d'autres enfants | 0 | 1 | 2 | 3 | 4 |
| 2. Les autres enfants ne veulent pas jouer avec lui/elle | 0 | 1 | 2 | 3 | 4 |
| 3. Les autres enfants se moquent de lui/d'elle | 0 | 1 | 2 | 3 | 4 |
| 4. N'est pas capable de faire des choses que d'autres enfants de son âge savent faire | 0 | 1 | 2 | 3 | 4 |
| 5. Suivre le rythme des autres enfants quand il/elle joue avec eux | 0 | 1 | 2 | 3 | 4 |

***Veuillez compléter cette section si votre enfant va à l'école, à la crèche ou à la garderie***

| **ACTIVITÉS À L'ÉCOLE/LA CRÈCHE/LA GARDERIE** ***(problèmes avec…)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Faire les mêmes activités que les autres à l'école/la crèche/la garderie | 0 | 1 | 2 | 3 | 4 |
| 2. Ne pas aller à l'école/la crèche/la garderie parce qu'il/elle ne se sent pas bien | 0 | 1 | 2 | 3 | 4 |
| 3. Ne pas aller à l'école/la crèche/la garderie parce qu'on l'emmène chez le médecin ou à l'hôpital | 0 | 1 | 2 | 3 | 4 |

PedsQL 4.0 - Parent (2-4) Ne peut être reproduit sans autorisation Copyright © 1998 JW Varni, Ph.D.
Tous droits réservés

PedsQL-4.0-Core-PT - Belgium/French - Version of 23 Oct 15 - Mapi.
ID044480 / PedsQL-4.0-Core-PT_AU4.0_fra-BE.doc

IDENTIFIANT PATIENT: |__|__| - |__|__|__|
N° de centre N° de Screening

INITIALES DU PATIENT: Nom: |__|__|__| Prénom: |__|__|
3 premières lettres 2 premières lettres

DATE A LAQUELLE LE QUESTIONNAIRE A ÉTÉ REMPLI:

|__|__| / |__|__| / |__|__|__|__|
jj mm aaaa

# PedsQL™

## Module neuromusculaire

Version 3.0 - French (France)

**RAPPORT PARENTS pour les TRES JEUNES ENFANTS (2 à 4 ans)**

**INSTRUCTIONS**

Les enfants qui ont une maladie neuromusculaire ont parfois des problèmes particuliers.
Veuillez indiquer si ces choses ont été **un problème** pour votre enfant au cours du **MOIS DERNIER** en entourant :

**0** si ce n'est **jamais** un problème
**1** si ce n'est **presque jamais** un problème
**2** si c'est **parfois** un problème
**3** si c'est **souvent** un problème
**4** si c'est **presque toujours** un problème

Il n'y a pas de réponses justes ou fausses.
Si vous ne comprenez pas une question, n'hésitez pas à demander de l'aide.


Copyright © 1998 JW Varni, Ph.D.
Tous droits réservés

PedsQL 2

*Au cours du **MOIS DERNIER**, les choses suivantes ont-elles représenté un **problème** pour votre enfant ?*

| **À PROPOS DE LA MALADIE NEUROMOSCULAIRE DE MON ENFANT *(problèmes avec...)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Mon enfant a du mal à respirer | 0 | 1 | 2 | 3 | 4 |
| 2. Mon enfant tombe facilement malade | 0 | 1 | 2 | 3 | 4 |
| 3. Mon enfant a des petites plaies et/ou des rougeurs | 0 | 1 | 2 | 3 | 4 |
| 4. Mon enfant a mal aux jambes | 0 | 1 | 2 | 3 | 4 |
| 5. Mon enfant se sent fatigué | 0 | 1 | 2 | 3 | 4 |
| 6. Mon enfant sent que son dos est raide | 0 | 1 | 2 | 3 | 4 |
| 7. Mon enfant est fatigué au réveil | 0 | 1 | 2 | 3 | 4 |
| 8. Mon enfant n'a presque pas de force dans les mains | 0 | 1 | 2 | 3 | 4 |
| 9. Mon enfant a du mal à utiliser les toilettes | 0 | 1 | 2 | 3 | 4 |
| 10. Mon enfant a du mal à prendre ou à perdre du poids quand il le veut | 0 | 1 | 2 | 3 | 4 |
| 11. Mon enfant a du mal à se servir de ses mains | 0 | 1 | 2 | 3 | 4 |
| 12. Mon enfant a du mal à avaler quand il mange | 0 | 1 | 2 | 3 | 4 |
| 13. Mon enfant a besoin de beaucoup de temps pour prendre sa douche ou son bain | 0 | 1 | 2 | 3 | 4 |
| 14. Mon enfant se blesse accidentellement | 0 | 1 | 2 | 3 | 4 |
| 15. Mon enfant a besoin de beaucoup de temps pour manger | 0 | 1 | 2 | 3 | 4 |
| 16. Mon enfant a du mal à se retourner pendant la nuit | 0 | 1 | 2 | 3 | 4 |
| 17. Mon enfant a du mal à aller dans certains endroits avec son matériel | 0 | 1 | 2 | 3 | 4 |

| **COMMUNICATION *(problèmes avec…)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Mon enfant a du mal à dire comment il se sent aux docteurs et aux infirmières | 0 | 1 | 2 | 3 | 4 |
| 2. Mon enfant a du mal à poser des questions aux docteurs et aux infirmières | 0 | 1 | 2 | 3 | 4 |
| 3. Mon enfant a du mal à expliquer sa maladie aux autres | 0 | 1 | 2 | 3 | 4 |

| **À PROPOS DE L'ORGANISATION DE NOTRE FAMILLE *(problèmes avec…)*** | **Jamais** | **Presque jamais** | **Parfois** | **Souvent** | **Presque toujours** |
|---|---|---|---|---|---|
| 1. Notre famille a du mal à prévoir des activités, comme partir en vacances | 0 | 1 | 2 | 3 | 4 |
| 2. Notre famille a du mal à se reposer suffisamment | 0 | 1 | 2 | 3 | 4 |
| 3. Je pense que l'argent est un problème pour notre famille | 0 | 1 | 2 | 3 | 4 |
| 4. Je pense que notre famille a beaucoup de problèmes | 0 | 1 | 2 | 3 | 4 |
| 5. Mon enfant ne dispose pas du matériel dont il a besoin | 0 | 1 | 2 | 3 | 4 |

PedsQL 3.0 Parent (2-4) Neuromuscular Reproduction interdite

Copyright © 1998 JW Varni, Ph.D.
Tous droits réservés

PedsQL 3.0 Neuromuscular PT - France/French - Version of 03 Nov 14 - Mapi.
ID8456 / PedsQL3.0-Neuromuscular_PT_AU3.0_fra-FR.doc

## Annexe VI. Liste des questionnaires en fonction de l'âge des patients (Chapitre II, 2)

| | 1-24 mois | 2-4 ans | 5-7 ans | 8-12 ans | 13-18 ans | 18-25 ans | Adulte |
|---|---|---|---|---|---|---|---|
| Antécédents / données médicales | X | X | X | X | X | X | X |
| Questionnaire Coût enfant | X | X | X | X | X | | |
| Questionnaire Coût adulte | | | | | | X | X |
| HUI | | X | X | X | X | X | X |
| EQ5D-5L | | | | | | X | X |
| EQ5D-5Y | | | X | X | X | | |
| PedsQl impact familial | X | X | X | X | X | X | |
| PedsQl Core rapport parents 2-4 ans | | X | | | | | |
| PedsQl Core rapport parents 5-7 ans | | | X | | | | |
| PedsQl Core 5-7 ans | | | X | | | | |
| PedsQl Core rapport parents 8-12 ans | | | | X | | | |
| PedsQl Core 8-12 ans | | | | X | | | |
| PedsQl Core rapport parents 13-18 ans | | | | | X | | |
| PedsQl Core 13-18 ans | | | | | X | | |
| PedsQl Core 18-25 ans | | | | | | X | |
| PedsQl Core Adulte | | | | | | | X |
| PedsQl Neuromusculaire 2-4 ans | | X | | | | | |
| PedsQl Neuromusculaire rapport parents 5-7 ans | | | X | | | | |
| PedsQl Neuromusculaire 5-7 ans | | | X | | | | |
| PedsQl Neuromusculaire rapport parents 8-12 ans | | | | X | | | |
| PedsQl Neuromusculaire 8-12 ans | | | | X | | | |
| PedsQl Neuromusculaire rapport parents 13-18 ans | | | | | X | | |
| PedsQl Neuromusculaire 13-18 ans | | | | | X | | |
| PedsQl Neuromusculaire Adulte (en utilisant 13-18 ans) | | | | | | X | X |

## Annexe VII. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: Current perspectives. (Chapitre III, 1)

Dangouloff T, Servais L. Therapeutics and Clinical Risk Management. 2019

Therapeutics and Clinical Risk Management

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

# Clinical Evidence Supporting Early Treatment Of Patients With Spinal Muscular Atrophy: Current Perspectives

This article was published in the following Dove Press journal:
*Therapeutics and Clinical Risk Management*

Tamara Dangouloff[1]
Laurent Servais[1,2]

[1]Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, Liège, Belgium; [2]MDUK Neuromuscular Center, Department of Paediatrics, University of Oxford, Oxford, UK

**Abstract:** Recent advances in the treatment of spinal muscular atrophy (SMA) have dramatically altered prognosis. Rather than a rapidly lethal disease, SMA type 1, the most severe form with the earliest onset of SMA, has become a disease in which long-term event-free survival with the acquisition of important motor milestones is likely. Prognosis for patients with SMA type 2 has shifted from slow and progressive deterioration to long-term stability. Nevertheless, there is a large heterogeneity in terms of clinical response to currently available treatments, ranging from absence of response to impressive improvement. The only factor identified that is predictive of treatment success is the age of the patient at the initiation of treatment, which is closely related to disease duration. The aim of this paper is to review available evidence that support early intervention using currently available treatment approaches.

**Keywords:** spinal muscular atrophy, nusinersen, zolgensma, risdiplam, branaplam, newborn screening

## Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive, inherited genetic disease characterized by degeneration of alpha motor neurons in the spinal cord.[1] It is the most common genetic cause of child mortality and has long been considered an incurable disease. The incidence is approximately 1 in 10,000 live births.[2,3] It is linked to a homozygous deletion of the *SMN1* gene. Humans have a variable number of copies of a very closely related gene, *SMN2*; splicing of the *SMN2* transcript usually results in an mRNA lacking exon 7.[4] The severity of the SMA depends largely on the number of copies of *SMN2*, a lower number of copies being associated with a more severe phenotype,[5] yet several exceptions and other genetic modifiers have been reported.[6]

Patients first present with a loss of muscle strength that progresses to paralysis, including paralysis of the respiratory muscles. Clinical phenotypes are grouped into five forms depending on the severity of the disease and the age of onset. SMA type 0 occurs in the neonatal period and causes rapid death. SMA type I (SMA1), also known as Werdnig–Hoffman disease, occurs during the first 6 months of life and is associated with death before 2 years of age in most of the cases in absence of supportive care. Spinal muscular atrophy type II (SMA2), also called "intermediate" SMA, occurs slightly later than type I, between the ages of 6 and 18 months, and is characterized

Correspondence: Laurent Servais
CRMN, CHU Liège, Boulevard du Douzième de Ligne, 1, Liège 4000, Belgium
Tel +33 6 22 59 22 43
Fax +32 4 321 83 28
Email lservais@chuliege.be

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/TCRM.S172291



© 2019 Dangouloff and Servais. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

by the absence of acquisition of autonomous ambulation. Type III (SMA3) or Kugelberg–Welander disease causes symptoms after the age of 18 months, and these patients acquire autonomous ambulation. SMA2 and SMA3 cause severe disability in children and adults at significant social lifelong costs, estimated at $US 8.4 and 6.4 million, respectively.[7] SMA2 and SMA3 progress more slowly than SMA1 but are clearly progressive diseases, even in adulthood.[8,9] SMA type IV (SMA4), also known as the adult form, occurs during the second or third decade of life, and the ability to walk is preserved.

Several innovative drugs have recently been developed that improve or ameliorate symptoms in many patients.[10] Nusinersen (marketed as Spinraza, Biogen, Cambridge, MA, USA) is an antisense oligonucleotide drug that is injected intrathecally; it modulates splicing of *SMN2* to enhance the production of a functional SMN protein.[11] Efficacy has recently been demonstrated in a double-blind, placebo-controlled study in patients with SMA1[12] and in non-ambulant SMA2 and SMA3 patients younger than 10 years.[13] Nusinersen was approved by the FDA in December 2016 and by the EMA in June 2017. Nusinersen is the first drug approved to treat pediatric and adult patients with SMA. Open-label studies[14–17] and real-world data[18,19] have confirmed the safety and efficacy of the treatment in these patient groups as well as in older SMA1 patients,[20] a population not covered by the Phase III study. An open-label study of patients previously included in the Phase III trials and a study in pre-symptomatic patients are currently ongoing (NURTURE: NCT02386553; SHINE: NCT02594124).

Other treatments for SMA of certain types are approved or under development. Zolgensma, previously known as zolgensma (Onasemnogene abeparvovec-xioi, Avxs-101, Avexis, Novartis, Bannockburn, IL, USA),[21,22] is an AAV9-based gene therapy that was approved by the FDA in May 2019 for the treatment of patients younger than 2 years of age. Zolgensma is given as a one-time intravenous administration. It delivers a copy of *SMN* in a self-complementary adeno-associated viral serotype 9 (scAAV9).[23] It is under review by the EMA. Large studies are ongoing in SMA1 patients (STR1VE: NCT03306277; STR1VE EU: NCT03461289), and in pre-symptomatic patients (SPR1NT: NCT03505099), Phase I study evaluating an intrathecal approach in SMA2 patients younger than 6 years is also ongoing (STRONG: NCT03381729).

Risdiplam (F. Hoffmann-La Roche Ltd., Basel, Switzerland) and branaplam (Novartis, Basel, Switzerland) are two compounds given orally that modify *SMN2* splicing to enhance the production of SMN.[24] Risdiplam is currently in Phase III testing in SMA1 patients (FIREFISH: NCT02913482) and in patients with SMA2 (SUNFISH: NCT02908685) and a pre-symptomatic trial is starting (Rainbowfish: NCT03779334). Phase II testing of Branaplam is ongoing in SMA1 patients (NCT02268552).

Some groups of patients have not been covered by these studies including SMA3 patients and adults with SMA2. In these patients, intrathecal administration, the route used for administration of nusinersen, can be challenging because of scoliosis and/or spinal fusion. Thus, the questions of the potential benefit of treatment, the ratio of benefit to risk, and, importantly, the cost-effectiveness of the treatment remains for several groups of patients. In animals, the importance of early treatment has been extensively demonstrated.[25] In humans, the main a priori predictive factor of treatment efficacy identified so far in the published studies is the age of patients at treatment initiation, which is closely related to disease duration since most patients for which data are available to have symptom onset between 0 and 18 months. Recently, baseline patients' motor condition was also recognized as a potential predictive factor in zolgensma[26] and in nusinersen.[27] The aim of this paper is to review the available evidence that early, pre-symptomatic, treatment of SMA is optimal. Since the data discussed here were acquired in different studies with different study designs with different patient number and characteristics, we chose to present only descriptive statistics but not to report on or to calculate comparative statistics. The various studies and data used are summarized in the following Table 1.

## Evidence Supporting Early Treatment With Nusinersen

### Nusinersen In SMA1

In a double-blind, placebo-controlled, multicenter study conducted in 121 patients with confirmed SMA1 aged between 30 days and 262 days old, two-thirds (n=80) of the children received nusinersen and one-third (n=41) were sham treated.[12] Of the patients who received nusinersen, 39 had a disease duration of less than 13.1 weeks, and 41 had a disease duration of over 13.1 weeks. Of the 39 patients treated early (ie, those with disease duration less than 13.1 weeks), 30 (77%) were not on permanent-assisted ventilation at the end of the trial, whereas only 19 of 41 (46%) in the latter group were not on permanent ventilation. The difference between untreated and treated patients for time to death or to permanent ventilation was

**Table 1** Summary of the different studies supporting better efficacy of early treatment

| | | Nusinersen | Zolgensma | Risdiplam | Branaplam |
|---|---|---|---|---|---|
| **SMA1** | Study phase completed | Phase 3 ENDEAR: NCT02193074 (12)<br>Phase 4 EAP: NCT02865109 (19,18) | | | |
| | Study phase ongoing | Phase 3 SHINE: NCT02594124 (28) | Phase 1 NCT NCT03421977 (22, 26, 32)<br>Phase 3 STR1VE: NCT03306277; STR1VE EU: NCT03461289 (21) | Phase 2-3 FIREFISH: NCT02913482 (34) | Phase 1-2 NCT02268552 (36) |
| | Blinding | Double-blinded, placebo-controlled (12) | Open-label studies | Open-label study | Open-label study |
| | | Open-label study (survivors from ENDEAR)(28) | | | |
| | | Open-label study (19,18) | | | |
| | Status | Terminated, peer-reviewed (12) | Published peer-reviewed (22, 26) | Ongoing, presented | Ongoing, presented |
| | | Ongoing, presented (28) | Presented (32, 21) | | |
| | | Peer-review (18,19) | | | |
| | Outcome | ≥ 2 points on HINE scale at day 394 ; time to death or permanent ventilation at day 394 (12) | Time to reach 40 points on CHOP INTEND; age at sitting position | Acquisition of sitting position | Increase in CHOP INTEND |
| | | CHOP INTEND after 1058 days of treatment; sitting position after 240 days on modified maintenance dosing regimen, assisted walking (28) | | | |
| | | ≥ 4 points increase on CHOP INTEND (19) | | | |
| | | Increase in CHOP INTEND (18) | | | |
| | Number of patients and age at treatment initiation and analysis | 80 patients on nusinersen (39 patients with disease duration <13.1 weeks and 41 patients > 13.1) (12) | 12 patients (6 patients < 3 months at treatment and 6 > 6 months | 14 patients (4 patients < 5 months at treatment initiation and 10 patients > 5 months) | 8 patients (4 patients < 4 months at treatment initiation and 4 patients > 4 months(8 patients followed for at least 85 days) |
| | | 41 patients (22 patients < 5.42 months at treatment initiation and 19 patients > 5.42 and ≤ 7.96 months) (28) | | | |
| | | 104 patients (9 patients < 7 months at treatment initiation and 95 patients > 7 months) (19) | | | |
| | | 61 patients (17 patients < 7 months at treatment initiation and 44 > 7 months) (18) | | | |
| | Cut off | 394 days post the first injection (12) | 18 months | 8 months | 85 days |
| | | 1058 days post the first injection (28) | | | |
| | | 180 days post the first injection (19) | | | |
| | | 180 days post the first injection (18) | | | |

(*Continued*)

**Table 1** (Continued).

| | | Nusinersen | Zolgensma | Risdiplam | Branaplam |
|---|---|---|---|---|---|
| **SMA2** | Study phase completed<br>Study phase ongoing | Phase 3 CHERISH: NCT02292537 (13)<br>Phase 3 SHINE: NCT 02594124 (29) | | | |
| | Blinding | Double-blind, placebo-controlled (13)<br>Open label study (29) | | Phase 2, 3 SUNFISH: NCT02908685 (35)<br>Double-blind, placebo-controlled | |
| | Status | Completed, peer-reviewed (13)<br>Ongoing, presented (29) | | Ongoing, presented | |
| | Outcome in SMA2 | Increase ≥ 3 points on HFMSE at 15 months treatments (13)<br>Increase in HFSME and in RULM score (29) | | Increase in MFM 32 in 1 year | |
| | Number of patients and age at treatment initiation and analysis | 66 patients with nusinersen / 59 patients under 6 years of age at treatment initiation (13)<br>110 patients (39 < 3.69 year at treatment initiation, 35 aged > 3.69 and < 4.92 years and 36 > 4.92 years) (29) | | 43 patients (19 > 11 years and 24 aged 2-11 years) | |
| | Cut off | 15 month of treatment (13)<br>690 days of treatment (29) | | 1 year | |
| **PRE-SYMPTOMATIC** | Study phase completed<br>Study phase ongoing | Phase 2 NURTURE: NCT02386553 (30) | Phase 1 SPRINT: NCT03505099 (33) | | |
| | Blinding | Open-label study | Open-label study | | |
| | Status | Ongoing, presented | Ongoing, presented | | |
| | Outcome in Pre-symptomatic SMA | Non permanent ventilation, acquisition of sitting position, acquisition of walking with assistance, acquisition of independent walking | Score on CHOP INTEND | | |
| | Number of patients and age at treatment initiation and analysis | 22 Newborns < 6 weeks | 18 Newborns < 6 weeks | | |
| | Cut off | 14 -34 months | 0.8-9.1 months follow-up | | |

statistically significant only in patients treated early (HR of 0.24). The patients treated early also presented with better motor outcomes, since 27 of 29 (93%) of the patients treated early who survived to the end of the study had an increase in HINE-2 score at last visit compared to pre-treatment levels. Only 13 of the 29 (45%) surviving patients in the group that began treatment more than 13.1 weeks after the onset of symptoms had improvements in motor skills.

The survivors were followed in an open-label study.[28] The 22 children younger than 5.42 months of age at the time of the first injection improved by an average of 19.4 their CHOP INTEND scores (14.8 to 23.9) at 1058 days post the first treatment, whereas the 19 who were between 5.42 months and 7.96 months of age at the time of their first injection improved by 13.8 points (9.2 to 18.4). Similarly, an unsupported sitting position was attained 240 days after modified maintenance dosing regimen was achieved in 18 of 30 (60%) of children treated before 5.42 years but in only 8 of 21 (38%) of those treated later. Three of the 30 (10%) treated before 5.42 months were able to walk with assistance, but none of those treated later were able to walk with assistance.

As part of the Early Access Program (NCT02865109), different teams have continued to observe the effectiveness of nusinersen in a broad cohort of children with SMA1. Of 104 SMA1 patients treated over 6 months in Italy,[19] seven of the nine patients younger than 7 months at treatment initiation presented with an improvement of more than 4 points (77%) on the CHOP INTEND motor evaluation scale, whereas of the 95 patients over 7 months of age at treatment initiation, only 37 (38.94%) had an improvement of more than 4 points. Similar conclusions were drawn from observation of 61 SMA1 patients treated with nusinersen in Germany.[18] The 17 patients younger than 7 months at treatment initiation had an average of 14.4 ± 9.2 points improvement in CHOP INTEND score compared to 7.0 ± 6.6 points for the 44 in whom treatment was initiated after the age of 7 months.

## Nusinersen In SMA2

A double-blind, placebo-controlled study of nusinersen effectiveness was conducted in 126 patients with SMA2. These patients were aged 2 to 12 years at the time of treatment, had symptoms that appeared after 6 months of age, were able to sit without assistance, had no history of independent walking, and had Hammersmith Functional Motor Scale-Expanded (HFMSE) scores of 10 to 54.[13] Among these patients, 100 completed the 15-month treatment regimen with 66 allocated to the nusinersen arm and 34 to the sham-treatment arm. Of the 66 patients treated, seven were over 6 years of age and 59 were under 6 years. Only one patient (14%) older than 6 years of age at baseline was considered as a responder based on improvement by 3 points or more on the HFMSE, whereas 38 of the 59 patients (64%) under 6 years of age at treatment initiation improved by 3 points or more.

The duration of the disease also significantly impacted motor progress: in the group of children treated with nusinersen who had disease duration of less than 25 months, 18 of 20 (90%) progressed by 3 points or more, whereas of the 26 first treated when disease duration was between 25 and 44 months only 16 (61%) had a score improvement of 3 points or more. Of the 20 treated after 44 months of disease, only five (25%) were considered responders.

Patients in the nusinersen-treated cohort were included in an open-label extension study.[29] The youngest patients (under 3.69 years of age at their first injection, n=39) had an average HFMSE scale improvement of 8.6 ± 0.89 points after 690 days of treatment, compared to an improvement of 3.0 ± 0.68 points for those aged 3.69 to 4.92 years of age at first treatment (n=35). Those treated at over 4.92 years of age (n=36) lost an average of 2.0 ± 0.71 points. The same pattern of improvement according to age at treatment initiation was observed when patients were evaluated based on the Revised Upper Limb Module score, which is used to evaluate the motor performance in the upper limbs for individuals with SMA. Patients younger than 3.69 years had an average improvement of 7.9 ± 0.78 points, those in the intermediate group had an average improvement of 3.4 ± 0.54, and no change (+0.6 ± 0.49) was observed for patients older than 4.92 years at treatment initiation.

## Nusinersen In Pre-Symptomatic Patients

NURTURE is an open-label study designed to evaluate the safety and efficacy of nusinersen administered to pre-symptomatic patients. Twenty-five newborns with two (n=15) or three (n=10) copies of *SMN2* were included and received the treatment before 6 weeks of age.[30] At the time of the interim analysis (May 2018), the median (range) age at last visit was 26.0 (14.0–34.3) months. All the children were alive, and none needed permanent ventilation. All (100%) had reached the sitting position milestone, 22 of 25 (88%) could walk with assistance, and 17 of 22 patients aged more than 18 months (77%) could walk independently. This is an outcome dramatically different from patients treated post-symptomatically,[28] in

whom 60% of patients sit independently and 10% walk with assistance in the group treated early (<5.5 months of age at treatment onset) at 8 months after the modified maintenance dosing regimen was initiated. An anecdotal case of a pre-symptomatically treated patient climbing stairs has also been reported.[31]

## Data Supporting Early Treatment With Zolgensma

During a Phase I/II study to evaluate the safety and efficacy of zolgensma, 15 children with SMA1 received a single intravenous injection of the gene therapy agent.[26,32] All patients are alive at approximately 2 years after treatment, and none required permanent mechanical ventilation. The six patients who received treatment before the age of 3 months reached a CHOP INTEND score of more than 40 more rapidly (median of 11.9 months) than the six patients who received treatment after the age of 3 months (median of 22.2 months).[21,22] Patients treated before the age of 3 months acquired the sitting position (>5 s) at a mean age of 9.4 months for those with a high motor function baseline (n=3) and at 17 months (n=3) for those with a low motor function at baseline. In contrast, patients treated after the age of 3 months (n=6) reached an unassisted sitting position at the median age of 22 months.[26]

SPR1NT[33] is a Phase III study designed to assess the safety and efficacy of zolgensma in pre-symptomatic SMA patients treated before the age of 6 weeks. Eight patients with two copies of *SMN2*, nine with three copies, and one with four copies were included. In March 2019 (after follow-up ranging from 0.8 to 9.1 months), all patients were alive, and none required permanent ventilation. On the CHOP INTEND scale, of the eight patients with two copies of *SMN2*, all had obtained a score higher than 50 points, six had scores higher than 60, and three had obtained the maximum score of 64. Comparing the results of these two different studies – one still ongoing – is challenging, but these results indicate that when SMA patients are treated pre-symptomatically with zolgensma the increase in CHOP INTEND score is more rapid than when patients are treated after symptom onset and that in symptomatic patients treatment before 3 months is more beneficial than treatment after the age of 3 months.

## Data Supporting Early Treatment With Risdiplam

Better efficacy when treatment is initiated early is also suggested in the first results from the FIREFISH (NCT02913482), an open-label two-part trial to evaluate the optimal dose, the safety, and the efficacy of oral treatment of SMA1 patients with risdiplam. In 17 patients with SMA1 treated with the highest dose of risdiplam, six were younger than 5 months, and 11 were older. Fourteen children survived through 8 months of follow-up. Four of the survivors had been included before the age of 5 months and 10 after the age of 5 months. In the earlier treatment group, three of four (75%) reached the sitting position (independent and with support at hips), compared to three of ten (30%) in those treated after 5 months.[34] In 43 patients with SMA2 and SMA3 treated for 1 year with risdiplam,[35] the mean improvement on the MFM32 scale was 1.64 points in patients older than 11 years (n=19) and 3.47 points in patients aged 2–11 years (n=24). The proportion of patients who improved by more than 3 points was 71% in the younger patients and 42% in the older.

## Data Supporting Early Treatment With Branaplam

The first results of clinical evaluation of the oral therapy branaplam (NCT02268552) in an open-label, multi-part study in infants with SMA1 having two copies of *SMN2* suggested a better improvement in patients included before the age of 4 months than in those included after the age of 4 months.[36] Twenty-five patients with onset of symptoms before 6 months of age and less than 180 days of age at screening were included in this study. As of April 10, 2019, with a median follow-up of 2.2 months (0.3–10 months), the mean CHOP INTEND increase in the eight patients followed for at least 85 days of treatment was 6.0 in four patients younger than 4 months at inclusion and 3.5 in four patients older than 4 months.

## Discussion

There is a concordant set of data from different trials in SMA1 and SMA2 patients that indicate that efficacy of treatment is enhanced when patients are treated soon after or before symptom onset. Some of these data were acquired during completed double-blind, randomized, placebo-controlled studies, others were collected during open-label studies and very preliminary. Some of the data reviewed here are published in peer-reviewed journals and some have been publically presented and are available only as abstracts. Thus, the strength of the data described here is very heterogeneous. Nevertheless, all the data suggest that efficacy is optimal when treatment is initiated before or soon after the onset of symptoms. We chose to

discuss here not only peer-reviewed, but also non-peer-reviewed data since meeting presentations are mostly confined to a very specialized audience, but decision-making on newborn screening or treatment of patients does not rely only on the limited circle of clinical trial investigators. Our goal with this review is to ensure that policy makers and physicians are aware of the body of evidence – which is publically available although not necessarily peer-reviewed – that indicates the value of early treatment of SMA1 and SMA2 patients. The data presented here consider early treatment as the time of instauration of a disease-modifying drug. Nevertheless, all data were acquired in patients who were also treated with standard of care, which was an inclusion criterion in all studies. Therefore, early treatment should be also understood as early management, including multidisciplinary care follow-up.

Achieving a better treatment response is important not only from the patient perspective but also from an economic point of view. Although the costs of these treatments are very high, so is the social cost of the disease. The cost of treatment with nusinersen is $558,000 in the first year (six doses) and $279,000 per year for maintenance treatment (three doses).[37] The announced price of zolgensma is $2.125 million for the single injection.[38] In comparison, however, the estimated lifelong cost of medical support for SMA2 and SMA3 patients has been estimated at $8.4 and $6.4 million, respectively.[7]

The cost of untreated SMA1 ($120,000 per year) is much lower than that for medical support for SMA2 and SMA3 patients. Patients with SMA1 currently have a life expectancy of only 2 years. By increasing the life expectancy of these patients, the cost related to their disability will dramatically increase resulting in a negative cost-to-effectiveness evaluation. For example, nusinersen treatment provides overall benefits in terms of adjusted survival and quality of life per year, both for patients and their caregivers.[39] However, with additional costs in excess of $2.4 million,[39] mainly associated with maintenance treatment over the lifetime of the patient, and frequent hospitalization for respiratory events,[40] this is not considered a cost-effective threshold, even for a rare disease. Obtaining a much better efficacy from the same drug by initiating the treatment earlier has the potential to improve this ratio sufficiently to make treatment worthwhile.

Pre-symptomatic studies conducted with zolgensma and nusinersen indicate an efficacy far above than observed in post-symptomatic patients.[30,33] Although longer follow-up is needed to confirm that this short-term efficacy translates into a significant long-term benefit for the patient, it appears that early diagnosis should be facilitated. A meta-analysis published in 2015[41] showed that the time between symptom onset to diagnosis was considerable: the weighted mean ages of confirmed SMA genetic diagnoses were 6.3, 20.7, and 50.3 months in SMA1, 2, and 3 patients, respectively. It is likely that physician and caregiver awareness related to media attention surrounding the innovative medications now available to treat SMA will decrease time to diagnosis. Nevertheless, given the rapid evolution of the disease, especially in SMA1 patients, even reducing the diagnosis delay by 50% will not allow treatment of more than 50% of patients below the age of 3 months.

Neonatal screening would expedite diagnosis and ensure early treatment. Two pilot programs in Taiwan[42] and New York[43] validated the feasibility of SMA newborn screening (NBS). NBS for SMA is now performed in Taiwan and is registered in the Recommended Uniform Screening Panel (RUSP) in the USA. It is recommended in many states in the USA but is not mandatory. Extended pilot programs started in early 2018 in Germany and Belgium[44,45] and in early 2019 in Italy. Similar programs are planned to start elsewhere in Europe in the coming years.[46]

## Conclusion

Innovative therapeutic approaches for the treatment of spinal muscular atrophy have altered the prognosis for patients with this generally fatal disease. Independently of the mode of action, emerging data suggest that the treatments discussed here have better efficacies when patients are treated pre-symptomatically or soon after symptoms are observed rather than months after symptom onset. In the context of ultra-expensive medication and burdensome disease leading to severe disability in patients treated late, newborn screening is arguably the best solution to optimize the effect of the innovative therapies that are changing the prognosis for patients with spinal muscular atrophy.

## Acknowledgments

We thank Jacqueline R. Wyatt for editing the manuscript.

## Disclosure

TD received honorarium for lectures from Biogen. LS is principal investigator in Biogen-, Roche-, and Avexis-sponsored studies; serves on scientific advisory boards of Biogen, Roche, Avexis, and the SMA foundation; and received

honorarium for lectures and consultancies from Roche and Biogen. The authors report no other conflicts of interest in this work.

## References

1. Kolb SJ, Kissel JT. Spinal muscular atrophy. *Neurol Clin*. 2015;33(4):831–46. doi:10.1016/j.ncl.2015.07.004
2. Pearn J. Incidence, prevalence, and gene frequency studies of chronic childhood spinal muscular atrophy. *J Medical Genet*. 1978;15(6):409–413. doi:10.1136/jmg.15.6.409
3. Prior TW, Snyder PJ, Rink BD, et al. Newborn and carrier screening for spinal muscular atrophy. *Am J Med Genet A*. 2010;152a(7):1608–1616. doi:10.1002/ajmg.a.33474
4. Lefebvre S, Burglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell*. 1995;80(1):155–165. doi:10.1016/0092-8674(95)90460-3
5. Calucho M, Bernal S, Alias L, et al. Correlation between SMA type and SMN2 copy number revisited: an analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. *Neuromuscul Disord*. 2018;28(3):208–215. doi:10.1016/j.nmd.2018.01.003
6. Wirth B, Garbes L, Riessland M. How genetic modifiers influence the phenotype of spinal muscular atrophy and suggest future therapeutic approaches. *Curr Opin Genet Dev*. 2013;23(3):330–338. doi:10.1016/j.gde.2013.03.003
7. Klug C, Schreiber-Katz O, Thiele S, et al. Disease burden of spinal muscular atrophy in Germany. *Orphanet J Rare Dis*. 2016;11(1):58. doi:10.1186/s13023-016-0424-0
8. Chabanon A, Seferian AM, Daron A, et al. Prospective and longitudinal natural history study of patients with type 2 and 3 spinal muscular atrophy: baseline data NatHis-SMA study. *PLoS One*. 2018;13(7):e0201004. doi:10.1371/journal.pone.0201004
9. Mazzone E, Bianco F, Main M, et al. Six minute walk test in type III spinal muscular atrophy: a 12 month longitudinal study. *Neuromuscul Disord*. 2013;23(8):624–628. doi:10.1016/j.nmd.2013.06.001
10. Daron A, Delstanche S, Dangouloff T, Servais L. [Infantile spinal muscular atrophy: therapeutic (R)evolution]. *Rev Med Liege*. 2019;74(2):82–85.
11. Hua Y, Sahashi K, Hung G, et al. Antisense correction of SMN2 splicing in the CNS rescues necrosis in a type III SMA mouse model. *Genes Dev*. 2010;24(15):1634–1644. doi:10.1101/gad.1941310
12. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J M*. 2017;377(18):1723–1732. doi:10.1056/NEJMoa1702752
13. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J M*. 2018;378(7):625–635. doi:10.1056/NEJMoa1710504
14. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet*. 2016;388(10063):3017–3026. doi:10.1016/S0140-6736(16)31408-8
15. Hache M, Swoboda KJ, Sethna N, et al. Intrathecal injections in children with spinal muscular atrophy: nusinersen clinical trial experience. *J Child Neurol*. 2016;31(7):899–906. doi:10.1177/0883073815627882
16. Chiriboga CA, Swoboda KJ, Darras BT, et al. Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. *Neurology*. 2016;86(10):890–897. doi:10.1212/WNL.0000000000002445
17. Darras BT, Chiriboga CA, Iannaccone ST, et al. Nusinersen in later-onset spinal muscular atrophy: long-term results from the phase 1/2 studies. *Neurology*. 2019;92(21):e2492–e2506. doi:10.1212/WNL.0000000000007527
18. Pechmann A, Langer T, Schorling D, et al. Evaluation of children with SMA type 1 under treatment with nusinersen within the expanded access program in Germany. *J Neuromuscul Dis*. 2018;5(2):135–143. doi:10.3233/JND-180315
19. Pane M, Coratti G, Sansone VA, et al. Nusinersen in type 1 spinal muscular atrophy: 12-month real world data. *Ann Neurol*. 2019. Epub 2019 Jul 8. doi:10.1002/ana.25533
20. Aragon-Gawinska K, Seferian AM, Daron A, et al. Nusinersen in patients older than 7 months with spinal muscular atrophy type 1: a cohort study. *Neurology*. 2018;91(14):e1312–e1318. doi:10.1212/WNL.0000000000005773
21. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med*. 2017;377(18):1713–1722. doi:10.1056/NEJMoa1706198
22. Lowes L, Al-Zaidy S, Shell R, et al. AVXS-101 phase 1 gene therapy clinical trial in SMA type 1: patients treated early with the proposed therapeutic dose were able to sit unassisted at a younger age. *Neuromuscul Disord*. 2017;27:S208–S209. doi:10.1016/j.nmd.2017.06.414
23. Avexis. What is ZOLGENSMA? Published 2019. [Updated June, 2019]. Available from: https://www.zolgensma.com/what-is-zolgensma. Accessed July 26, 2019.
24. Naryshkin NA, Weetall M, Dakka A, et al. Motor neuron disease. SMN2 splicing modifiers improve motor function and longevity in mice with spinal muscular atrophy. *Science (New York, NY)*. 2014;345(6197):688–693. doi:10.1126/science.1250127
25. Sleigh JN, Gillingwater TH, Talbot K. The contribution of mouse models to understanding the pathogenesis of spinal muscular atrophy. *Dis Model Mech*. 2011;4(4):457. doi:10.1242/dmm.007245
26. Lowes LP, Alfano LN, Arnold WD, et al. Impact of age and motor function in a phase 1/2A study of infants with SMA type 1 receiving single-dose gene replacement therapy. *Pediatr Neurol*. 2019. Epub 2019 May 13. doi:10.1016/j.pediatrneurol.2019.05.005
27. Aragon-Gawinska K, Daron A, Ulinici A, et al. Sitting in nusinersen-treated spinal muscular atrophy type 1 patients. *Dev Med Child Neurol*. In revision.
28. Finkel R, Castro D, Farrar M, et al. Interim report on the safety and efficacy of longer-term treatment with nusinersen in infantile-onset Spinal Muscular Atrophy (SMA): updated results from the SHINE study. Communication presented at American Academy of Neurology 2019 – 71st Annual Meeting; May 4-10, 2019; Philadelphia, PA, USA.
29. Darras B, Farrar M, Mercuri E, et al. Interim report on the safety and efficacy of longer-term treatment with nusinersen in later-onset Spinal Muscular Atrophy (SMA): results from the SHINE study. Communication presented at American Academy of Neurology 2019-71st Annual Meeting; May 4-10, 2019; Philadelphia, PA, USA.
30. De Vivo DC, Topaloglu H, Swoboda KJ, et al. Nusinersen in infants who initiate treatment in a presymptomatic stage of Spinal Muscular Atrophy (SMA): interim efficacy and safety results from the phase 2 NURTURE study (S25.001). Communication presented at American Academy of Neurology 2019-71st Annual Meeting; May 4-10, 2019; Philadelphia, PA, USA.
31. Gidaro T, Servais L. Nusinersen treatment of spinal muscular atrophy: current knowledge and existing gaps. *Dev Med Child Neurol*. 2019;61(1):19–24. doi:10.1111/dmcn.14027
32. Mendell J, Lehman K, McColly M, et al. AVXS-101 Gene-Replacement Therapy (GRT) in Spinal Muscular Atrophy type 1 (SMA1): long-term follow-up from the phase 1 clinical trial (S25.006). Communication presented at American Academy of Neurology 2019-71st Annual Meeting; May 4-10, 2019; Philadelphia, PA, USA. doi:10.1017/cjn.2019.166
33. Strauss KA, Swoboda KJ, Farrar M, et al. AVXS-101 gene-replacement therapy in presymptomatic spinal muscular atrophy: SPR1NT study update. Communication presented at American Academy of Neurology 2019-71st Annual Meeting; May 4-10, 2019; Philadelphia, PA, USA.

34. Seabrook T, Baranello G, Servais L, et al. FIREFISH part 1: early clinical results following an increase ofSMN protein in infants with type 1 spinal muscular atrophy (SMA) treated with risdiplam (RG7916). Communication presented at MDA Clinical & Scientific Conference; April 13-17, 2019; Orlando, Florida.
35. Mercuri E, Baranello G, Kirschner J, et al. Update from SUNFISH part 1: safety, tolerability and PK/PD from the dose-finding study, including exploratory efficacy data, in patients with type 2 or 3 spinal muscular atrophy (SMA) treated with risdiplam (RG7916). Communication presented at American Academy of Neurology 2019-71st Annual Meeting; May 4-10, 2019 Philadelphia, PA, USA.
36. Jevtic S, Carr D, Dobrzycka-Ambrozevicz A, et al. Branaplam in type 1 spinal muscular atrophy: second part of a phase I/II study. Communication presented at 23rd SMA researcher meeting, Cure SMA; June 28-30, 2019; Disneyland hotel in Anaheim, California.
37. CADTH Common Drug Reviews. *Pharmacoeconomic Review Report: Nusinersen (spinraza): (biogen Canada Inc.): Indication: Treatment of Patients with 5q SMA*. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018.
38. Relations NM AveXis Announces Innovative Zolgensma® Gene Therapy Access Programs for US Payers and Families. Published 2019, May 24. Available from: https://www.novartis.com/news/media-releases/avexis-announces-innovative-zolgensma-gene-therapy-access-programs-us-payers-and-families. Accessed July 26, 2019.
39. Zuluaga-Sanchez S, Teynor M, Knight C, et al. Cost effectiveness of nusinersen in the treatment of patients with infantile-onset and later-onset spinal muscular atrophy in Sweden. *PharmacoEconomics*. 2019;37(6):845–865. doi:10.1007/s40273-019-00769-6
40. Ali I, Gilchrist F, Carroll WD, et al. G176(P) healthcare utilisation in SMA type 1 patients treated with nusinersen. *Arch Disease Child*. 2019;104(Suppl 2):A71.
41. Lin CW, Kalb SJ, Yeh WS. Delay in diagnosis of spinal muscular atrophy: a systematic literature review. *Pediatr Neurol*. 2015;53(4):293–300. doi:10.1016/j.pediatrneurol.2015.06.002
42. Chien YH, Chiang SC, Weng WC, et al. Presymptomatic diagnosis of spinal muscular atrophy through newborn screening. *J Pediatr*. 2017;190:124–129.e121. doi:10.1016/j.jpeds.2017.06.042
43. Kraszewski JN, Kay DM, Stevens CF, et al. Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. *Genet Med*. 2018;20(6):608–613. doi:10.1038/gim.2017.152
44. Boemer F, Caberg JH, Dideberg V, et al. Newborn screening for SMA in Southern Belgium. *Neuromuscul Disord*. 2019;29(5):343–349. doi:10.1016/j.nmd.2019.02.003
45. Boemer F, Caberg J, Dideberg V, et al. (S)un (M)ay (A)rise on SMA: l'espoir d'une région sans amyotrophie spinale [(S)un (M)ay (A)rise on SMA: the hope of a region without spinal muscular atrophy]. *Rev Med Liege*. 2019;74(9):461–464. In Press.
46. Dangouloff T, Burghes A, Bertini E, et al. 244th ENMC international workshop: newborn screening in spinal muscular atrophy,10th-12th May 2019, Hoofdorp, The Netherlands. *Neuromuscul Disord*. Submitted.

Therapeutics and Clinical Risk Management

Dovepress

Publish your work in this journal

Therapeutics and Clinical Risk Management is an international, peer-reviewed journal of clinical therapeutics and risk management, focusing on concise rapid reporting of clinical studies in all therapeutic areas, outcomes, safety, and programs for the effective, safe, and sustained use of medicines. This journal is indexed on PubMed Central, CAS, EMBase, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

**Submit your manuscript here:** https://www.dovepress.com/therapeutics-and-clinical-risk-management-journal



Annexe VIII. Newborn screening for SMA in Southern Belgium. (Chapitre III, 2)

Boemer F, Caberg J-H, Dideberg V, Dardenne D, Bours V, Hiligsmann M, Dangouloff T, Servais L. Neuromuscular Disorders. 2019.

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 29 (2019) 343–349

www.elsevier.com/locate/nmd

# Newborn screening for SMA in Southern Belgium

François Boemer[a,1,*], Jean-Hubert Caberg[b,1], Vinciane Dideberg[b], Domien Dardenne[b], Vincent Bours[c], Mickaël Hiligsmann[d], Tamara Dangouloff[e,f], Laurent Servais[e,f]

[a] *Biochemical Genetics Lab, Department of Human Genetics, CHU of Liege, University of Liege, Liege 4000, Belgium*
[b] *Molecular Genetics Lab, Department of Human Genetics, CHU of Liege, University of Liege, Liege, Belgium*
[c] *Department of Human Genetics, CHU of Liege, University of Liege, Liege, Belgium*
[d] *Department of Health Services Research, CAPHRI Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands*
[e] *I-Motion, Platform for Pediatric Clinical Trials, Arnold Trousseau Hospital, Paris, France*
[f] *Neuromuscular Center, CHR Citadelle, University of Liege, Liege, Belgium*

Received 24 May 2018; received in revised form 7 February 2019; accepted 11 February 2019

**Abstract**

Approval was recently granted for a new treatment for spinal muscular atrophy (SMA). Given that the treatment is effective when administered early and the societal burden of SMA-related disability, the implementation of a newborn screening program is warranted. We describe the stepwise process that led us to launch a newborn screening program for SMA in Southern Belgium. Different political, ethical, and clinical partners were informed about this project and were involved in its governance, as were genetic and screening labs. We developed and validated a newborn screening method to specifically recognize homozygous deletions of exon 7 in the *SMN1* gene. Subsequently, a 3-year pilot study has been recently initiated in one Belgian neonatal screening laboratory to cover 17.000 neonates per year. Coverage extension to all of Southern Belgium to screen 55.000 babies each year is underway.
© 2019 Elsevier B.V. All rights reserved.

*Keywords:* Spinal muscular atrophy; Werdnig-Hoffmann disease; Newborn screening; *SMN1*; qPCR.

## 1. Introduction

Spinal muscular atrophy (SMA) is an inherited neuromuscular disorder that is characterized by the degeneration of motor neurons in the spinal cord and muscle atrophy. The spectrum of the SMA phenotype is stratified into five types depending on the age of onset, which can range from before birth to young adulthood. Motor neuron loss often results in severe muscle weakness, causing affected infants to die before 2 years of age (type 0 with neonatal onset, or type 1 in approximately 50% of all cases). Patients with milder forms of SMA exhibit muscle weakness that progressively worsens over several years (type 2–4) [1].

SMA is caused by recessive mutations in the *survival motor neuron 1* (*SMN1*) gene [2]. About 95% of SMA cases are caused by homozygous deletions of exon 7 in *SMN1*, whereas the remaining cases exhibit a heterozygous mutation on one allele and other deleterious variants on the other. The human genome harbors a paralogous gene, *SMN2,* that differs from *SMN1* by only a few nucleotides including a C to T transition in exon 7. This base change causes the skipping of exon 7 in most *SMN2* transcripts. Approximately 90% of transcript isoforms encode a truncated unstable protein; full-length, functional SMN protein results from approximately 10% of *SMN2* transcripts.

Recently, two phase 3 trials of nusinersen demonstrated increased event-free survival and motor milestone acquisition in patients with SMA types 1 [3] and 2 [4], leading to market authorization of this drug by the Food and Drug Administration and the European Medicines Agency among others. Type 1 patients with a disease course shorter than

* Corresponding author.
*E-mail address:* f.boemer@chuliege.be (F. Boemer).
[1] Both authors contributed equally to this work.

https://doi.org/10.1016/j.nmd.2019.02.003
0960-8966/© 2019 Elsevier B.V. All rights reserved.

12 weeks are more likely to benefit from the treatment than type 1 patients for whom treatment is begun later [3]. In SMA type 2, patients younger than 6 years presented with better improvement upon treatment than did patients older than 6 years [4]. For patients with type 1 treated after the age of 7 months clinical improvement was of smaller amplitude than patients treated before 7 months [3,5–7]. A phase 2 trial is underway to examine the efficacy of multiple doses of nusinersen administered intrathecally in preventing or delaying the need for respiratory intervention or death in infants with genetically diagnosed and presymptomatic SMA (ClinicalTrials.gov identifier: NCT02386553).

In addition to nusinersen, other potential treatments have promise. A small uncontrolled study recently demonstrated the efficacy of gene replacement therapy in SMA type 1 [8], and a larger phase 3 non-controlled study is underway (NCT03461289). Phase 1–3 trials in SMA type 1 and SMA type 2 (ClinicalTrials.gov identifier: NCT02268552, NCT02908685, NCT02913482, NCT03032172) are currently being conducted using small molecules that interfere with the splicing of *SMN2* [9]. These different therapeutic advances have led to the general understanding that management of SMA is changing considerably, from palliative and symptomatic care towards disease-modifying treatment.

Although the American College of Medical Genetics recommends routine carrier screening for SMA in the general population [10] and prenatal carrier screening pilot experiences have been conducted in some countries [11], population coverage of such initiatives remains currently limited. Given the physiopathology of the disease and data from pre-clinical models demonstrating rapid death of motor neurons [12], a large benefit of early intervention in affected patients is anticipated, and, indeed, this was demonstrated clinically in clinical trials of nusinersen [3] and gene therapy [10] as well as by the presentation of the intermediary results from the nusinersen pre-symptomatic study [13] and case reports [14]. Considering the efficiency of the new treatments when they are administered early and the societal costs of SMA-related disability [15], the implementation of newborn screening (NBS) programs for SMA appears ethically and medically obvious as long as the societal decision to reimburse a medication in SMA has been made. SMA is also now included in the Recommended Uniform Screening Panel, which is the official list of disorders to which US public health departments refer to screen newborns. To date, two pilot studies have already demonstrated the feasibility of population-based screening at affordable costs [16,17].

We have developed a newborn screening method for SMA and initiated a 3-year pilot study implementing the program in Southern Belgium. The first babies were screened on March 5, 2018. Covering the full population of Southern Belgium would increase the number of screenings to approximately 55.000 births per year. The aim of this paper is to report the implementation of our SMA newborn screening program to facilitate similar initiatives in other countries.

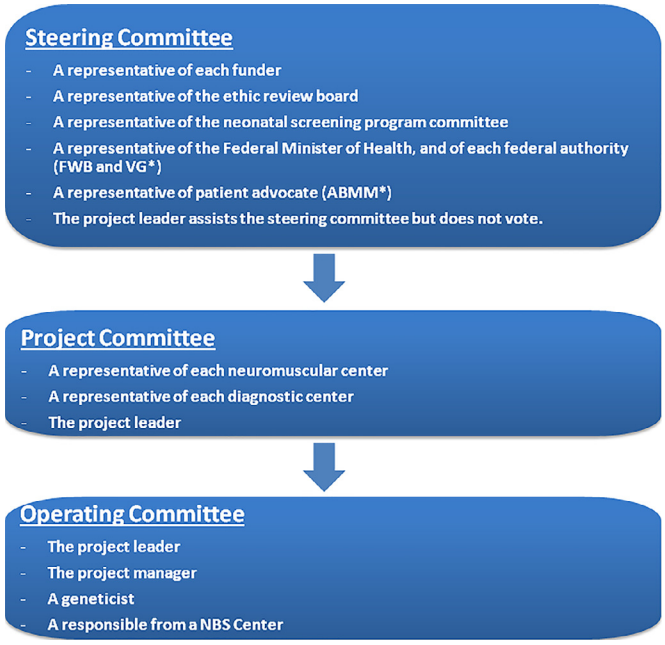



Fig. 1. Governance infrastructure for SMA newborn screening program. *FWB and VG: Federation Wallonie Bruxelles and Vlaams government; ABMM: Association Belge contre les Maladies neuro-Musculaires.

## 2. Stepwise implementation of NBS program

### *2.1. Governance*

Initiated on September 1, 2017, our project was conducted through a clear governance system that included a steering board and both project and operative committees (Fig. 1). The steering board was composed of representatives of politicians, ethics experts, NBS specialists, funders, and patient associations. This committee supervised the overall project and ensured that it was conducted according to the initial plan and met ethical, legal, and scientific standards. The project committee, including representatives of neuromuscular and diagnostic centers, was in charge of project oversight. It approved amendments and oversaw the global management. The operating committee was composed of geneticists, NBS specialists, and the project leader.

### *2.2. Engagement of community, politicians, and policy makers*

The implementation of this new NBS program was first promoted among different community partners. Political support was gathered over several meetings with politicians from different parties from both the regional and federal governments. The project was presented twice to the boards of the “Office de la Naissance et de l’Enfance” (ONE), the governmental agency in charge of NBS in Southern Belgium. ONE issued a positive opinion on the project. Accordingly, SMA was included in the list of disorders to be evaluated during the future revision of the NBS core panel in Southern

Belgium. The Belgian patient advocacy group (*Association Belge contre les Maladies Musculaires* or ABMM*)* strongly supported the project. A Facebook page called "Sun May Arise on SMA" was created to inform followers about the project's progress. The project was regularly mentioned during conferences and received mainstream media coverage, which contributed to awareness among politicians and their eventual support.

### 2.3. Ethical considerations

Genetic population screening raises ethical concerns, and informed consent from the patients may be required based on the opinion of the local ethical review board (ERB). The project was orally discussed with the institutional ERB of Liege, which provided initial written guidance. The final project, taking this guidance into consideration, was finally approved on December 5, 2017 (B412201734396), in accordance with the Declaration of Helsinki. The ERB decision was that parents had the right to be informed that a screening procedure is conducted and that they have the right to refuse it, which is the standard procedure for all NBS in Southern Belgium.

The ERB also indicated that the framework of our project should not go beyond the prerogatives fixed by our steering authorities for official NBS, namely, the identification and the preventive support of a limited list of congenital disorders. In accordance with the criteria of Wilson and Jungner [18], our objective is limited to expanding the current NBS program to preemptively identify a newly treatable, well-known disorder: spinal muscular atrophy. The project does not identify heterozygous carriers, thus avoiding the corresponding ethical debate.

According to Southern Belgium current local legislation, general information on the NBS is systematically provided to all pregnant women, and the list of screened diseases is available on the website of the public agency in charge. The ERB deemed that parental information should not include the listing of screened diseases because the risk of inducing unjustified anxiety in a significant proportion of parents by listing 14 rare diseases far outweighs the aim of providing such extended information. Additionally, while strongly recommended, NBS is not mandatory in Southern Belgium: Parents are informed that they have then the right to refuse the newborn screening for their child. Accordingly, such opting-out is not disease-specific, but would concern the entire program. We should note that in Southern Belgium refusal of NBS is extremely rare.

The ERB also stated that informed consent is meaningful only if sufficient time is devoted to receiving it. Considering the psychological context (birth of a child) and the large proportion of non-French native speakers, the advantages of SMA screening cannot be comprehensively explained to "naive" parents, especially just after birth, in less than 15 min. Additional impediments to overcome before considering a meaningful systematic consent collection include developing an infrastructure to collect and store consent, and the time required to confirm the validity of the consent before conducting the analysis. In addition, inducing non-justified anxiety in parents with a limited ability to understand the non-targeted screening constitutes a risk that cannot be underestimated.

Ultimately, the ERB considered that the information regarding the SMA screening should not be different from that provided for any other newborn screening. Identifying the homozygous deletions of a single exon rather than a metabolic anomaly was not considered sufficient to change the overall philosophy of screening. Positive test results should be confirmed by testing an independent sample, with the appropriate patient information obtained by specific healthcare providers and after informed consent. The ERB recommended that heterozygous parents be informed about the risk of subsequent homozygous pregnancies but agreed that this could be considered in a second step.

This position was approved by the state agency in charge of NBS in Southern Belgium and the project was supported by the Belgian Council of Genetics.

### 2.4. Patient flow

The sample flowchart of SMA screening does not differ from that of systematic NBS in Southern Belgium. NBS cards are collected between 72 and 120 h of life, either in maternity wards or at home. The samples are addressed to the selected neonatal screening laboratories. No additional sampling is required because the residual blood spots collected for mandated NBS are sufficient for the SMA testing. After analysis, the dried blood spot (DBS) cards are stored over a five-year period, according to our local legislation.

As is the case in the event of positive results for other diseases, positive results for SMA will be simultaneously communicated by the screening laboratory both to the pediatrician and to referent neurologists in neuromuscular centers. The parents will be contacted on the same day by the referent neuro-pediatrician of the neuromuscular center, and a consultation will be planned as soon as possible to initiate confirmatory testing using an alternative technique. The result of this second testing performed on a second independent sample, realized after parents have signed an informed consent will be available at our center within three business days. Given the importance of concomitant *SMN2* number of copies in SMA patient management [19], our confirmatory assay, involving a multiplex ligation-dependent probe amplification (MLPA) technique, will also provide information on neonate's *SMN2* status.

In Belgium, nusinersen is reimbursed for patients with two or three copies of *SMN2*. Patients can also be included in the Sprint trial (pre-symptomatic trial with gene therapy, NCT03505099). Patients with four copies can either opt for clinical surveillance or inclusion in Rainbowfish, a pre-symptomatic trial with splice modifiers (NCT pending). This is in agreement with a recent Delphi survey that recommended treatment for patients with two or three copies of *SMN2*, and

where no consensus was reached for patients with four copies of *SMN2* [19].

There are eight neuromuscular reference centers in Belgium that cover the population of 10 million people. Three of these centers cover the French-speaking Belgium, and two of the pre-symptomatic studies for gene therapy and splice modifiers are being conducted in one of them. Ultimately, the decision of parents to include their infant in any therapeutic protocol will rely on information provided by their referent neuro-pediatrician within these centers. Because approximately 98% of parents of an affected child are heterozygous carriers of one *SMN1* pathogenic variant [20], genetic counseling will also be offered to parents and at-risk family members.

### 2.5. Funding

The project was initially funded through a private donation. Subsequent support was provided by ABMM and other private donations addressed to ABMM and directed to the project. Additionally, grants were awarded from the Southern Belgium Ministry of Childhood and Investigator Initiated Trials were conducted by Avexis (a Novartis company), Biogen, and Roche.

### 2.6. Technical setup

Our analytical methodology relies on a qPCR assay of the *SMN1* gene on DNA extracted from DBS, using *RPP30* as the reference gene (Additional file 1). *SMN1* genotyping was designed to detect only homozygous deletions of exon 7 with a specific locked nucleic acid probe. Our method does not identify heterozygous carriers of the deletion, *SMN1* point mutations, or the number of copies of the *SMN2* modifier gene. The analytical method development was based on previous reports [16,17]. We designed the primers and probes used for the qPCR assay to decrease the cost and dependency on industrial producers.

To validate our assay, 53 SMA patients with homozygous deletions of *SMN1* exon 7 identified by MLPA were sampled on DBS. DBS from 93 heterozygous carriers of the deletion (one compound heterozygous for the deletion and the pathogenic c.827A>G mutation) were also collected. All patients or guardians gave their informed consent to participate in the study. Concurrently, 1000 newborn screening samples were tested.

All samples were correctly characterized. The absence of fluorescence corresponding to the *SMN1* probe was noted for all patients with homozygous deletions of exon 7 in *SMN1,* and a significant signal was observed both for heterozygous and wild-type patients. Interestingly, among the 53 confirmed SMA samples, four patients carrying four copies of *SMN2* were correctly genotyped. We thus assume that our method is not affected by the number of copies of *SMN2*.

To interpret the results on a larger scale, the *SMN1* results were integrated with the *RPP30* amplification results by calculating the endpoint-fluorescence ratios. This approach rules out the presence of any polymerase inhibitors that could interfere with the qPCR. Based on endpoint-fluorescence scatter plots (Fig. 2), a genotypic dispersion plot (Fig. 3) was created that allowed us to define an unequivocal threshold to detect homozygous deletions. Based on results for this initial population, the cutoff for the *SMN1*/*RPP30* ratio was fixed at 0.15. This threshold is estimated to be highly reliable due to the large gap in the *SMN1*/*RPP30* ratio between affected patients and individuals carrying at least one copy of exon 7. As stated previously, for ethical reasons, our method was not designed to identify carriers of the deletion and should not be used for this purpose because there is clearly a large overlap in the ratio between normal and heterozygous individuals.

The analytical costs, including material, reagents, and personnel expenses, were less than 3.00 €/newborn; therefore, the expenditures dedicated to including the SMA screening assay are reasonable and do not exceed the costs of other commonly accepted screenings (e.g., tandem-mass-spectrometry-related assays) [21]. Currently, because the sample number is modest (approximately 300 neonates per week), the DNA used for SMA testing is extracted manually. With larger population coverage in the future, process automation (i.e., the use of automatic DNA extraction), which would further decrease the cost and workload, will be warranted.

Since our screening method only identifies affected neonates carrying the homozygous deletions of exon 7 in *SMN1*, compound heterozygous patients carrying point mutations in *SMN1,* accounting for approximately 5% of SMA cases, will be missed. The long-term risk associated with systematic SMA screening is that symptomatic SMA cases will become ultra-rare, and pediatricians will become less familiar with the clinical presentations of SMA. When the symptom recognition is less accurate, the diagnosis of SMA in neonates carrying point mutations could be significantly delayed in the far future. By that time, however, large-scale screening methods (i.e., next-generation sequencing) could possibly be more widespread, thus enabling the identification of such sporadic cases.

### 2.7. Economic considerations

The cost of nusinersen in Belgium is 88,298 € per vial. Were the alternative between NBS and treatment or no treatment, NBS would not be cost effective. However, nusinersen is currently reimbursed in all patients but the presymptomatic with four copies of *SMN2* and patients supported by permanent invasive ventilation. The alternative is thus between NBS and pre-symptomatic treatment of all cases with two or three copies of *SMN2* and post symptomatic treatment of patients whom parents opt for treatment rather than palliative care. In this situation, NBS for SMA is cost effective. Indeed, as reported by Klug et al. [15], the average annual cost of illness for SMA is estimated to be approximately 70,000 € per patient in 2013 for SMA type 3

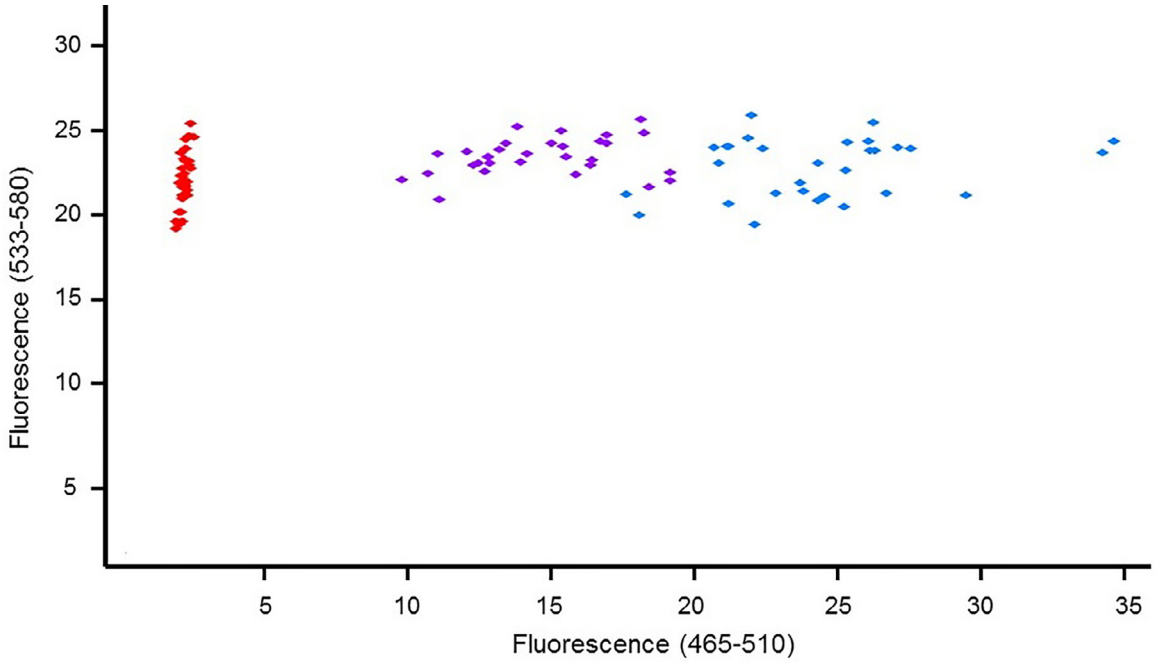



Fig. 2. Endpoint fluorescence scatter plot with *X* coordinates representing fluorescence relative to *SMN1* amplification and *Y* coordinates representing fluorescence relative to *RPP30* amplification. Red points correspond to 30 DBS samples carrying a homozygous deletion of *SMN1* exon 7. Purple points represent 30 DBS samples carrying a heterozygous deletion of *SMN1* exon 7. Blue points illustrate 30 wild-type DBS samples.

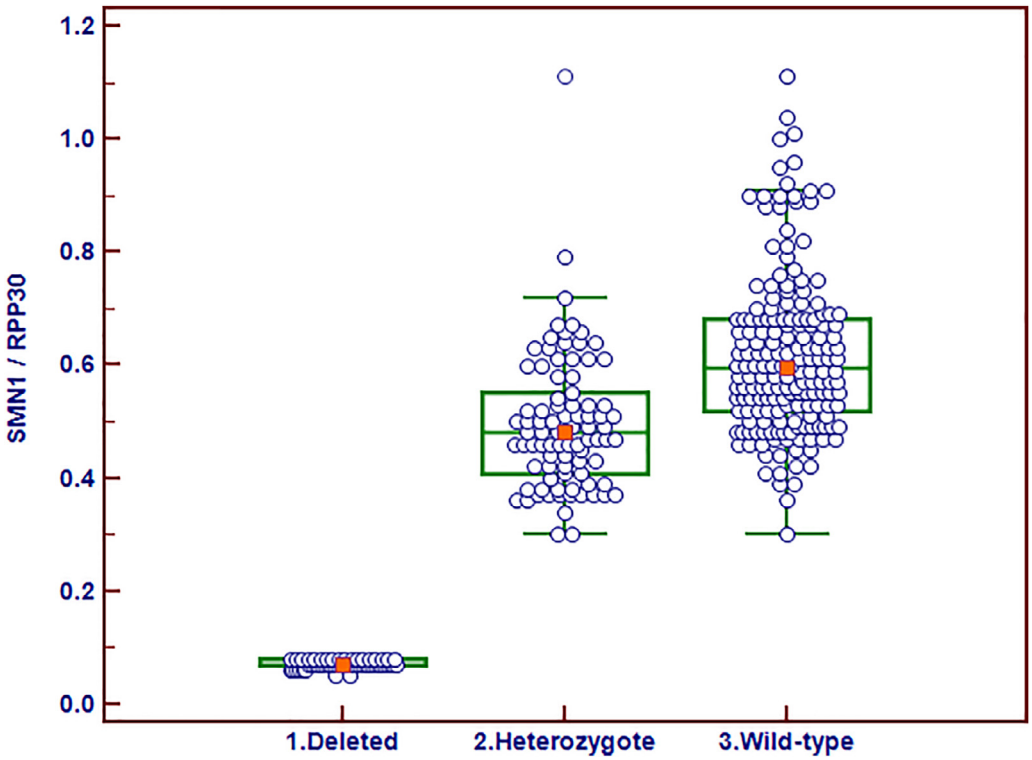



Fig. 3. Box-and-whisker plot of the ratio of *SMN1* to *RPP30* endpoint fluorescence for different genotypes: wild-type ($n = 1000$), heterozygous ($n = 93$), and homozygous deletion of exon 7 in *SMN1* ($n = 53$).

and 90.000 € for type 2. The authors stated that their results suggested a notable potential for reducing the overall costs of treating the illness and improving the health-related quality of life if the therapeutic intervention could lead to a less severe course of the disease. Disease burden for families in terms of hospitalization and life impact was confirmed in a recent natural history study [22].

Since interim results from the NURTURE study indicate that patients treated with nusinersen before the appearance of symptoms achieve a normal (for patients with three copies of *SMN2*) or nearly normal (for patients with two copies of *SMN2*) motor development with a therapeutic effect far above the one observed in post-symptomatically treated patients [13], it is thus not unreasonable to speculate that a pre-symptomatic intervention will yield better cost-effectiveness than post-symptomatic care, provided that patients treated pre-symptomatically would have been treated after the appearance of symptoms.

To better assess the issue of cost-effectiveness, a medico-economic analysis is embedded in our NBS program. Integrated evaluation of both costs of the treatment and expenditures for patient care will provide a clear overview of societal costs of screening. Whether or not NBS will lead to an increase in the number of treated patients remains to be demonstrated. Outcomes of the cost-effectiveness assessment will allow decision makers to decide whether or not to extend the project beyond the pilot phase. For comparison, neonatal screening for cystic fibrosis is a well-accepted program, even though quantifying its cost-benefit still remains challenging despite a large number of empirical studies reporting long-term outcomes in both screened and unscreened cohorts [23].

### *2.8. Communication*

The entire planning and implementation process for SMA screening could be followed on the Facebook page, which also noted that the Belgian Patients Advocacy group ABMM was collecting donations for the project. National press groups were notified when the first baby was screened on March 05, 2018, leading to national newspaper press releases and radio interviews that further informed the general population about this new program. All reactions on the Facebook page and online media were positive.

## 3. Conclusions

We share here our experience regarding the rapid implementation of a genetic-based newborn screening program for SMA. Our governance system was established on September 1, 2017, and the first babies were screened 6 months later, on March 5, 2018. The Southern Belgian organization of NBS and neuromuscular centers were suited to this rapid achievement. The position of the ERB, which considered the pros and the risks of signing consent, considerably supported the rapid advancement of the program. We anticipate that the position of the Belgian ERB could benchmark similar positions elsewhere and facilitate the acceptance of SMA screening. The introduction of qPCR techniques into our NBS program, first implemented as described here for SMA, could be broadened in the near future to the screening for severe combined immunodeficiencies or other genetic disorders. Our pilot study will be conducted over the next three years, following which the healthcare authorities will have to determine whether testing for SMA as part of newborn screening will continue. A concomitant medico-economic assessment is embedded to this project to inform decision-making in Belgium and other countries regarding the medical and economic value of the program.

## Ethics approval and consent to participate

Ethical approval (reference B412201734396) was obtained from the Institutional Review Board (Ethical Committee of the hospital CHR Citadelle, Liège, Belgium), in compliance with the Declaration of Helsinki. All patients or guardians gave informed consent to participate in the study.

## Competing interests

LS is member of Biogen, AveXis, Roche and Cytokinetics Scientific advisory boards and has provided consultancy to Roche, Avexis and Biogen. The other authors have no financial disclosures relevant to this article. The authors declare that they have no competing interests.

## Funding

This pilot study is supported by Biogen, AveXis, and the ABMM (Association Belge contre les Maladies neuro-Musculaires), Minister's Office Alda GREOLI (Wallonia-Brussels Community)

## Acknowledgments

Authors thank the paramedical team of the Neuromuscular Center at CHR Citadelle and the technical team of the Biochemical Genetics Laboratory at CHU Liege.

## Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.02.003.

## References

[1] Kaufmann P, McDermott MP, Darras BT, Finkel R, Kang P, Oskoui M, et al. Observational study of spinal muscular atrophy type 2 and 3: functional outcomes over 1 year. Arch Neurol 2011;68:779–86. doi:10.1001/archneurol.2010.373.

[2] Lefebvre S, Bürglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell 1995;80:155–65. doi:10.1016/0092-8674(95)90460-3.

[3] Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017;377:1723–32. doi:10.1056/NEJMoa1702752.

[4] Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus Sham control in later-onset spinal muscular atrophy. N Engl J Med 2018;378:625–35. doi:10.1056/NEJMoa1710504.

[5] Pechmann A, Langer T, Schorling D, Stein S, Vogt S, Schara U, et al. Evaluation of children with SMA Type 1 under treatment with nusinersen within the expanded access program in Germany. J Neuromuscul Dis 2018. doi:10.3233/JND-180315.

[6] Pane M, Palermo C, Messina S, Sansone VA, Bruno C, Catteruccia M, et al. Nusinersen in type 1 SMA infants, children and young adults: preliminary results on motor function. Neuromuscul Disord 2018;28:582–5. doi:10.1016/j.nmd.2018.05.010.

[7] Aragon-Gawinska K, Seferian AM, Daron A, Gargaun E, Vuillerot C, Cances C, et al. Nusinersen in patients older than 7 months with spinal muscular atrophy type 1: a cohort study. Neurology 2018;91:e1312–18. doi:10.1212/WNL.0000000000006281.

[8] Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med 2017;377:1713–22. doi:10.1056/NEJMoa1706198.

[9] Naryshkin NA, Weetall M, Dakka A, Narasimhan J, Zhao X, Feng Z, et al. SMN2 splicing modifiers improve motor function and longevity in mice with spinal muscular atrophy. Science 2014;345:688–93 (80-). doi:10.1126/science.1250127.

[10] Prior TWProfessional Practice and Guidelines Committee. Carrier screening for spinal muscular atrophy. Genet Med 2008;10:840–2. doi:10.1097/GIM.0b013e318188d069.

[11] Su Y-N, Hung C-C, Lin S-Y, Chen F-Y, Chern JPS, Tsai C, et al. Carrier screening for spinal muscular atrophy (SMA) in 107,611 pregnant women during the period 2005–2009: a prospective population-based cohort study. PLoS One 2011;6:e17067. doi:10.1371/journal.pone.0017067.

[12] Govoni A, Gagliardi D, Comi GP, Corti S. Time is motor neuron: therapeutic window and its correlation with pathogenetic mechanisms in spinal muscular atrophy. Mol Neurobiol 2018:1–12. doi:10.1007/s12035-017-0831-9.

[13] Bertini E, Hwu W-L, Reyna SP, Farwell W, Gheuens S, Sun P, et al. Efficacy and safety of nusinersen in infants with presymptomatic spinal muscular atrophy (SMA): interim results from the NURTURE study. Eur J Paediatr Neurol 2017;21:e14. doi:10.1016/j.ejpn.2017.04.1218.

[14] Gidaro T, Servais L. Nusinersen treatment of spinal muscular atrophy: current knowledge and existing gaps. Dev Med Child Neurol 2018. doi:10.1111/dmcn.14027.

[15] Klug C, Schreiber-Katz O, Thiele S, Schorling E, Zowe J, Reilich P, et al. Disease burden of spinal muscular atrophy in Germany. Orphanet J Rare Dis 2016;11:58. doi:10.1186/s13023-016-0424-0.

[16] Chien YH, Chiang SC, Weng WC, Lee NC, Lin CJ, Hsieh WS, et al. Presymptomatic diagnosis of spinal muscular atrophy through newborn screening. J Pediatr 2017;190:124–9 e1. doi:10.1016/j.jpeds.2017.06.042.

[17] Kraszewski JN, Kay DM, Stevens CF, Koval C, Haser B, Ortiz V, et al. Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. Genet Med 2017. doi:10.1038/gim.2017.152.

[18] Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: WHO; 1968.

[19] Glascock J, Sampson J, Haidet-Phillips A, Connolly A, Darras B, Day J, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through Newborn screening. J Neuromuscul Dis 2018;26:1–14. doi:10.3233/JND-180304.

[20] Wirth B, Schmidt T, Hahnen E, Rudnik-Schöneborn S, Krawczak M, Müller-Myhsok B, et al. De novo rearrangements found in 2% of index patients with spinal muscular atrophy: mutational mechanisms, parental origin, mutation rate, and implications for genetic counseling. Am J Hum Genet 1997;61:1102–11. doi:10.1086/301608.

[21] Feuchtbaum L, Cunningham G. Economic evaluation of tandem mass spectrometry screening in California. Pediatrics 2006;117:S280–6. doi:10.1542/peds.2005-2633G.

[22] Chabanon A, Seferian AM, Daron A, Péréon Y, Cances C, Vuillerot C, et al. Prospective and longitudinal natural history study of patients with Type 2 and 3 spinal muscular atrophy: baseline data NatHis-SMA study. PLoS One 2018;13:e0201004. doi:10.1371/journal.pone.0201004.

[23] Grosse SD. Showing value in newborn screening: challenges in quantifying the effectiveness and cost-effectiveness of early detection of phenylketonuria and cystic fibrosis. Healthcare 2015;3:1133–57. doi:10.3390/healthcare3041133.

## Annexe IX. Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium. (Chapitre III, 2)

Boemer F, Caberg JH, Beckers P, Dideberg V, Di Fiore S, Bours V et Al. Scientific Reports. 2021

scientific reports

Check for updates

OPEN

# Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium

François Boemer[1]✉, Jean-Hubert Caberg[2], Pablo Beckers[1], Vinciane Dideberg[2], Samantha di Fiore[1], Vincent Bours[3], Sandrine Marie[4], Joseph Dewulf[4], Lionel Marcelis[5], Nicolas Deconinck[6], Aurore Daron[7], Laura Blasco-Perez[8], Eduardo Tizzano[8], Mickaël Hiligsmann[9], Jacques Lombet[10], Tatiana Pereira[10], Lucia Lopez-Granados[10], Sarvnaz Shalchian-Tehran[11], Véronique van Assche[12], Arabelle Willems[12], Sofie Huybrechts[13], Bénédicte Mast[14], Rudolf van Olden[15], Tamara Dangouloff[7] & Laurent Servais[7,16]

**Three new therapies for spinal muscular atrophy (SMA) have been approved by the United States Food and Drug Administration and the European Medicines Agency since 2016. Although these new therapies improve the quality of life of patients who are symptomatic at first treatment, administration before the onset of symptoms is significantly more effective. As a consequence, newborn screening programs have been initiated in several countries. In 2018, we launched a 3-year pilot program to screen newborns for SMA in the Belgian region of Liège. This program was rapidly expanding to all of Southern Belgium, a region of approximately 55,000 births annually. During the pilot program, 136,339 neonates were tested for deletion of exon 7 of *SMN1*, the most common cause of SMA. Nine SMA cases with homozygous deletion were identified through this screen. Another patient was identified after presenting with symptoms and was shown to be heterozygous for the *SMN1* exon 7 deletion and a point mutation on the opposite allele. These ten patients were treated. The pilot program has now successfully transitioned into the official neonatal screening program in Southern Belgium. The lessons learned during implementation of this pilot program are reported.**

**Abbreviations**

| | |
|---|---|
| ABMM | Association Belge contre les Maladies neuro-Musculaires |
| CHMP | Committee for Medicinal Products for Human Use |
| CHOP-INTEND | Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders |
| DBS | Dried blood spot |
| EMA | European Medicines Agency |
| EMG | Electromyography |
| ERB | Ethical review board |

[1]Biochemical Genetics Laboratory, Human Genetics, CHU Sart-Tilman, University of Liège, B35, 4000 Liège, Belgium. [2]Molecular Genetics Lab, Department of Human Genetics, CHU of Liège, University of Liège, Liège, Belgium. [3]Department of Human Genetics, CHU of Liège, University of Liège, Liège, Belgium. [4]Department of Laboratory Medicine, Cliniques Universitaires Saint-Luc, UCLouvain, Brussels, Belgium. [5]Laboratory of Pediatric Research, Free University of Brussels, Brussels, Belgium. [6]Neuromuscular Reference Center, Hôpital des Enfants Reine Fabiola (HUDERF), Université Libre de Bruxelles, Brussels, Belgium. [7]Division of Child Neurology, Reference Center for Neuromuscular Diseases, Department of Pediatrics, CHR Citadelle, University of Liège, Liège, Belgium. [8]Department of Clinical and Molecular Genetics, Hospital Valle Hebron, Barcelona, Spain. [9]Department of Health Services Research, CAPHRI Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands. [10]ONE, Office de la Naissance et de l'Enfance, Herstal, Belgium. [11]Department of Neurology and Ethic Committee, CHR Citadelle, Liège, Belgium. [12]ABMM, Association Belge contre les Maladies neuro-Musculaires ASBL, La Louvière, Belgium. [13]Biogen, Cambridge, MA, USA. [14]Roche, Basel, Switzerland. [15]Novartis Gene Therapies Switzerland GmbH, Zürich, Switzerland. [16]MDUK Neuromuscular Center, Department of Paediatrics, University of Oxford, Oxford, UK. ✉email: F.Boemer@chuliege.be

Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium (Chapitre III, 2)

| | |
|---|---|
| FDA | Food and Drug Administration |
| HINE | Hammersmith Infant Neurologic Examination |
| MLPA | Multiplex ligation-dependent probe amplification |
| NBS | Newborn screening |
| NMRC | Neuro Muscular Reference Centers |
| ONE | Office de la Naissance et de l'Enfance |
| qPCR | Quantitative polymerase chain reaction |
| RUSP | Recommended Uniform Screening Panel |
| SMA | Spinal muscular atrophy |
| SMN | Survival of Motor Neuron |
| TAT | Turnaround time |

Spinal muscular atrophy (SMA) is a neuromuscular disorder characterized by muscle atrophy resulting from the degeneration of motor neurons in the spinal cord. SMA is caused by biallelic pathogenic variants in the *SMN1* gene, which encodes Survival of Motor Neuron (SMN), a protein essential for survival of motor neurons[1]. Approximately 95% of patients carry a homozygous deletion of exon 7 in the *SMN1* gene, the remaining 5% of cases are due to the deletion of exon 7 on one allele and a deleterious variant on the opposite allele. *SMN2* is a pseudogene that differs from *SMN1* by only a few nucleotides, including a C to T transition in exon 7. This variant results in the skipping of exon 7 in about 90% of *SMN2* transcripts, thereby encoding a truncated, unstable protein. The full-length, functional SMN protein results from approximately 10% of *SMN2* transcripts. The number of *SMN2* copies is inversely correlated with the severity of the phenotype. Patients with two copies usually present with the most severe and frequent form of spinal muscular atrophy, SMA1. In these patients, symptom onset usually occurs before the age of 6 months, and this type of SMA is associated with high mortality and morbidity[2]. Patients with a larger number of copies of *SMN2* may present with symptoms long after acquisition of ambulation; a limited few even develop symptoms in adulthood. Currently, SMA is classified into four types, SMA1, SMA2, SMA3, and SMA4, based on maximal motor ability achieved.

Over the last few years, several new treatments for SMA have dramatically improved the prognosis of affected patients[3]. Nusinersen[4] was the first drug to be approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in December 2016 and June 2017, respectively. In Belgium, nusinersen has been reimbursed by the healthcare system since September 2018. More recently, onasemnogene abeparvovec-xioi gene therapy[5] also received FDA and EMA approval, in May 2019 and May 2020 respectively. The marketing authorization of a third drug, risdiplam[6], was granted by the FDA last year, and it also received a positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) in February 2021. Several other drugs are currently in development[7].

Based on these recent advances in SMA management and on evidence showing that patients treated presymptomatically have better outcomes[8,9], newborn screening (NBS) for SMA has begun in several countries[10–18]. Moreover, in 2018 SMA was included in the Recommended Uniform Screening Panel (RUSP), the list of disorders that the US Department of Health and Human Services recommends be screened for as part of NBS programs[19].

In early 2018, the authors of this paper and Neuromuscular Reference Centers (NMRCs) of Southern Belgium launched a 3-year NBS pilot program for SMA under the project title "Sun May Arise on SMA". The pilot project was done in close collaboration with our industry partners AveXis, Biogen, and Roche, who funded a significant part of the program, as well as with the governmental agency in charge of NBS in Southern Belgium, the Office of Birth and Childhood (Office de la Naissance et de l'Enfance, ONE)[20,21]. It should be noted that NBS is not a federal competency in Belgium, and therefore such initiatives are conducted by a separate government agency in Northern Belgium.

The initial pilot phase of the 'Sun May Arise on SMA' project transitioned into an official program in Southern Belgium on 1 March 2021. Northern Belgium has correspondingly made a political commitment to include SMA in their official program in 2022.

This manuscript reports the key insights gained during the pilot effort.

## Results

**Inclusion of SMA in the NBS program.** The process that led to implementation of the NBS program for SMA in Southern Belgium has been previously reported[20]. A key principle was involvement of all stakeholders from the beginning. Political, ethical, and clinical partners, including genetic and screening labs, were involved in the project's governance.

**Incidence.** Over the 3-year pilot study from March 2018 to February 2021, 136,339 neonates were tested for the *SMN1* exon 7 deletion using a previously described qRT-PCR test with fluorescence read-out[20]. The dispersion plot of the ratio of *SMN1* to the housekeeping gene *RPP30* allowed clear discrimination between positive (i.e., SMA patients with a homozygous deletion of exon 7) and negative results (Fig. 1).

Nine SMA cases were identified. To our knowledge, no newborn carrying a homozygous deletion was missed over this period. All patients with symptoms of neuromuscular disease in Belgium are referred to an NMRC, thus it is quite unlikely that such a case could happen without one of the centers being informed. Nevertheless, we cannot rule out the possibility that a patient with SMA3 or SMA4 born during the period of the pilot study may be diagnosed in the future.

One SMA1 patient was not be diagnosed through NBS. The neonate was heterozygous for the *SMN1* exon 7 deletion and had the c.815A>G (p.Tyr272Cys) point mutation on the opposite allele. This patient was referred to an NMRC at the age of 4 months, after the onset of symptoms compatible with SMA.

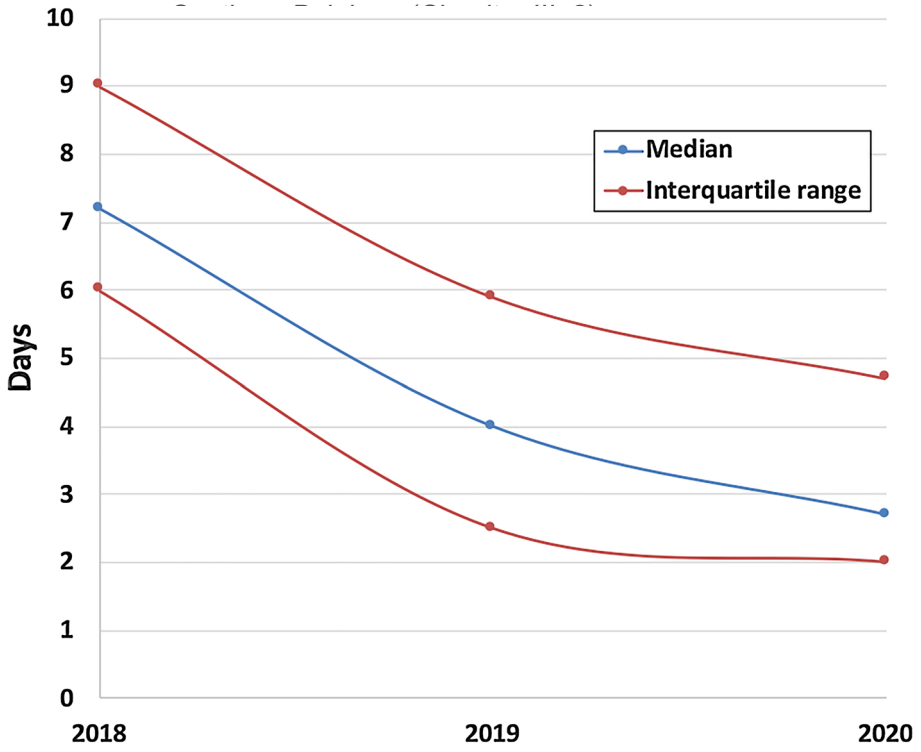



**Figure 1.** TAT improvement over the study period.

| ID | DBS sampling | DBS received by NBS center | DBS received by Liège lab | First-tier results | Second-tier results | Parents contacted | First visit | Treatment initiation | Delay between first visit and treatment initiation |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 3 | 4 | 4 | 11 | 18 | 20 | 21 | 32 | 11 |
| 2 | 3 | 8 | 8 | 27 | 30 | 30 | 31 | 38 | 7 |
| 3 | 4 | 5 | 9 | 13 | 13 | 13 | 14 | 41 | 27 |
| 4 | 4 | 13 | 19 | 27 | 27 | 31 | 32 | 54 | 22 |
| 5 | 4 | 9 | 29 | 31 | 35 | 35 | 37 | 49 | 12 |
| 6 | 3 | 4 | 11 | 18 | 22 | 20 | 21 | 39 | 18 |
| 7 | 3 | 7 | 15 | 17 | 21 | 18 | 20 | 29 | 9 |
| 8 | 3 | 5 | 15 | 18 | 19 | 22 | 23 | 32 | 9 |
| 9 | 3 | 6 | 6 | 9 | 10 | 9 | 10 | 30 | 20 |
| Median | 3 | 6 | 11 | 18 | 21 | 20 | 21 | 38 | 12 |

**Table 1.** Screening and diagnostic timeline (in post-natal days) for SMA patients identified by NBS.

This corresponds to an incidence for SMA in Southern Belgium of 1 in 13,634 newborns (95% confidence interval: 1/8417 to 1/35,858). The incidence of homozygous deletion is 1 in 15,149 individuals (95% confidence interval: 1/9163 to 1/43,696).

**Neonate referral.** Positive screening results were immediately communicated by the laboratory to both the neonate's pediatrician and to referent neurologists in NMRC. The parents were contacted on the same day by a referent neuro-pediatrician or by a pediatrician of the maternity ward and consultation was planned as soon as possible. Thanks to the second-tier MLPA testing performed on DBS-extracted DNA, the number of *SMN2* copies was available to the clinician at the patient's first visit, and therefore the clinician could immediately explain relevant therapeutic options to parents. The neonate's blood was then drawn to perform the MLPA confirmatory analysis. There were no false positives from the initial DBS testing.

The screening and diagnostic timelines for the ten SMA patients are detailed in Table 1. All nine patients identified through NBS began treatment before the age of 2 months. In order to ensure the most efficient management of patients, it is important to save time. Over the course of the project, the turnaround time (TAT) was considerably improved. For the first 9 months, the population coverage was limited to Liège NBS center, where about 300–350 samples were analyzed each week. The median TAT, calculated for the interval between DBS

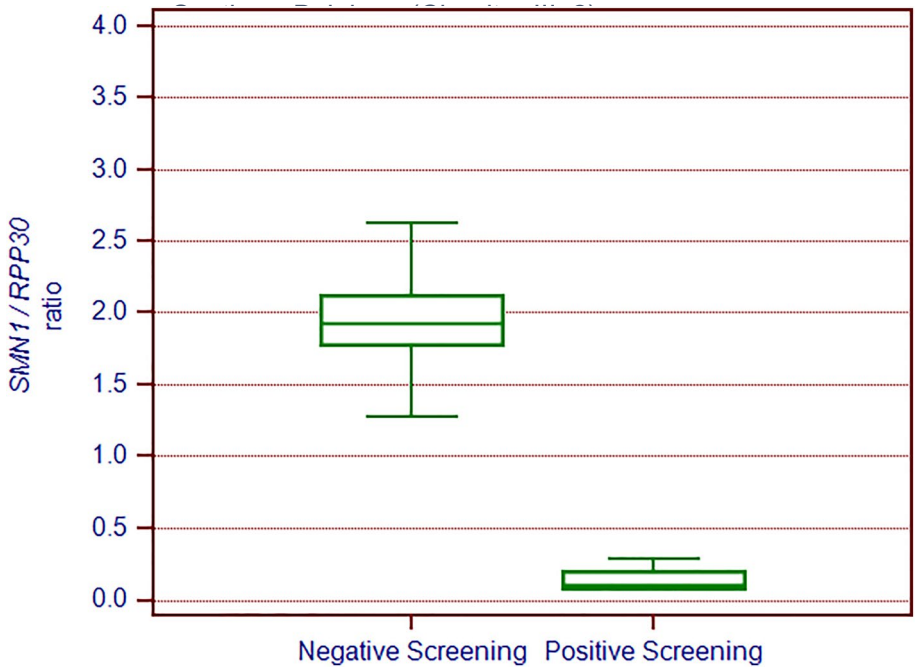



**Figure 2.** Box-and-whisker plot of the endpoint-fluorescence *SMN1* to *RPP30* ratio for negative (n = 136.330) and positive (n = 9) screening results.

reception in Liège's center and validation of the result, was 7.2 days (interquartile range: 6.0–9.0 days). At the beginning of 2019, the other two NBS centers in Southern Belgium joined the project, outsourcing their analytical process to Liège's center, and the number of samples analyzed increased to approximately 1200 samples per week. Early in 2019, acquisition of a dedicated qPCR instrument and hiring of a devoted lab technician permitted a considerable scale-up of our analytical throughput. Subsequently, TAT was reduced from 7.2 days in 2018 (interquartile range: 6.0–9.0 days) to 4.0 days later in 2019 (interquartile range: 2.5–5.9 days) and to 2.7 days in 2020 (interquartile range: 2.0–4.7 days) (Fig. 2).

**Patient treatment and outcomes.** Parents were informed about the different therapeutic options during first visit. Nusinersen was available in Belgium from the start of the study. Risdiplam and the gene therapy onasemnogene abeparvovec-xioi were not commercially available in the country during the pilot study but were accessible through several concurrent clinical trials in NMRC (Spr1nt: NCT03505099, STRIVE-EU: NCT03461289, Rainbowfish: NCT03779334). For the six patients who received nusinersen, treatment began an average of 10 days after the first consultation (7–20). Parents of Patient 9 initially refused the treatment, which explains the delay in initiation. The delay between the first consultation and the initiation of treatment was the longest for the three patients who participated in the therapeutic trials (18, 22, and 27 days) as participation in a trial required testing prior to inclusion. Patients who showed early clinical manifestations of the disease, even if weak (i.e., only areflexia), were those who had two copies of *SMN2*. These patients had developmental delays despite treatment. Patients with three or four copies of *SMN2* showed no symptoms at the time of treatment initiation and hit motor developmental milestones at the usual ages. *SMN2* copy number and modifier variants, treatment regimen, and evolution of symptoms in identified patients are summarized in Table 2.

**Lessons learned from individual cases.** *The case of treatment refusal.* The parents of one patient initially refused treatment. The child had three copies of *SMN2* and was asymptomatic at the time of diagnosis. The parents were not French speakers, and at the initial consultation were accompanied by a French-speaking cousin serving as a translator. This was not an optimal situation, as the translator was emotionally invested and only partially translated the physician's explanation to the parents. Following their refusal, they were offered a second consultation with two different child neurologists and a psychologist with a professional translator in attendance, and a further consultation was also proposed with a German-speaking neurologist. The parents stated several times that they would prefer to wait for their daughter to present with symptoms before discussing treatment. This prompted internal discussions among the clinical team to balance the right of parents to make decisions regarding the care of their child with the rights of the child given that clinical evidence clearly indicates that treatment before symptom onset is necessary to ensure the possibility of normal development[8,9].

After requesting several external medical and external opinions, we explained to the parents that the clinical team could not carry the responsibility of withholding care, and that the family court would have to be consulted. After receiving initial opinions from the prosecutor supportive of intervention, the parents accepted the necessity of treatment. Interestingly, the relationship between the clinical care team and the family remained positive,

| Id | Sex | *SMN2* copy number | *SMN2 polymorphism* | | Treatment | Treatment initiation in days | Phenotype at treatment start | Sitter (in months) | Walker (in months) | Age at last assessment (in months) | Max score on CHOP-INTEND scale[c] | Max score on HINE 2 scale[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | c.859G > C | c.835-44A > G | | | | | | | | |
| 1 | M | 3 | Negative | Negative | Nusinersen | 32 | Asympto-matic | 7 | 13 | 33 | 64 | 26 |
| 2 | F | 2 | Negative | Negative | Nusinersen | 38 | Areflexia, discrete hypotonia, | 7 | 27 with help | 32 | 58 | 24 |
| 3 | M | 3 | Negative | Negative | OA[b] | 41 | Asympto-matic | 7 | 15 | 24 | 64 | 24 |
| 4 | M | 2 | / | / | OA[b] | 54 | Discrete hypotonia | 6,5 | Stand up alone | 22 | 51 | 20 |
| 5 | M | 4 | Negative | Negative | Nusinersen | 49 | Asympto-matic | 6 | 12 | 22 | 64 | – |
| 6 | F | 4 | Negative | Negative | Risdiplam | 39 | Asympto-matic | 5 | 12 | 20 | 64 | 26 |
| 7 | M | 2 | Negative | Negative | Nusinersen | 29 | Areflexia | 6 | No | 18 | 60 | 17 |
| 8 | M | 2 | Negative | Negative | Nusinersen | 32 | Areflexia | 6 | No | 14 | 54 | – |
| 9 | F | 3 | Negative | Negative | Nusinersen | 30 | Asympto-matic | 7 | 11 | 12 | 62 | 21 |
| 10[a] | M | 2 | / | / | Nusinersen | 150 | Proximal hypotonia, areflexia, tongue fas-ciculations | No | No | 17 | 34 | 2 |

**Table 2.** *SMN2* copy number and polymorphisms, treatment, and evolution of symptoms of SMA patients identified during the study period. [a]Compound heterozygous patient identified at the age of 4 months. [b]Onasemnogene abeparvovec-xioi. [c]CHOP-INTEND maximum score is 64. [d]HINE Sect. "Results" maximum score is 26. A dash indicates that the test was not given.

and 1 year after birth the mother stated that they had been in such an emotional state that they were 'unable to make the right decision' and now recognized that treatment was the best solution.

No other parents refused treatment. Some parents indicated their preference for a particular treatment. The choice to proceed with a treatment was always made in light of treatment availability, the child's clinical condition, and the scientific data available at the time, and with the mutual agreement of the treating physicians and the parents.

*Patients and siblings with four copies of SMN2.* As mentioned earlier, treatment of children is specifically discussed with the parents. In the two cases with four copies of *SMN2* identified during the pilot study, the parents promptly agreed to the proposal to initiate early treatment.

One of the patients identified with four copies of *SMN2* had two older siblings, aged 4 years and 6 years and 6 months, respectively. Interestingly, the mother presented with two copies of *SMN1* and the father with one copy. We then discovered that the maternal grandmother had three copies of *SMN1*, two on the same chromosome, and the paternal grandmother had only one copy. The mother was 2/0, which means that she would not have been identified as at-risk during carrier testing.

The initial clinical examination of the siblings of the patient indicated normal development, but the parents wished to have them tested. This was done, and we found that, like the infant, both children had the homozygous deletion of exon 7 of *SMN2* and four copies of *SMN2*. Their parents opted to delay treatment. Further evaluations of the siblings were performed after 3 months.

The physician had concerns regarding the potential muscle weakness of the older sibling, but the parents again opted to delay treatment. When the child was aged 7 years and 4 months, a video sent by the parents clearly confirmed a proximal weakness and fatigability. On examination, there was an absence of patellar reflex, and the need for the child to support himself with a hand on his leg when rising from the floor. The motor function measure and six-minute walk test were stable. The parents refused to treat at this stage.

At 7 years and 11 months, the electromyography (EMG) showed a 30% loss of motor amplitude. At 8 years, the same difficulties at the clinical examination were noticed with a complete absence of reflexes, and unchanged compound muscle action potential.

The second sibling, who was 4 years old at the time of diagnosis, showed no deficit in either the clinical examination, physiological tests or EMG. Follow-up is continuing with clinical and physiotherapy examinations every 6 months. To date, at the age of 5 years and 6 months, the second child is still wholly asymptomatic.

**Transition to health authorities: a strong partnership among stakeholders.** Retrospectively, the key element in the successful transition from the trial project to a government-sanctioned public health program was the involvement and unanimous support of all stakeholders from the beginning of the project and throughout its duration. Transitioning to an official program was an initial objective of the pilot program. The involvement of patient advocacy groups, neuromuscular reference centers, and newborn screening centers, as well as

| Screening period | 03/2018–02/2019 | 03/2019–02/2020 | 03/2020–02/2021 |
|---|---|---|---|
| Number of screened newborns | 22,930 | 57,607 | 55,802 |
| Expected number of SMA cases (λ) | 1.51 | 3.80 | 3.68 |
| Probability of 0 cases during period | 0.220 | 0.022 | **0.025** |
| Probability of 3 cases during period | **0.127** | 0.204 | 0.209 |
| Probability of 6 cases during period | 0.004 | **0.094** | 0.087 |

**Table 3.** Poisson probability of case occurrence in Southern Belgium based on annual periods. Bold values correspond to the number of SMA cases actually identified during the designated period.

public engagement through broadcast and social media (such as on the study's Facebook page, www.facebook.com/sunmayariseonsma) also significantly facilitated the rapid and smooth transition to an official program.

A clear governance structure helped to build a strong partnership between pilot study leaders, the regional agency in charge of NBS, and NBS centers. Public involvement gave rise to support from across the political spectrum in Belgium. The ordinance incorporating SMA into the NBS list for Southern Belgium was passed by the Parliament of Wallonia on 4 February 2021 for implementation on 1 March 2021, with immediate handover from the study team to the public health service after the completion of the 3-year pilot project. UCLouvain and ULBruxelles NBS centers are incorporating the SMA screening test into their own infrastructure.

## Discussion

The incidence of SMA of 1 in 15,149 determined during the NBS pilot study in Southern Belgium is broadly consistent with previous studies. The incidence reported in Taiwan was 1 in 17,181 neonates[12]. In Germany, 30 SMA cases were identified during screening of 213,279 DBS cards for a incidence of 1 in 7109 infants[17,22]. Australian NBS has identified nine SMA patients in 103,903 newborns screened for an incidence of 1 per 11,544[18]. New York State recently screened more than 225,000 neonates and reported a much lower incidence of 1 per 28,137[23]. The authors of that study argued that the low SMA incidence reported in their area is likely due to biased estimates, coupled with increased awareness and access to carrier screening, genetic counselling, cascade testing, prenatal diagnosis, and advanced reproductive technologies. A better understanding of this low incidence is of primary importance since it could have consequences on reimbursement for disease-modifying therapies and NBS funding decisions[24].

Surprisingly, we did not identify any SMA neonates during the third year of our pilot study. Based on the Poisson distribution of rare events, the probability of diagnosing no cases of SMA over 1 year is 2.5% (Table 3). Given the low probability that there should be no cases in a year, we hypothesized that carrier screening and prenatal testing had contributed to this outcome. We therefore contacted various molecular genetics centers in Southern Belgium to request the number of positive results for SMA based on pre-conceptional and prenatal diagnosis during the corresponding period. However, they reported no positive results that could explain this absence of cases over the previous year. Subsequently, three new cases were identified in the first 4 months following the end of the pilot, which further reinforces the hypothesis of a pure random distribution.

Our study is, to our knowledge, the first to report a SMA patient compound heterozygous for the *SMN1* exon 7 deletion and a point mutation on the opposite allele, in the context of NBS. Because the first-tier assays specifically target the homozygous *SMN1* deletion, this patient was not be identified during the screening process. Rather, the patient was identified at the age of 4 months, after referral for mild hypotonia. The clinical sensitivity of SMA NBS is estimated between 95 and 98%, as affected individuals who are compound heterozygotes (i.e., those with one *SMN1* allele lacking exon 7 and a point mutation on the second allele) are missed[11,25]. To date, no false negatives or false positives have been identified in our screening program.

The five neonates with either three or four copies of *SMN2* were all asymptomatic at treatment start (Table 2). Most presented the highest Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) and Hammersmith Infant Neurologic Examination, Sect. "Results" (HINE-2) scores during their last motor assessment (age range: 12–33 months). The four newborns with two copies of *SMN2* showed a slight hypotonia and/or a discrete areflexia when the treatment was initiated. These patients did not get the highest scores on CHOP-INTEND and HINE-2 scales during their last motor assessment (age range: 14–32 months). Of these four patients, three were treated with the approved nusinersen therapy. Treatment initiation may thus be considered as relatively delayed (range: 29–54 days) when compared to first visit (range: 20–32 days). This lag may be a factor that has impaired the most favorable outcome for these patients. In the future, we hope that the recent transition of our pilot study into the official neonatal screening program will facilitate a more prompt care.

The overall evidence for the efficacy of early treatment of patients with SMA has been recently reviewed[26]. It is likely that the cost of the new SMA treatments initially hampered the implementation of NBS programs by the political authorities. Presently, the substantial cost burden of standard care for patients with SMA is estimated to be between US$ 75,047 and US$ 196,429 per year for SMA1 patients, and between US$ 27,157 and US$ 82,474 for other types of SMA[27]. Therefore, given the high cost-to-benefit ratio of drugs approved at current prices when administered to post-symptomatic patients[27], we know it is critical to identify patients prior to symptom onset. A medico-economic evaluation with assessment of patient quality of life is also currently ongoing to assess the cost-effectiveness of our NBS program[20]. Pre-treatment levels of phosphorylated neurofilaments are a validated marker of nerve cell damage in pre-symptomatic and in young SMA1 patients[28]. These levels decrease exponentially in pre-symptomatic SMA patients with two *SMN2* copies, indicating acute and severe neuronal loss[9].

Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium (Chapitre IV/2)

These data indicate that it is critical to begin treatment of SMA1 patients with as little delay as possible. An NBS program is accordingly an ideal method for early identification of these infants.

There were several incidents encountered during this pilot program, the description of which may help other NBS programs more effectively communicate with the parents of recently diagnosed infants.

In one case, parents initially refused treatment. In hindsight, this might have been avoided if a professional translator had been present during the first consultation. In another case, three SMA-affected children of a mother with two copies of *SMN1* on the same allele were diagnosed as a result of NBS: the youngest through the NBS pilot program itself and his siblings following this initial positive identification. As the mother would not have been identified as at-risk during carrier testing, this clearly indicates that carrier screening should not be relied upon as the sole strategy against SMA.

Finally, we were faced with a case of a patient with symptoms that the parents refused to recognize. Political authorities must therefore put plans in place to deal with cases of refusal of treatment. Presently, some countries leave the decision of treatment to a multidisciplinary consultation meeting, whereas others leave all choice to the parents. The present authors believe that the interest of the child must take priority over parents' rights. A collegial discussion of these potential issues prior to implementation of an NBS program is necessary.

Our study suffers from the small size of the studied population. Southern Belgium has a total population of approximately 4.5 million people; therefore the number of cases identified in the neonate population remains low.

Today, nine countries around the world have started SMA NBS, with the number of newborns screened set to increase in the coming years as further countries embark on similar programs[29]. Our project confirms that a pilot program can be rapidly transitioned into the official NBS program. Given the effective treatments now available for SMA and the importance of treatment prior to the onset of symptoms, testing for SMA should be incorporated into screening of all newborns.

## Materials and methods

**Newborn samples.** NBS samples were collected on Whatman® 903 cards between 48 and 120 h of life either in maternity wards or at home, in accordance with legal requirements of the federal authority (Wallonie–Bruxelles Federation) in charge of NBS in Southern Belgium.

The dried blood spot (DBS) cards were sent to selected neonatal screening laboratories. No additional sampling was required to incorporate SMA testing in the standard NBS panel as the residual blood spots collected for conventional NBS were sufficient to test for SMA. After analysis, filter papers are stored at room temperature for 5 years.

As detailed in our previous manuscript[20], parental consent was not required for participation in this study. While strongly recommended, NBS is not mandatory in Southern Belgium and parents are informed that they have the right to refuse screening for their child. This opt-out option is not disease-specific; it applies to the neonatal screening panel as a whole. The project was approved by our ethical review board (reference number B412201734396), in accordance with the Declaration of Helsinki.

**NBS assay and confirmatory method.** The flow chart for screening for SMA is shown in Fig. 3. We designed a quantitative polymerase chain reaction (qPCR) assay to specifically detect homozygous deletions of *SMN1* exon 7 on DNA extracted from DBS[20]. DNA extraction was performed by alkaline denaturation at 98 °C. qPCR amplification was performed in 96-well plates, preloaded with primers, dye-labeled probes, and master mix provided by Eurogentec. This assay cannot identify heterozygous carriers of the deletion of exon 7 or *SMN1* point mutations, and the number of copies of *SMN2* were not determined in this first-tier assay. Given the importance of *SMN2* copy number in SMA management, qPCR-positive results were confirmed by the multiplex ligation-dependent probe amplification (MLPA) technique, which also provided information on *SMN2* status. For this purpose, we used the Salsa MLPA Probemix P021 SMA diagnostic kit (MRC Holland).

First-tier positive samples were re-analyzed twice from the same DBS. Simultaneously, a second-tier MLPA assay was performed from the same DNA extracted for the first-tier qPCR. Upon positive results from confirmatory testing, neonates were immediately referred to a neuro-pediatrician in one of the NMRCs involved in the trial. At the first visit, fresh blood was collected to confirm the positive screening result by MLPA on an independent sample. Additionally, we also sequenced the *SMN2* gene to look for the presence of both c.859G>C and c.835-44A>G intragenic modifier variants. A *SMN2*-specific PCR has been used to amplify exons 7 and 8 and study the presence or absence of the positive modifier variants. The primers (available on request) were designed based on the paralogous sequence variants described by Blasco-Pérez et al.[30], in order to achieve specificity towards *SMN2* (Blasco-Perez et al., in preparation).

**Population coverage.** There are approximately 55,000 annual births in Southern Belgium, and NBS for these infants is carried out by three independent academic centers. The current project was launched in March 2018 in Liège's NBS laboratory, which screens about 16,000 newborns per year. Due to strong support from the supervisory authorities and the efforts of the project management team to promote the project, the pilot study rapidly expanded to include the two other screening centers of Southern Belgium, UCLouvain and ULBruxelles. In order to rapidly implement the program in these two centers, DNA was extracted in the lab to which the DBS card was sent. Sealed microtiter plates containing samples for SMA screening were then transferred to the lab in Liège, which ran qPCR assays on all samples. SMA screening was offered to the entire neonate population of Southern Belgium beginning in early 2019.

**Clinical and therapeutic protocol.** All patients were examined by board certified neuro-paediatricians with expertise in SMA. The different therapeutic options were proposed to parents during the first visit. The

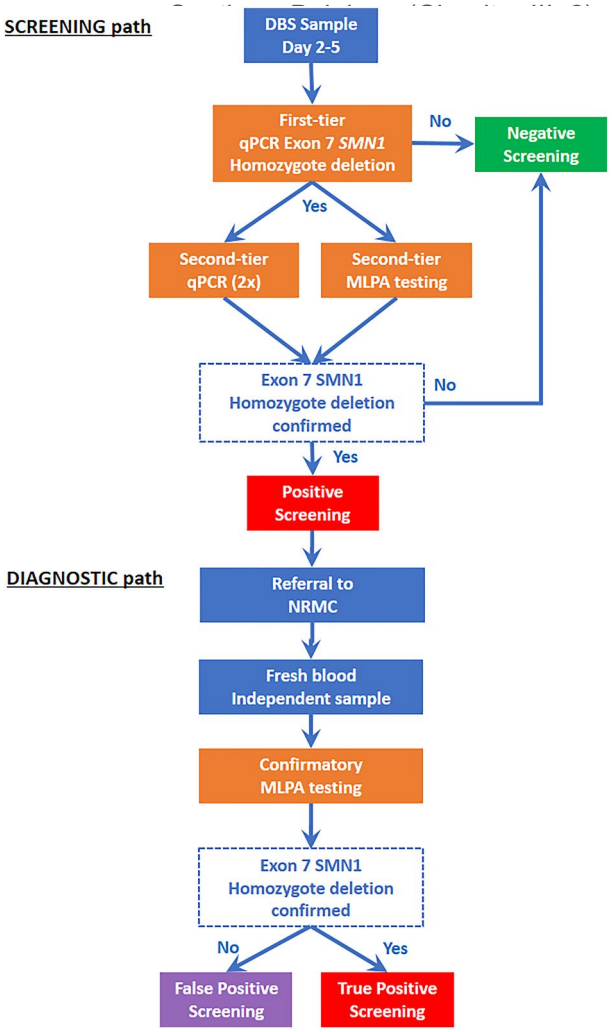



**Figure 3.** Screening and diagnostic flowchart.

phenotype at the start of treatment and the ages of sitting and walking acquisitions were recorded. Longitudinal motor milestone assessment was evaluated by trained physiotherapists, using CHOP-INTEND and HINE-2 scales.

**Statistical analyses.** Exact probability of rare event occurrence was estimated by a Poisson distribution in which the probability mass function is $p(x) = e^{-\lambda} \cdot \lambda^x / x!$, where $\lambda$ is the average number of events per year, and x is number of events in each interval.

**Ethics approval.** Ethical approval (reference B412201734396) was obtained from the Institutional Review Board (Ethical Committee of the Hospital CHR Citadelle, Liège, Belgium) in compliance with the Declaration of Helsinki.

## Data availability

The data that support the findings of this study are available from the corresponding author, FB, upon reasonable request.

Received: 13 April 2021; Accepted: 27 September 2021
Published online: 07 October 2021

## References

1. Lefebvre, S. *et al.* Identification and characterization of a spinal muscular atrophy-determining gene. *Cell* **80**, 155–165 (1995).
2. Kolb, S. J. *et al.* Natural history of infantile-onset spinal muscular atrophy. *Ann. Neurol.* **82**, 883–891 (2017).
3. Ramdas, S. & Servais, L. New treatments in spinal muscular atrophy: An overview of currently available data. *Expert Opin. Pharmacother.* **21**, 307–315 (2020).

Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium. (Chapitre IV, 2)


4. Finkel, R. S. *et al.* Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N. Engl. J. Med.* **377**, 1723–1732 (2017).
5. Mendell, J. R. *et al.* Single-dose gene-replacement therapy for spinal muscular atrophy. *N. Engl. J. Med.* **377**, 1713–1722 (2017).
6. Baranello, G. *et al.* Risdiplam in type 1 spinal muscular atrophy. *N. Engl. J. Med.* **384**, 915–923 (2021).
7. Servais, L., Baranello, G., Scoto, M., Daron, A. & Oskoui, M. Therapeutic interventions for spinal muscular atrophy: Preclinical and early clinical development opportunities. *Expert Opin. Investig. Drugs* https://doi.org/10.1080/13543784.2021.1904889 (2021).
8. Govoni, A., Gagliardi, D., Comi, G. P. & Corti, S. Time is motor neuron: Therapeutic window and its correlation with pathogenetic mechanisms in spinal muscular atrophy. *Mol. Neurobiol.* **55**, 6307–6318 (2018).
9. De Vivo, D. C. *et al.* Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscul. Disord.* **29**, 842–856 (2019).
10. Pyatt, R. E. & Prior, T. W. A feasibility study for the newborn screening of spinal muscular atrophy. *Genet. Med.* **8**, 428–437 (2006).
11. Prior, T. W. *et al.* Newborn and carrier screening for spinal muscular atrophy. *Am. J. Med. Genet. Part A* **152**, 1608–1616 (2010).
12. Chien, Y.-H. *et al.* Presymptomatic diagnosis of spinal muscular atrophy through newborn screening. *J. Pediatr.* **190**, 124-129.e1 (2017).
13. Kraszewski, J. N. *et al.* Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. *Genet. Med.* **20**, 608–613 (2018).
14. Dangouloff, T. *et al.* 244th ENMC international workshop: Newborn screening in spinal muscular atrophy May 10–12, 2019, Hoofdorp, the Netherlands. *Neuromuscul. Disord.* **30**, 93–103 (2020).
15. McMillan, H. J. *et al.* Newborn screening for spinal muscular atrophy: Ontario testing and follow-up recommendations. *Can. J. Neurol. Sci.* (2020). https://doi.org/10.1017/cjn.2020.229
16. Shinohara, M. *et al.* A novel system for spinal muscular atrophy screening in newborns: Japanese pilot study. *Int. J. Neonatal Screen.* **5**, 41 (2019).
17. Vill, K. *et al.* One year of newborn screening for SMA—results of a German pilot project. *J. Neuromuscul. Dis.* **6**, 503–515 (2019).
18. Kariyawasam, D. S. T. T., Russell, J. S., Wiley, V., Alexander, I. E. & Farrar, M. A. The implementation of newborn screening for spinal muscular atrophy: The Australian experience. *Genet. Med.* **22**, 557–565 (2020).
19. Kemper, A. R. *et al.* Evidence-based review of newborn screening for spinal muscular atrophy (SMA): Final report (v5.2). *USA Matern. Child Heal. Bur. United States Secr. Heal. Hum. Serv. Advis. Comm. Heritable Disord. Newborns Child.* **5**, 108 (2018).
20. Boemer, F. *et al.* Newborn screening for SMA in Southern Belgium. *Neuromuscul. Disord.* **29**, 343–349 (2019).
21. Boemer, F. *et al.* (S)un (M)ay (A)rise on SMA: The hope of a region without spinal muscular atrophy. *Rev. Med. Liège* **74**, 461 (2019).
22. Czibere, L. *et al.* High-throughput genetic newborn screening for spinal muscular atrophy by rapid nucleic acid extraction from dried blood spots and 384-well qPCR. *Eur. J. Hum. Genet.* **28**, 23–30 (2020).
23. Kay, D. M. *et al.* Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy. *Genet. Med.* **22**, 1296–1302 (2020).
24. Dangouloff, T., Boemer, F., Caberg, J.-H. & Servais, L. Correspondence on: "Discrepancy in Spinal Muscular Atrophy Incidence findings in newborn screening programs: The influence of carrier screening?" by Kay et al. *Genet. Med.* (2020). https://doi.org/10.1038/s41436-020-0887-1
25. Wirth, B. An update of the mutation spectrum of the survival motor neuron gene (SMN1) in autosomal recessive spinal muscular atrophy (SMA). *Hum. Mutat.* **15**, 228–237 (2000).
26. Dangouloff, T. & Servais, L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: Current perspectives. *Ther. Clin. Risk Manag.* **15**, 1153–1161 (2019).
27. Dangouloff, T., Botty, C., Beaudart, C., Servais, L. & Hiligsmann, M. Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments. *Orphanet J. Rare Dis.* **16**, 47 (2021).
28. Darras, B. T. *et al.* Neurofilament as a potential biomarker for spinal muscular atrophy. *Ann. Clin. Transl. Neurol.* **6**, 932–944 (2019).
29. Dangouloff, T., Vrščaj, E., Servais, L., Osredkar, D. & Group, S. N. W. S. Newborn screening programs for spinal muscular atrophy worldwide: Where we stand and where to go. *Neuromusc. Disord.* **31**(6), 574–582 (2021).
30. Blasco-Pérez, L. *et al.* Beyond copy number: A new, rapid, and versatile method for sequencing the entire SMN2 gene in SMA patients. *Hum. Mutat.* **42**, 787–795 (2021).


## Acknowledgements

Authors thank the paramedical teams of Neuromuscular Centers of CHU of Liège and the technical teams of newborn screening and molecular laboratories of CHU of Liège. We thank Dominic Tromans for the English edition of the manuscript.

## Author contributions

F.B. wrote the manuscript, and contributed to study design and to method development. J.H.C. contributed to study design and to method development; he reviewed the manuscript. P.B. and V.D. contributed to method development and reviewed the manuscript. S.D.F., L.B.P. and E.T. performed technical experiments and revised technical aspects of the manuscript. V.B. provided genetic advice on method development and reviewed the manuscript. S.M., J.D., and L.M. contributed to sample collection and reviewed the manuscript. N.D., A.D., S.S.T., V.V.A., and A.W. ensured SMA patient follow-up and reviewed the manuscript. M.H., S.H., B.M., and R.V.O. contributed to study design and reviewed the manuscript. T.D. is the project manager; she contributed to the study design, ensured SMA patient follow-up, and reviewed the manuscript. L.S. is the project leader; he contributed to study design, ensured SMA patient follow-up, and reviewed the manuscript. All authors reviewed and approved the final manuscript.

## Funding

This pilot study is supported by AveXis, Biogen, Roche, the ABMM (Association Belge contre les Maladies neuro-Musculaires), Minister's Office Alda GREOLI (Wallonia-Brussels Community) and donations from individuals.

## Competing interests

L.S. is member of Biogen, AveXis, Roche, and Cytokinetics scientific advisory boards and has provided consultancy to Roche, AveXis, and Biogen. E.T. has received grant support to conduct clinical trials on SMA from Ionis/Biogen and serves as a consultant to AveXis, Novartis, Biogen, Biologix, Cytokinetics, Roche. A.D. is investigator of SMA studies for Roche and Novartis Gene Therapies and received honoraria for consultancy for the scientific advisory board of AveXis Belgium. B.M. is an employee of Roche. S.H. is an employee of and has stock/stock

options in Biogen. R.V.D.'s employer is Novartis Gene Therapies and owns Novartis stock or other equities. T.D. and F.B. have given lectures sponsored by Biogen, Novartis and Roche. The other authors have no financial disclosures relevant to this article.

## Additional information

**Correspondence** and requests for materials should be addressed to F.B.

**Reprints and permissions information** is available at www.nature.com/reprints.

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2021



## Annexe X. Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments. (Chapitre III, 3)

Dangouloff T, Botty C, Beaudart C, Servais L, Hiligsmann M. Orphanet. 2021.

Dangouloff *et al. Orphanet J Rare Dis* (2021) 16:47
https://doi.org/10.1186/s13023-021-01695-7

Orphanet Journal of Rare Diseases

REVIEW Open Access

# Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments

Tamara Dangouloff[1], Camille Botty[1], Charlotte Beaudart[2], Laurent Servais[1,3,4] and Mickaël Hiligsmann[2*]

## Abstract

**Background:** Spinal muscular atrophy (SMA) is a rare and devastating condition for which new disease-modifying treatments have recently been approved. Given the increasing importance of economic considerations in healthcare decision-making, this review summarizes the studies assessing the cost of SMA and economic evaluations of treatments. A systematic review of the literature in PubMed and Scopus up to 15 September 2020 was conducted according to PRISMA guidelines.

**Results:** Nine studies reporting the annual cost of care of patients with SMA and six evaluations of the cost-effectiveness of SMA treatments were identified. The average annual cost of SMA1, the most frequent and severe form in which symptoms appear before the age of 6 months were similar according to the different studies, ranged from $75,047 to $196,429 per year. The yearly costs for the forms of the later-onset form, called SMA2, SMA3, and SMA4, which were usually pooled in estimates of healthcare costs, were more variable, ranging from $27,157 to $82,474. The evaluations of cost-effectiveness of treatment compared nusinersen treatment against standard of care (n = 3), two treatments (nusinersen and onasemnogene abeparvovec) against each other and no drug treatment (n = 1), nusinersen versus onasemnogene abeparvovec (n = 1), and standard of care versus nusinersen with and without newborn screening (n = 1). The incremental cost-effectiveness ratio (ICER) of nusinersen compared to standard of care in SMA1 ranged from $210,095 to $1,150,455 per quality-adjusted life years (QALY) gained and that for onasemnogene abeparvovec ranged from $32,464 to $251,403. For pre-symptomatic patients, the ICER value ranged from $206,409 to $735,519. The ICERs for later-onset forms of SMA (2, 3 and 4) were more diverse ranging from $275,943 to $8,438,049.

**Conclusion:** This review confirms the substantial cost burden of standard of care for SMA patients and the high cost-effectiveness ratios of the approved drugs at the current price when delivered in post-symptomatic patients. Since few studies have been conducted so far, there is a need for further prospective and independent economic studies in pre- and post-symptomatic patients.

**Keywords:** Burden, Cost, Cost-effectiveness, Economic, ICER, Nusinersen, Spinal muscular atrophy, Onasemnogene abeparvovec

## Background

Spinal muscular atrophy (SMA) is the most common genetic cause of death in children, with an incidence of approximately 1 in 12,000 live births and a prevalence of approximately 1–2 per 100,000 persons [1]. Patients present with loss of muscle strength followed by onset of progressive paralysis including in the respiratory

*Correspondence: m.hiligsmann@maastrichtuniversity.nl
[2] Department of Health Services Research, CAPHRI Care and Public Health Research Institute, Maastricht University, P.O. Box 616, Maastricht 6200 MD, The Netherlands
Full list of author information is available at the end of the article

© The Author(s) 2021. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

muscles. Clinical phenotypes are grouped into four forms according to disease severity and age of onset. The most severe form, called type I or "Werdnig-Hoffman disease" (SMA1), manifests during the first 6 months of life. Without respiratory assistance, children with SMA1 usually die during the first 2 years of life [2]. Onset of type II or "intermediate" SMA (SMA2) occurs between the ages of 6 and 18 months. Type 2 can be divided into 2a (patients who sit independently) and 2b (patients who have acquired the standing position but cannot walk). Of patients with SMA type 2a 81% and 67.7% survive without permanent ventilation at ages 30 and 50 years, respectively. Survival without permanent ventilation of patients with SMA type 2b is normal at least within the first 60 years of life [3]. The first symptoms of type III or Kugelberg–Welander disease (SMA3) appear after the age of 18 months. The life expectancy of SMA3 patients is not different from that of the general population [3]. Patients with type IV SMA (SMA4) develop symptoms during the second or third decade of life; patients with this form, also known as "adult form" retain the ability to walk. SMA has severe consequences for patients in terms of mobility and quality of life for patients with all forms [4] and in terms of life expectancy for the most severe and most common forms. SMA is a major cause of disability in children and adults [2, 5] and leads to a substantial economic burden.

An increasing number of studies have investigated the economic impact of SMA in terms of quality of life and cost. One recent study [6] systematically reviewed quality of life studies in SMA and concluded that despite heterogeneous results, quality of life is substantially impaired in SMA, mainly due to poor physical health. To the best of our knowledge, no study has yet systematically reviewed the studies assessing the cost of SMA. Given the increasing importance of economic considerations in pricing and reimbursement decisions, it is important to provide an overview of the overall costs and economic consequences of the SMA.

Recently, three disease-modifying drugs have reached patients' bedsides [7]: The first to be approved by both the FDA in December 2016 and the EMA in June 2017 was nusinersen [8], marketed as Spinraza by Biogen (Cambridge, MA, USA). Onasemnogene abeparvovec [9, 10], marketed as Zolgensma by Novartis (Basel, Switzerland), was approved by the FDA in May 2019 and the EMA in August 2020. The third entry is risdiplam, an oral compound marketed as Evrisdy, developed by F. Hoffmann-La Roche (Basel, Switzerland), PTC Therapeutics (South Plainfield, NJ, USA), and the SMA Foundation, approved by the FDA in August 2020 [11]; the application to the EMA is pending as of October 2020. Each of these treatments has better efficacy when delivered early [12], which has prompted pre-symptomatic trials [13] and newborn screening programs [14, 15]. Economic comparisons of the costs and the outcomes of these options are necessary as policy makers and payers seek to determine their economic values. Economic evaluations also drive reimbursement and pricing decisions. In this study, we systematically review the economic burden of SMA (in terms of costs) and provide an overview and critical appraisal of economic evaluations in SMA.

## Methods

### Literature search

Two literature searches were conducted using Medline (PubMed) and Scopus (Elsevier) following the PRISMA checklist [16]: one for cost studies of SMA and the second for economic evaluations in the field of SMA. We searched for original, full-text articles reporting costs or economic evaluations of SMA published after January 1, 1998. To identify relevant articles, Medical Subject Headings (Mesh terms) (indexed on Pubmed) and key terms regarding SMA (i.e., "spinal muscular atrophy" OR "Werdnig-Hoffmann" OR "Kugelberg-Welander") were combined with key terms for costs and economic evaluation. The details of the search strategy are shown schematically in Additional files 1 and 2. In the search for cost studies, the following terms were used: "cost of illness", "price", "pricing", "cost", "costing", "costly", costed", "or healthcare cost". In the search for economic evaluation studies, the following terms were used: "economic", "health economic", "cost-effectiveness", "cost effective", "healthcare cost", "health-allocation", "health-utilization", "cost-utility", "cost–benefit analysis", "cost analysis", or "economic impact". Identified articles were manually searched to identify additional articles of relevance. The literature search was last updated on September 15, 2020.

### Selection of studies

Two researchers (TD, CB) first screened titles and abstracts independently for eligibility and then evaluated the full text. To be included, the articles had to be published original research, in English or French, and had to report on cost or economic evaluation in SMA. Economic evaluations were included if they compared both costs and outcomes (e.g., in quality-adjusted life years (QALYs)) between two or more interventions. Articles where SMA was not specifically studied (some articles cover neuromuscular diseases broadly without specific analysis of SMA) and articles where the cost of only a single specific dimension (e.g., ventilation) was reported were excluded. The two reviewers compared their findings, and a list of studies for full-text screening was created. The reasons for article exclusion were recorded, and potential disagreements were specified to be resolved by

consensus or, if necessary, with the involvement of a third investigator (MH).

To assess the quality of the economic evaluation, the Consensus on Health Economics Checklist-extended (CHEC-extended) was used [17]. This checklist is an extension of the original CHEC checklist that includes questions about model-based economic evaluations [18, 19]. To limit the possibility of biased results, two reviewers (ChB and TD) independently reviewed the quality appraisal of the included studies. Possible differences in scoring were discussed until consensus was reached. To calculate an overall quality score for each article based on the CHEC-extended checklist, each time a "Yes" was scored, 1 point was allocated, and each time "suboptimal" was scored, 0.5 points were allocated.

### Data extraction and presentation

Studies were thus classified as reporting costs or economic evaluation. Study characteristics related to publication (authors, year of publication, journal name) and study design (country, sample size, population age and gender) were first extracted. For cost studies, we further extracted type of costs, year of costing, time horizon, estimation method, and primary and secondary results. For economic evaluations we extracted type of economic evaluation, perspective, year of costing, time horizon, intervention, comparator, method (trial-based or model-based), outcomes used, results base case, results sensitivity analyses, and funding source. The incremental cost-effectiveness ratio (ICER) is defined as the difference between an alternative and the comparator in terms of costs, divided by their differences in outcomes. The ICER representing the additional cost per QALY gained due to the intervention is then compared to a cost-effectiveness threshold representing the willingness of the decision-maker to pay.

Costs and ICERs were converted to 2020 US dollars to facilitate comparison (data from the Bureau of Labor Statistics' consumer Price index obtained in October 2020 was used) [20, 21]. For non-US dollars costs, we first translated cost into US dollars of the same year using the exchange rates in the Organisation for Economic Co-operation and Development database [22] and then converted amounts into 2020 US dollars. Cost data are presented by SMA types. SMA1 is typically defined as a SMA that starts before 6 months of age in infants who do not spontaneously acquire independent sitting position. Three articles [23–25] included in our analysis do not use the current classification and consider only two groups: "early onset" (patients who develop symptoms during the first year of life) and "other" (patients who develop symptoms after 1 year of age). We grouped the "early onset" SMA with SMA1. In doing so, some SMA2 patients were categorized as SMA1.

## Results

### Study selection process

The initial searches (conducted in December 2019) identified 447 articles that describe cost studies of SMA and 124 economic evaluations of SMA. After removing 232 and 62 duplicates, respectively, and screening by title and abstract, 93 and 76 articles, respectively, were identified for full-text screening. A second search conducted in September 2020 identified 64 references to be screened for costs and 43 for economic evaluation for full-text screening. Of these, nine articles describing the cost of SMA and six describing economic evaluation were included. Figure 1 shows the flow chart based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16] used for the identification of these studies.

### Costing studies

Nine cost studies were identified. One study provided cost perception through interviews with seven families [26]. It was excluded because no monetary values were provided. The characteristics of included studies for the cost of SMA are reported in Table 1.

Some studies presented only direct healthcare costs, and others also included direct non-medical costs of the disease (vehicle and home modification, for example). A few studies also estimated indirect costs. Indirect costs were collected through questionnaires submitted to families and captured informal care provided by parents and loss of income of the primary caregiver due to absenteeism from work [35]. Two studies presented costs for all types of SMA together [27, 28]. For the remaining seven articles, costs were classified by type of SMA. With the exception of one study [29] that compared the costs with and without therapy, the other studies reported costs of the disease and are not based on a potential treatment or a comparison of treatment costs. The average annual costs of SMA1 (including early onset and SMA before one year) for the six studies for which these costs were determined, ranged from $75,047 to $196,429 per year [23–25, 29–31]. The costs for the other groups were also variable, ranging from $27,157 [30] to $82,474 [31]. Figure 2 presents the costs by type of SMA.

One study [29] estimated the costs of patients treated with nusinersen compared to those not treated. Total cost per year of a patient with SMA1 decreased significantly from $142,386 without treatment to $95,820 with nusinersen treatment when excluding drug cost. The cost of nusinersen included in these studies varied from $516,896 [35] to $907,665 [29] in the first year, and from

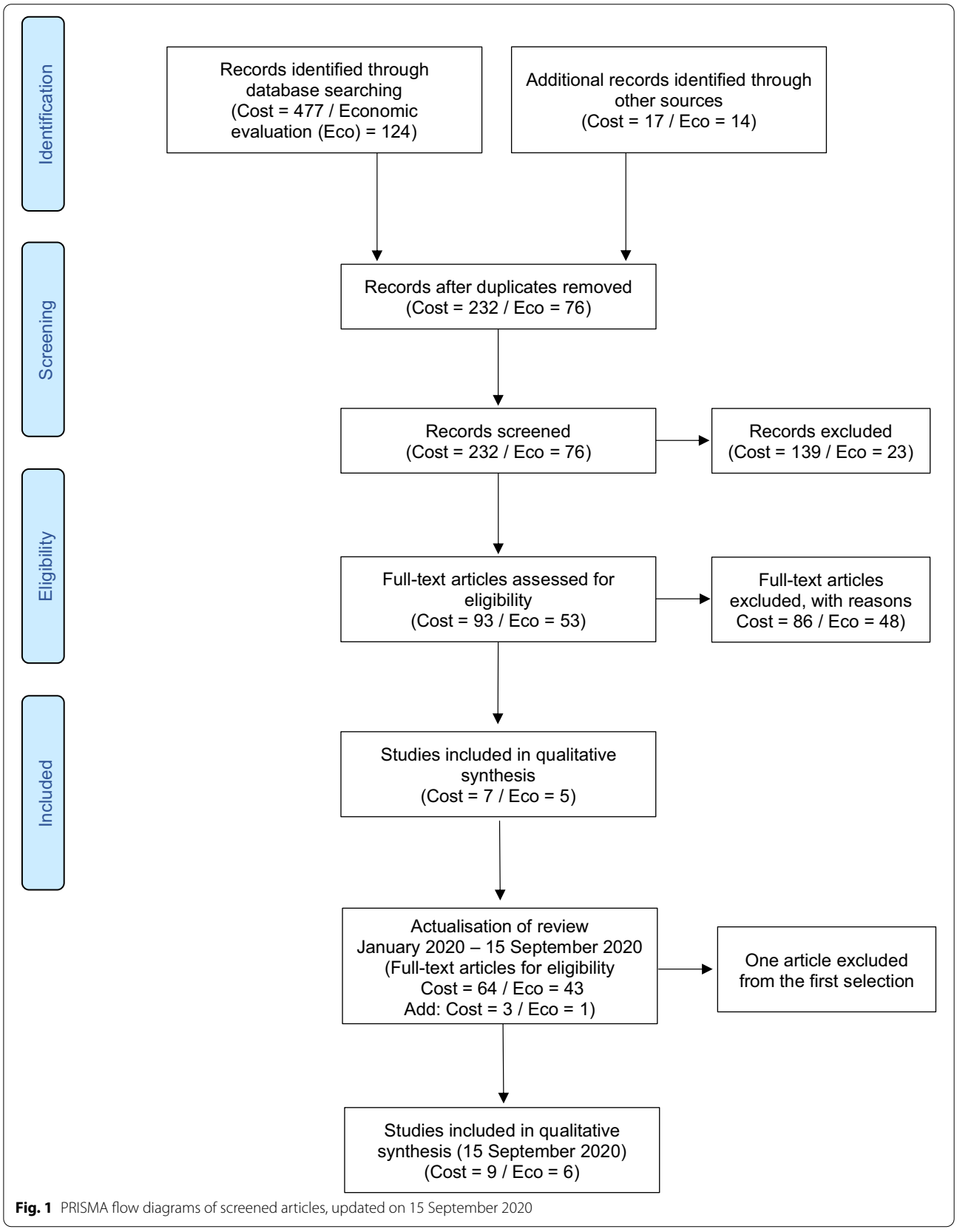



**Fig. 1** PRISMA flow diagrams of screened articles, updated on 15 September 2020

**Table 1 Overview of literature on cost of SMA**

| References | Country Year | Sample size | Population age | Type of study | Perspective | Type of cost | Year of costing | Funding |
|---|---|---|---|---|---|---|---|---|
| Armstrong et al. [24] | USA 2016 | 239: 45 < 1 year 194 > 1 year | 7.5+/− 6.4 | Cross-sectional, retrospective, and prospective | Healthcare costs | Direct healthcare | 2003–2012 | Conducted by Biogen |
| Chambers et al. [31] | Australia 2020 | 40: 4 SMA1 26 SMA2 10 SMA3 | SMA1: 2.7 (1–5) SMA2: 9.8 (2–22) SMA3: 6.9 (1–12) | Cross-sectional retrospective | Societal costs | Direct healthcare Direct non-healthcare Indirect | 2016–2017 | Funded by the Motor Neurone Diseases Research institute of Australia Beryl Bayley |
| Darba et al. [27] | Spain 2020 | 396 SMA1, 2 3 and 4 | | Cross-sectional retrospective | Healthcare costs | Direct healthcare | 2014–2016 | No |
| Droege et al. [29] | USA 2019 | 6526: 349 SMA1 45 SMA1 treated with nusinersen 5728 SMA2, 3, 4 404 SMA2, 3, 4 treated with nusinersen | SMA1: 9.2 months SMA1 nusinersen: 12.2 months SMA others: 30.9 years SMA others nusinersen: 14.8 years | Retrospective | Healthcare costs | Direct healthcare | 09/2016–08/2018 | Conducted by Avexis |
| Klug et al. (30) | Germany 2016 | 189: 12 SMA1 73 SMA2 104 SMA3 | < 1 to 73 | Cross-sectional retrospective | Healthcare and societal costs | Direct healthcare Direct non-healthcare Indirect | 2013 | Grant of the Friedrich-Baur-GmbH m' |
| Lee et al. (25) | USA 2019 | 229 severe SMA (< 1 year) | | Cross-sectional retrospective | Healthcare costs | Direct healthcare | 2005–2013 | No |
| Lewin Group (23) | USA 2012 | 745: 14 early onset SMA 731 SMA other (3–4) | < 1 to 65 | Cross-sectional retrospective | Healthcare and societal costs | Direct healthcare Direct non-healthcare Indirect | 2008 | Conducted by Muscular Dystrophy Association |
| Lopez-Bastida et al. [61] | Spain 2017 | 81: 8 SMA1 60 SMA2 13 SMA3 | 7.22 | Cross-sectional retrospective | Healthcare and societal costs | Direct healthcare Direct non-healthcare | 2015 | Supported by Biogen |
| Peña-Longobardo et al. [28] | France, German, UK 2020 | 86: 23 SMA1 45 SMA2 18 SMA 3 | 6.9 | Cross-sectional prospective | Societal costs | Direct healthcare Direct non-healthcare | 2015 | Supported by Biogen |

$ 258,448 [35] to $457,889 [29] in the second year. For SMA2, 3, and 4 patients, the costs excluding drug costs increased from $50,875 to $79,012 without treatment compared to with treatment. This suggests that nusinersen lowered health care costs, but this should be interpreted with caution as drug costs were not included in the analysis. Comparing total health care costs including drug costs is necessary to provide a fair comparison between active drugs (such as nusinersen and onasemnogene abeparvovec) and standard of care.

### Economic evaluations

Six economic evaluations were identified. The characteristics of included studies are reported in Table 2. Given the heterogeneity between studies, a narrative analysis was conducted.

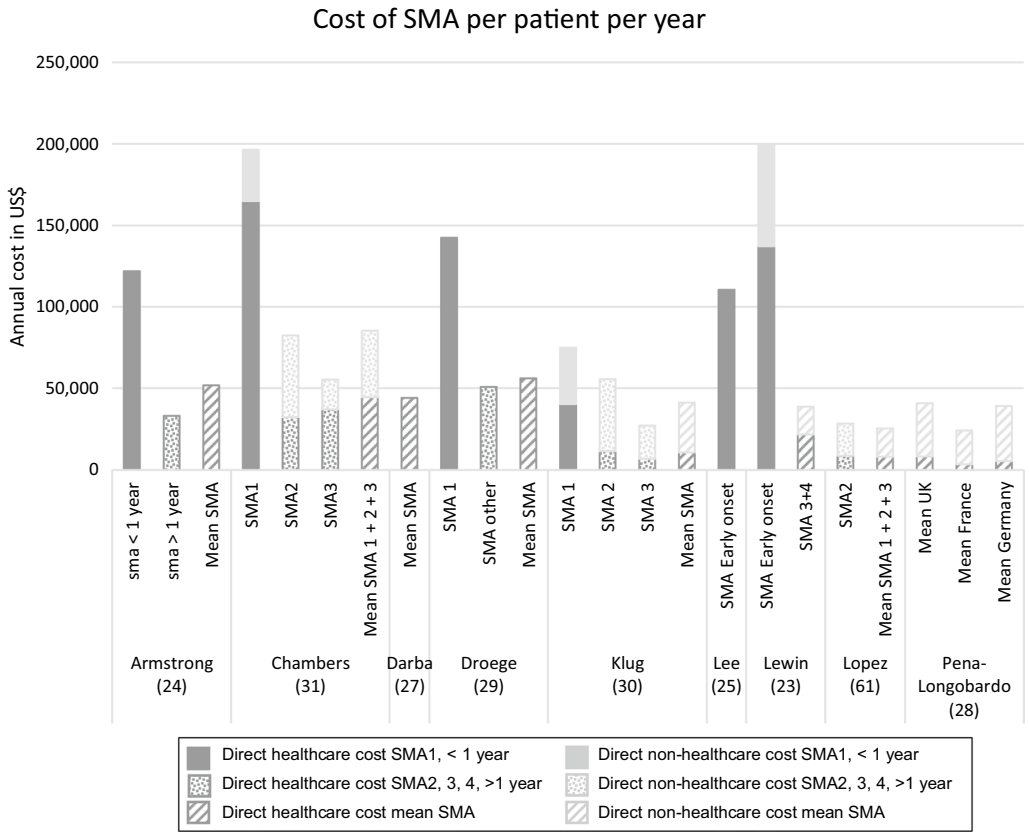



**Fig. 2** Yearly cost of the illness (US$) in SMA by type

Clinical results for all of the identified studies used data from the following clinical trials:

- Randomized controlled trials:
  - o ENDEAR (NCT02193074), which assessed safety and efficacy of nusinersen in SMA1.
  - p CHERISH (NCT02292537), which assessed safety and efficacy of nusinersen in SMA2. All studies used QALYs as outcome, and health-state values (or utilities) were derived from this trial
- Non-randomized uncontrolled trials:
  - o NURTURE (NCT02386553), that assessed safety and efficacy of nusinersen in pre-symptomatic patients
  - p START (NCT03421977), which assessed safety and efficacy of onasemnogene abeparvovec in patients with SMA1.

Each of these four trials showed that treatment statistically and significantly improved motor milestones and resulted in sustained and clinically significant improvements in event-free survival, overall survival, and motor function for children, although follow-up periods were limited. All economic evaluation studies used QALYs as outcome, and health-state values (or utilities) were derived from the CHERISH trial. All studies used trials Endear for motor evolution with nusinersen and one of them [32] used Nurture. Vignette studies were also used to obtain utility values in the pediatric and later-onset models [33–35]. Characteristics of these studies by population, intervention, and results are listed in Table 3.

All studies used a decision-analytic model, specifically the Markov model. The models were built on different health states: the motor function milestones achieved, the need for permanent ventilation, and the time to death. For the motor function, the CHOP INTEND or HFMSE scales were used as a reference. The baseline scores were those before the start of treatment. The studies assume that motor function does not improve naturally in SMA patients. These scores were then compared to the scores at the ends of the trials. Patients' ability to sit and walk was also taken into account. The health states used differed slightly in each study. For example,

**Table 2 Overview of economic evaluation studies of SMA**

| References | Country | Perspective | Time horizon | Method | Outcomes used | Industry funding |
|---|---|---|---|---|---|---|
| CADTH [34] | Canada 2018 | Healthcare payer | SMA1: 25 years SMA2: 50 years SMA3: 80 years | Three Markov models: for SMA1, for SMA2, for SMA3 | Life years QALY | No, commissioned by health authorities |
| ICER [36] | England 2018 | Healthcare payer and societal perspective | Two scenarios: 5 years 10 years | Three Markov models: for SMA1, for SMA2 and SMA3, for pre-symptomatic SMA | QALY | No, commissioned by health authorities |
| Jalali [32] | USA 2020 | Societal perspective | 30 months | Four Markov models: for untreated patients SMA1, for treated SMA1 identified by symptoms, for untreated patients identified by newborn screening, for nusinersen-treated patients identified by newborn screening | Life Years QALY | No |
| Malone et al. [33] | USA 2019 | Healthcare payer | Lifetime horizon | Markov model comparing nusinersen and Onasemnogene abeparvovec for SMA1 | QALY | Avexis |
| National Center for Pharmaco-economics [37] | Ireland 2017 | Societal perspective | Lifetime horizon | Two separate Markov models: for early-onset SMA, for later-onset SMA | QALY | No, commissioned by health authorities |
| Zuluaga-Sanchez et al. [35] | Sweden 2018 | Societal and payer perspective | SMA1: 40 years SMA2: 80 years | Markov model: incremental cost QALY gained and overall survival. Two models: for early-onset SMA, for later-onset SMA | QALY | Biogen |

two studies follow the same model and used the same health states that were used for the submission of the file for drug reimbursement [34, 35]: capacity to sit without support, to stand with assistance, to walk with assistance, to stand unaided, and to walk unaided. Ventilation was also studied with patients categorized as completely autonomous, with need for partial ventilation (during the night), or with permanent ventilation.

### Quality of the economic evaluations

Critical appraisal of the quality of the studies was assessed with the CHEC-extended. The results are available in Table 4. The studies are most often non-qualitative, do not generalize the results to another dimension or pathology, and do not approach the question from an ethical point of view. Most approach the sensitivity of the results only in a probabilistic and non-deterministic way. For half of the studies, the sources of cost data were not clearly identified. Apart from these shortcomings, the studies had scores showing high quality.

Results of economic evaluation.

Of the 6 comparisons, five compared a drug treatment to standard of care (no treatment). Only one study compares the two treatments, i.e., onasemnogene abeparvovec compared to nusinersen [33]. In this study, at the price of $5 million the ICER of onasemnogene abeparvovec compared to nusinersen was $32,464 per QALY (i.e., the total cost of onasemnogene abeparvovec was greater and effectiveness higher than nusinersen). The ICER per QALY gained upon treatment of SMA1 patients with nusinersen compared to standard of care ranged from $210,095 [33] to $1,150,455 [36]; for treatment with Onasemnogene abeparvovec the range was from $32,464 [33] to $251,403 [36]. The ICER per QALY gained with nusinersen versus standard of care for SMA1 patients treated before the age of 12 weeks or pre-symptomatically was $206,409 [32], $293,447 [37] and $710,758 [36]. Figure 3 summarizes the findings from each study.

In the three studies that evaluated ICERs from both societal and healthcare perspectives [35–37], the results

**Table 3 Overview of the characteristics of the six economic evaluations by population, intervention, and results**

| References | Population | Intervention/comparator/(including drug prices) | Results (Drugs costs are never included in the analysis) |
|---|---|---|---|
| CADTH [34] | SMA1, 2, 3 | Nusinersen versus standard of care<br>Nusinersen:<br>First year:<br>578,916 US $<br>Per year after 289,458 US $ | For SMA 1:<br>Nusinersen led to greater QALYs (gain of 4.80), life years (gain of 4.79), and cost (increase of $3.1 million) for an incremental cost per QALY gained of $665,570<br>For SMA2:<br>Nusinersen led to greater QALYs (gain of 3.67), life years (gain of 2.18), and cost (increase of $7.6 million) for an incremental cost per QALY gained of $2.1 million<br>For SMA3:<br>Nusinersen led to greater QALYs (gain of 1.56), no difference in life years (gain of 2.18), and an increase in cost ($4.5 million) for an incremental cost per QALY gained of $2.9 million<br>For all three SMA types:<br>The probability that nusinersen was cost effective assuming that the threshold value for a QALY was $300,000 was 0% |
| ICER [36] | SMA1, 2, 3 and pre-symptomatic | Nusinersen versus standard of care and Onasemnogene abeparvovec versus standard of care<br>Nusinersen:<br>Per year after the first:<br>396,443 US $<br>Onasemnogene abeparvovec: 2 million US$ | ICER of nusinersen is $709,000 per QALY gained from a healthcare-sector perspective and $687,000 from a modified societal perspective, far exceeding usual cost-effectiveness thresholds<br>For Onasemnogene abeparvovec (at a placeholder price of $2 million) the ICER from a healthcare-sector perspective in patients with symptomatic SMA1 is $243,000 per QALY gained |
| Jalali [32] | SMA1 and pre-symptomatic | Standard of care compared to Nusinersen with and without newborn screening<br>Nusinersen:<br>First year:<br>776,000 US $<br>Per year after: 388,000 US $ | Compared with no screening and no treatment, the ICER for nusinersen with screening was $330 558 per event-free life year saved<br>The ICER for nusinersen treatment without screening was $508,481 per event-free life year saved<br>For nusinersen with screening to be cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per event-free LY saved, the price would need to be $23,361 per dose, less than one-fifth its current price of $125,000<br>Preliminary data from the NURTURE trial indicated an 85.7% improvement in expected LYs saved compared with our base results<br>-In probabilistic sensitivity analysis, nusinersen and screening was a preferred strategy 93% of the time at a $500,000 WTP threshold |
| Malone et al. [33] | SMA1 patients with 2 copies of *SMN2* | Onasemnogene abeparvovec was compared to nusinersen.<br>Nusinersen:<br>First year:<br>776,000 US $<br>Per year after: 388,000 US $<br>Onasemnogene abeparvovec: between 2,5 and 5 million of US$ | Expected survival (undiscounted) over a lifetime predicted by the model was 37.20 life years for Onasemnogene abeparvovec and 9.68 life years for nusinersen (discounted QALYs, 15.65 and 5.29, respectively)<br>Using a potential Onasemnogene abeparvovec price range ($2.5–5.0 M/treatment), the average lifetime cost/patient was $4.2–6.6 M for Onasemnogene abeparvovec and $6.3 M for nusinersen<br>The ICER range was (-$203,072) to $31,379 per QALY gained for Onasemnogene abeparvovec versus nusinersen, indicating that Onasemnogene abeparvovec was cost-effective when priced at ≤ $5 M per treatment |

**Table 3 (continued)**

| References | Population | Intervention/comparator/(including drug prices) | Results (Drugs costs are never included in the analysis) |
|---|---|---|---|
| National Center for Pharmaco-economics [37] | SMA1, 2, 3, 4 | Nusinersen versus standard of care<br>First year:<br>681,421 US$<br>Per year after:<br>341,105 US$ | Nusinersen cannot be considered cost-effective at current price<br>A tenfold reduction in the price of nusinersen for the treatment of infantile SMA is required to produce an ICER approaching the € 45,000/QALY threshold<br>For later-onset SMA, nusinersen is less cost-effective and a 20-fold price reduction results in an ICER just under € 100,000/QALY<br>The 5-year net budget impact for Ireland is estimated at €37.88 million |
| Zuluaga-Sanchez et al [35] | SMA1, 2 | Nusinersen versus standard of care<br>First year:<br>516,896 US$<br>Per year after:<br>258,448 US$ | For SMA1:<br>Nusinersen resulted in 3.86 patient incremental QALYs<br>Nusinersen resulted in 0.02 caregiver incremental QALYs<br>Nusinersen incremental cost was $280,000 over standard of care<br>ICER for nusinersen (including caregiver QALYs) of $544,000 per QALY gained<br>For SMA2:<br>Nusinersen resulted in 9.54 patient incremental QALYs<br>Nusinersen resulted in 2.39 caregiver incremental QALYs<br>Nusinersen incremental cost of $3.6 million over standard of care<br>ICER for nusinersen (including caregiver QALYs) of $308,000 per QALY gained |

**Table 4 Critical appraisal of the quality of the economic evaluation (CHEC-extended scores)**

| Authors | CADTH [34] | ICER [36] | Jalali [32] | Malone [33] | NCP [37] | Zuluaga-Sanchez [35] |
|---|---|---|---|---|---|---|
| 1. Is the study population clearly described? | 1 | 1 | 1 | 1 | 1 | 1 |
| 2. Are competing alternatives clearly described? | 1 | 1 | 1 | 1 | 0.5 | 1 |
| 3. Is a well-defined research question posed in answerable form? | 1 | 1 | 1 | 1 | 1 | 1 |
| 4. Is the economic study design appropriate to the stated objective? | 1 | 1 | 1 | 1 | 1 | 1 |
| 5. Is the chosen time horizon appropriate in order to include relevant costs and consequences? | 1 | 1 | 1 | 1 | 1 | 1 |
| 6. Is the actual perspective chosen appropriate? | 0.5 | 1 | 1 | 0.5 | 1 | 1 |
| 7. Are all important and relevant costs for each alternative identified? | 0 | 1 | 1 | 1 | 1 | 1 |
| 8. Are all costs measured appropriately in physical units? | 0 | 1 | 1 | 1 | 0 | 1 |
| 9. Are costs valued appropriately? | 0 | 0.5 | 1 | 1 | 0 | 1 |
| 10. Are all important and relevant outcomes for each alternative identified? | 1 | 1 | 1 | 1 | 1 | 1 |
| 11. Are all outcomes measured appropriately? | 1 | 1 | 1 | 1 | 1 | 1 |
| 12. Are outcomes valued appropriately? | 1 | 1 | 0 | 1 | 1 | 1 |
| 13. Is an incremental analysis of costs and outcomes of alternatives performed? | 1 | 1 | 1 | 1 | 1 | 1 |
| 14. Are all future costs and outcomes discounted appropriately? | 1 | 1 | 0.5 | 0.5 | 0 | 1 |
| 15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis? | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| 16. Do the conclusions follow from the data reported? | 1 | 1 | 1 | 1 | 1 | 1 |
| 17. Does the study discuss the generalizability of the results to other settings and patient/client groups? | 0 | 1 | 0 | 0 | 0 | 0.5 |
| 18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)? | 1 | 1 | 1 | 1 | 1 | 1 |
| 19. Are ethical and distributional issues discussed appropriately? | 0 | 0 | 0.5 | 0 | 0 | 0 |
| Total % | 68.4% | 89.5% | 81.6% | 81.6% | 68.4% | 89.5% |

for patients treated pre-symptomatically showed a lower ICER from the societal perspective compared to the healthcare payer perspective: for example, $293,447 versus $564,657 for treatment with nusinersen [37]. A similar finding was reported in patients with later-onset SMA: $1,228,612 versus $2,496,442 [37]. No difference was, however, observed between ICERs as evaluated from a societal or healthcare payer perspective in SMA1 treated by nusinersen: ($670,756 for societal perspective versus $658,578 for healthcare payer) [35].

In one study that evaluated the ICER in pre-symptomatic patients [36], the authors assumed that in absence of treatment 60% of patients would develop SMA1, 30% would developed SMA2, and 10% SMA3. This distribution is slightly different from that reported in a recent literature review [1] that found 20–30% of subjects would develop SMA2 and 10–20% would develop SMA3. This discrepancy may have affected the results of the original studies. Scenario analyses were also conducted for a hypothetical drug therapy ("drug X") that had the unique costs of Onasemnogene abeparvovec with QALYs associated with nusinersen in patients with pre-symptomatic SMA. Given the uncertainty in the long-term prognosis of the pre-symptomatic population, scenario analyses for Drug X were performed assuming lower survival. In this study, the cost of the nusinersen treatment was assumed to be $776,000 for the first year and $388,000 per year for the following years [32].

ICER per QALY in SMA1 for the use of nusinersen or Onasemnogene abeparvovec compared to standard of care. Values are shown for all SMA1 patients and for SMA1 treated before 12 weeks, which is usually pre-symptomatically, with nusinersen or drug X. Drug X is hypothetical and has the costs associated with Onasemnogene abeparvovec and efficacy associated with nusinersen. Figure 4 shows the ICER per QALY for SMA types with later-onset treated with nusinersen compared to the standard of care from a societal perspective. The ICERs for these forms of SMA [2, 3 and 4] varied considerably depending on both the study and the type of SMA from $379,011 [35] to $8,438,049 [36].

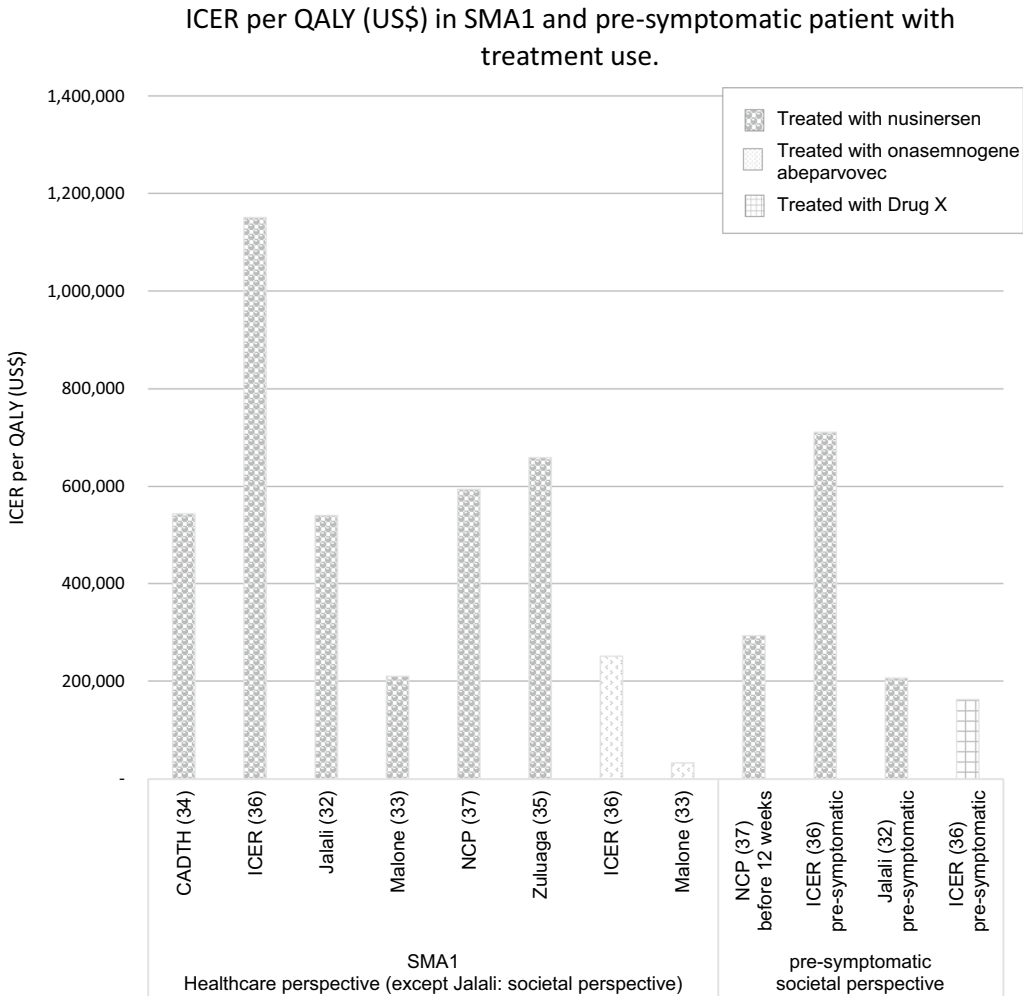



**Fig. 3** ICER per QALY (US$) in SMA1 and pre-symptomatic patient with treatment use

## Discussion

This study systematically reviewed all cost studies (n = 9) and economic evaluations (n = 6) of SMA care and treatment up to September 2020. Cost studies quantify the substantial cost of SMA, particularly of SMA1, which has annual costs estimated to range from $75,047 to $196,429 per year, exclusive of drug costs. For other SMA types, a much broader range of costs were observed. The broad range is probably related to the fact that SMA2, SMA3, and SMA4 were considered as a single group, yet their health resource consumptions are very different: Patients with SMA2 are wheelchair ambulant, whereas SMA4 patients remain ambulant. Most SMA2 patients eventually develop restrictive pulmonary syndrome, leading to frequent infections and need of chronic respiratory support; this syndrome is observed much less frequently in SMA3 patients and rarely in SMA4 patients [4]. Another reason for this discrepancy could be the countries in which these different studies were conducted, and the methodologies used. The two studies that reported the highest costs were conducted in European countries, and the others were conducted in the US. In terms of methodology, the two studies that reported the highest costs took indirect cost of illness into account [23, 31].

The yearly cost of SMA1 is significantly higher than those of SMA2 and SMA3. Because life expectancy is shorter in SMA1 [38–40], the total lifetime cost and budgetary impact may be lower than for SMA 2 and SMA3. These huge costs for the later-onset forms are exclusive of new disease-modifying drugs. Nusinersen, the first FDA-approved medication costed from $516,896 [35] to $907,665 [29] in the first year, and from $ 258,448 [35] to $457,889 [29] in the second year. (Different prices estimated between 2017 and 2020, in the US and Europe). Onasemnogene abeparvovec, the second FDA approved drug is considered to be the most expensive

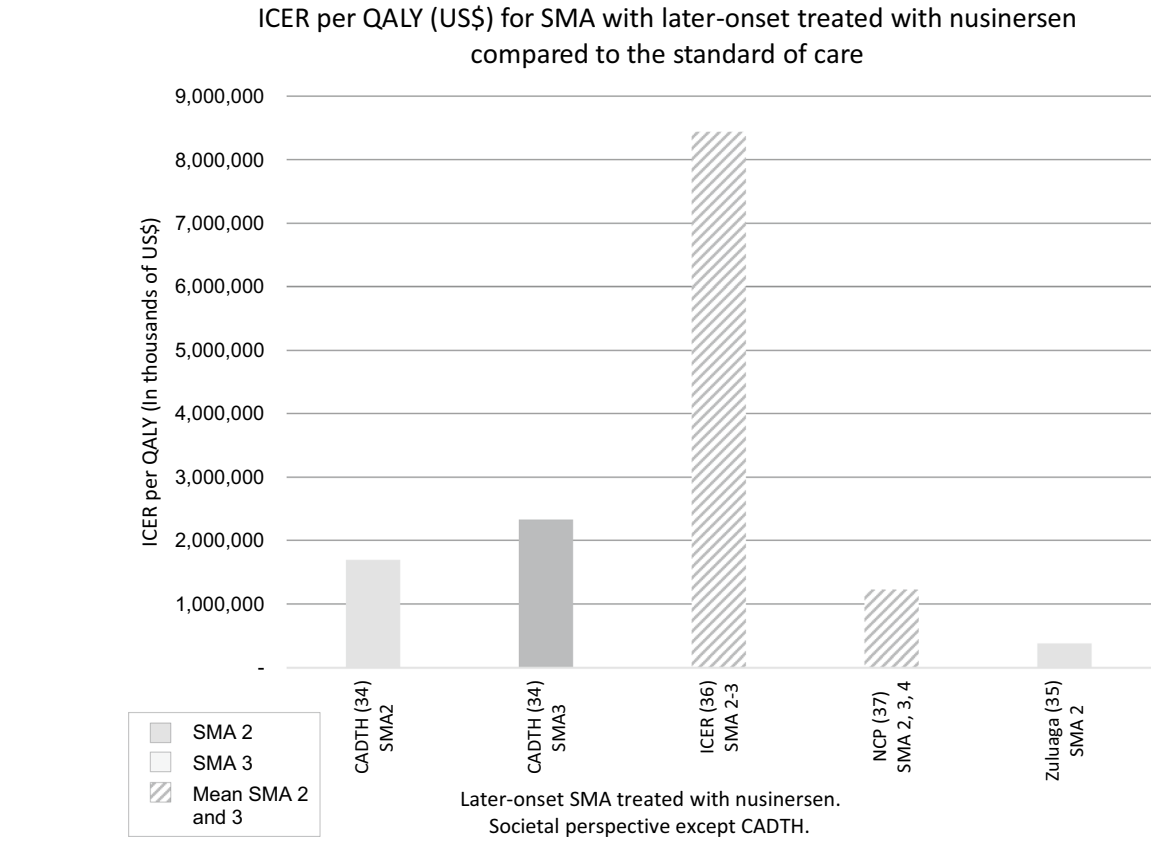



**Fig. 4** ICER per QALY (US$) for SMA with later-onset treated with nusinersen compared to the standard of care

drug of the world and is priced at $2.1 million in the US for a single injection. Nusinersen has been approved for use for all types of SMA, yet pivotal studies were conducted only in SMA1 patients younger than 7 months and in SMA2 patient younger than 9 years [8, 41]. Two studies with data from patients followed outside clinical trials confirmed this efficacy in patients from 8 months to 9 years. Patients were followed for 6 months in the first study [42]. In the second study, patients ranged in age from 2.5 years to 8.5 years and were followed for 14 months [43]. Progression was more limited in older than in younger patients.

In one study funded by a pharmaceutical companies [29], a substantial yearly decrease of healthcare costs of $45,000 per patient was observed after nusinersen treatment. However, this decrease was not inclusive of the cost of treatment. A yearly cost comparison in SMA1 patients on treatment or on best standard of care but without treatment is only partially relevant. Indeed, survival of SMA1 patients without treatment and without mechanical ventilation beyond the age of two years is rare [3], which limits the budget impact of these patients. Since treated patients survive longer, the total lifetime cost, and thus the budget impact, of these patients could be much larger than for those on standard of care therapy [44].

Although it has been hypothesized that treated patients are those who have very severe symptoms who would have very high healthcare costs if left untreated, there is currently no data to support this hypothesis. Those who did not benefit from treatment, and whose costs were collected for the study retrospectively from a database that captures prescriptions claims, medical utilization, and costs, would be those who did not urgently require treatment. These are patients for whom the healthcare costs are consequently lower than for the patients on treatment. This suggests that the cost of the disease for people with later-onset SMA who receive treatment is greater than for those given standard of care. As these are two different populations, cost analysis should treat them differently. Treatment of prior to symptom onset has been shown to be more effective than is treatment after symptoms develop [13]. Pre-symptomatic treatment may result in a greater reduction in SMA costs, as shown in the economic evaluation reported by Jalali et al. [32]. This type

of analysis could have a major impact on the launch of newborn screening programs.

It should be noted that these costs are not surprising in the context of rare diseases, even if the treatment for SMA is exceptionally high (as a reminder: the cost for nusinersen was estimated in 2020 at $776,000 for the first year, and $388,000 per year for the years after). For example, the infantile form of Pompe disease results in annual costs of $41,667 for standard of care, whereas treatments are estimated at $287,870 annually [45]. The burden of cystic fibrosis, a severe pulmonary disease characterized by frequent pulmonary infections and median survival of about 50 years, can to a certain extend be compared to the burden of SMA2. The estimated yearly cost of cystic fibrosis in 2016 is $131,879 for standard of care therapy including respiratory management and nutrition management [46]. Since 2016, new treatments have been approved that cost $300,000 per year [47]. Duchenne muscular dystrophy, whose level of disability can be compared to SMA3, has annual costs for standard of care around $50,000 [48, 49]. Altogether, the reported cost for SMA benchmarks closely with the costs of other rare diseases that present with a similar level of disability.

Economic evaluations of new drug treatments for SMA have been conducted, but these studies are based on very few trials that included a limited number of patients followed for a very limited period of time. For these reasons, extrapolations were made. The medical data concerning the evolution of treated patients, as well as the costs generated by the disease in treated patients, are understudied. For example, the QALYs used for the ICERs for nusinersen in SMA2 patients all come from a single study (CHERISH). Caution should also be exercised when comparing data between treatments, as the populations studied are not always comparable. Indeed, disease duration has been consistently shown to be the main predictor of treatment efficacy [12], and disease duration significantly differed between the two therapeutics trials conducted in patients with SMA1 (ENDEAR and START). Motor baseline levels, which has also been shown a predictive factor [42, 50], also differed between the two studies. Another limitation resides in the fact that trials did not collect utility values from patients or caregivers. Only vignettes were used to consider utility; these are not qualitative and are highly variable (e.g., the same health status was assessed at—0.13 to 0.73 [35]), and no single study appeared to capture the burden of disease in all the health states of interest. A final limitation is that all studies conducted to date have been retrospective. Long-term prospective follow-up of patients is needed to capture costs and outcomes for all types of SMA.

In addition, only one economic evaluation has examined specifically the cost-effectiveness of newborn screening for SMA. Given the increase in screening programs and their potential value [14, 15, 51, 52], such economic evaluations are needed. Recent data have suggested that patients treated before symptom onset will have a different future than children treated after symptoms appear [13]. If these patients have much less severe or no disabilities, the economics of treatment will be considerably impacted. Indeed, the cost of the treatment is the same whether it is provided before or after the first symptoms. The difference will be related to the cost of the associated handicap, which will be nil or almost nonexistent in pre-symptomatic patients.

Due to the extremely high drug costs, the ICER values for the currently approved SMA therapies are high, and, therefore, treatments are not cost effective. It is important to acknowledge that discounted prices for SMA drugs are confidentially negotiating with payers. Cost-effectiveness analyses based on official prices may therefore overestimate the real cost-effectiveness of SMA drugs. One of the studies [32] provides recommendations for alternative prices based on a sensitivity analysis. Using data from the ENDEAR trial, this analysis suggests that to achieve a willingness to pay threshold of $50,000 per life years saved, a nusinersen dosage price of 19% of the current price would be required. With the arrival on the market of three therapies, prices should tend to decrease, which could then make the prices more acceptable. In addition, these new therapies are expected to become the standard of care, and subsequent economic evaluations will need to include drug therapy as a comparator.

Despite high costs, the approved drugs have been granted reimbursement in several countries. In the domain of rare diseases, the small number of patients makes drug development economically challenging. For example, drugs for treatment of Duchenne muscular dystrophy, which results in costs comparable to SMA2 and SMA3, is associated with ICERs ranging from $944,975 to $2,341,474 [53]. Treatments for Fabry, Gaucher, and Pompe diseases range from $283,000 to $3,485,000, from $46,000 to $459,100, and from $162,800 to $1,108,050, respectively [54]. It is becoming accepted that in these types of conditions, the budget impact should be weighed more heavily than the rough ICER value. Since the frequency of the disease is very low, the budget impact is low despite high costs. Therefore, criteria other than cost-effectiveness are important for decision makers, especially for orphan drugs. Value frameworks have been proposed specifically for these rare and debilitating conditions. Garrison et al. have designed a framework value with SMA as an example. These authors suggest the importance of the “real option value”, the “value of hope”, and the "value of knowledge" [55]. Health equity (related to severity of disease), caregiver burden, and family

spillovers (in terms of the negative effect on the well-being of family members) are also important in these situations [56].

As treatments for rare diseases are unlikely to be cost effective given their high prices, additional criteria are already being used to inform reimbursement decisions in some countries. One relevant study analyzed use of public funds for orphan drugs in five European countries from the decision-maker's point of view [57]. Another study was conducted in Italy from the patient's point of view focusing on two diseases, cystic fibrosis and hemophilia; it also quantified individual preferences [58]. The two studies concluded that the important factors in the decision-to-pay process are the cost of treatment, the improvement in health of patients, and the value for money. The severity of the disease and the availability of alternative treatments should also be considered but are less important. Furthermore, the technical experts interviewed pointed out that an onset of symptoms in early childhood, diagnosis delay, and treatment side effects should also be considered as important social values. As several criteria are relevant, a multi-criteria decision analysis can constitute a valuable solution for decision-making. It allows the influence of each criterion on the decision and relative importance to be defined, going beyond the simple QALY analysis [57, 58].

This literature review has some limitations. First, only two databases (Medline and Scopus) were searched. The work of Sassi et al. [59] showed that by using only Medline, with appropriate search strategies, researchers can significantly reduce the number of irrelevant references retrieved by their electronic searches that require exclusion by manual selection. They point out that by not using Embase, there is a risk of losing some references compared to Medline, but that Embase does not include a large number of references. These authors conclude that manual searches and searches in databases other than Medline for reviewing economic evaluations have limited incremental return, so that Medline could be considered as the primary source. Nevertheless, we also investigated Scopus, in order to be as thorough as possible.

Second, we limited our search to original articles; conference proceedings were not included. It is likely that data presented at conferences on neuromuscular diseases or SMA will be published soon, as the SMA world is in a period of upheaval given that the recent approvals of effective therapies. Nevertheless, decisions on pricing are being made today on the basis of publicly data available. One of the studies we relied upon was itself a reanalysis and additional limitations were noted: Patient conditions reported are relative (stabilizing, improving, worsening) instead of absolute and were relative to individual patient's baseline conditions and not to motor scale numbers. With respect to clinical trial design, patients who participate in the trials are only a sample of the patient population, particularly in terms of age, and cannot be used as a projection to the entire patient population [34]. A final limitation is that studies funded by the pharmaceutical industry showed lower ICERs. Although the number of studies is too limited to make reliable comparison between industry-sponsored and non-industry sponsored economic evaluations, and the fact that no relationship was observed in other diseases [60], this remains a potential study publication bias as pharmaceutical companies could tend to present most favorable results. Despite the scarcity of economic evaluations of SMA, these few published studies will be central for health authorities who will use these data to drive policy choices. It therefore is important to also consider from research from independent institutes or unsubsidized academic groups.

## Conclusions

In conclusion, this literature review revealed the substantial cost burden of SMA and the high ratio of cost effectiveness of the approved drugs at the current price when delivered in post-symptomatic patients. Few studies evaluating cost and economic benefits of therapy have been conducted so far, and there is a need for further prospective and independent economic studies, in patients treated after symptom onset and in patients who are benefiting from pre-symptomatic treatment.

## Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s13023-021-01695-7.

**Additional file 1**. List of words used for the search

**Additional file 2**. Strategy for search of MEDLINE Ovid

### Abbreviations

EMA: European Medicines Agency; FDA: Food and Drug Administration; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Years; SMA: Spinal Muscular Atrophy.

### Acknowledgements

We thank Jacqueline R. Wyatt for editing the manuscript.

### Authors' contributions

TD, LS, and MH designed the study. TD, CB and ChB performed the literature search. TD and ChB checked the quality of the studies. MH verified the analytical methods. TD wrote the manuscript with support from MH and LS. MH and LS supervised the work. All authors read and approved the final manuscript.

### Funding

There was no funding for this study.

### Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
CB, ChB and MH declare that they have no competing interests relevant to this study. TD has given lectures sponsored by Biogen and Roche. LS has given lectures and has served as a consultant for Roche, Biogen, Avexis, and Cytokinetics. LS is the project leader of the newborn screening in Southern Belgium funded by Avexis, Roche, and Biogen.

**Author details**
[1] University of Liège, Liège, Belgium. [2] Department of Health Services Research, CAPHRI Care and Public Health Research Institute, Maastricht University, P.O. Box 616, Maastricht 6200 MD, The Netherlands. [3] Department of Paediatrics, Neuromuscular Reference Center Disease, Liège, Belgium. [4] Department of Paediatrics, MDUK Neuromuscular Center, University of Oxford, Oxford, UK.

Received: 3 April 2020 Accepted: 18 January 2021
Published online: 23 January 2021

**References**

1. Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy—a literature review. Orphanet J Rare Dis. 2017;12(1):124.
2. Zerres K, Rudnik-Schoneborn S. Natural history in proximal spinal muscular atrophy, Clinical analysis of 445 patients and suggestions for a modification of existing classifications. Arch Neurol. 1995;52(5):518–23.
3. Wijngaarde CA, Stam M, Otto LAM, van Eijk RPA, Cuppen I, Veldhoen ES, et al. Population-based analysis of survival in spinal muscular atrophy. Neurology. 2020;94(15):e1634–44.
4. Chabanon A, Seferian AM, Daron A, Pereon Y, Cances C, Vuillerot C, et al. Prospective and longitudinal natural history study of patients with Type 2 and 3 spinal muscular atrophy: baseline data NatHis-SMA study. PLoS ONE. 2018;13(7):e0201004.
5. Zerres K, Rudnik-Schoneborn S, Forrest E, Lusakowska A, Borkowska J, Hausmanowa-Petrusewicz I. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. J Neurol Sci. 1997;146(1):67–72.
6. Landfeldt E, Edstrom J, Sejersen T, Tulinius M, Lochmuller H, Kirschner J. Quality of life of patients with spinal muscular atrophy: a systematic review. Eur J Paediatr Neurol EJPN. 2019;23(3):347–56.
7. Ramdas S, Servais L. New treatments in spinal muscular atrophy: an overview of currently available data. Expert Opin Pharmacother. 2020;21(3):307–15.
8. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med. 2017;377(18):1723–32.
9. Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med. 2017;377(18):1713–22.
10. Lowes L, Al-Zaidy S, Shell R, Arnold W, Rodino-Klapac L, Prior T, et al. AVXS-101 phase 1 gene therapy clinical trial in SMA Type 1: patients treated early with the proposed therapeutic dose were able to sit unassisted at a younger age. Neuromuscular Disorders NMD. 2017;27:S208–9.
11. Roche. FDA approves Roche's Evrysdi (risdiplam) for treatment of spinal muscular atrophy (SMA) in adults and children 2 months and older 2020. https://www.roche.com/media/releases/med-cor-2020-08-10b.htm.
12. Dangouloff T, Servais L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: current perspectives. Ther Clin Risk Manag. 2019;15:1153–61.
13. De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscular Disorders NMD. 2019;29(11):842–56.
14. Boemer F, Caberg JH, Dideberg V, Dardenne D, Bours V, Hiligsmann M, et al. Newborn screening for SMA in Southern Belgium. Neuromuscular Disorders NMD. 2019;29(5):343–9.
15. Dangouloff T, Burghes A, Tizzano EF, Servais L. 244th ENMC international workshop: newborn screening in spinal muscular atrophy May 10–12, 2019, Hoofdorp, The Netherlands. Neuromuscular Disorders NMD. 2020;30(1):93–103.
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
17. Watts RD, Li IW. Use of checklists in reviews of health economic evaluations, 2010 to 2018. Value Health. 2019;22(3):377–82.
18. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. Int J Technol Assess Health Care. 2005;21(2):240–5.
19. Odnoletkova I. CHEC-extended: a tool for the quality assessment of economic evaluations of healthcare interventions 2014. https://www.researchgate.net/publication/314003661_CHEC-Extended_A_tool_for_the_quality_assessment_of_economic_evaluations_of_healthcare_interventions.
20. Webster I. Official Inflation Data, $100 in 2019 → 2020/Inflation Calculator. 2020 [Based on U.S. Bureau of Labor Statisctics (Consumer Price Index)]. https://www.officialdata.org/us/inflation/.
21. Statistics USBoL. Consumer Price Index 2020. https://www.bls.gov/cpi/.
22. OCDE. Exchange rate (indicator) 2020 [Taux de change (indicateur)]. https://data.oecd.org/fr/conversion/taux-de-change.htm#indicator-chart.
23. LewinGroup. Cost of Amyotrophic Lateral Sclerosis, Muscular Dystrophy, and Spinal Muscular Atrophy in the United States. Final Report—MDA Cost of Illness in the United States. 2012, March, 1.
24. Armstrong EP, Malone DC, Yeh WS, Dahl GJ, Lee RL, Sicignano N. The economic burden of spinal muscular atrophy. J Med Econ. 2016;19(8):822–6.
25. Lee M Jr, Franca UL, Graham RJ, McManus ML. Pre-nusinersen hospitalization costs of children with spinal muscular atrophy. Pediatr Neurol. 2019;92:3–5.
26. Farrar MA, Carey KA, Paguinto SG, Chambers G, Kasparian NA. Financial, opportunity and psychosocial costs of spinal muscular atrophy: an exploratory qualitative analysis of Australian carer perspectives. BMJ Open. 2018;8(5):e020907.
27. Darbà J. Direct medical costs of spinal muscular atrophy in the Catalonia region: a population-based analysis. Clin Drug Investig. 2020;40(4):335–41.
28. Peña-Longobardo LM, Aranda-Reneo I, Oliva-Moreno J, Litzkendorf S, Durand-Zaleski I, Tizzano E, et al. The economic impact and health-related quality of life of spinal muscular atrophy. An analysis across Europe. Int J Environ Res Public Health. 2020;17(16):5640.
29. Droege M, Sproule D, Arjunji R, Gauthier-Loiselle M, Cloutier M, Dabbous O. Economic burden of spinal muscular atrophy in the United States: a contemporary assessment. J Med Econ. 2020;23(1):70–9.
30. Klug C, Schreiber-Katz O, Thiele S, Schorling E, Zowe J, Reilich P, et al. Disease burden of spinal muscular atrophy in Germany. Orphanet J Rare Dis. 2016;11(1):58.
31. Chambers GM, Settumba SN, Carey KA, Cairns A, Menezes MP, Ryan M, et al. Prenusinersen economic and health-related quality of life burden of spinal muscular atrophy. Neurology. 2020;95(1):e1–10.
32. Jalali A, Rothwell E, Botkin JR, Anderson RA, Butterfield RJ, Nelson RE. Cost-effectiveness of Nusinersen and universal newborn screening for spinal muscular atrophy. J Pediatr. 2020;227:274–80.
33. Malone DC, Dean R, Arjunji R, Jensen I, Cyr P, Miller B, et al. Cost-effectiveness analysis of using onasemnogene abeparvocec (AVXS-101) in spinal muscular atrophy type 1 patients. J Mark Access Health Policy. 2019;7(1):1601484.
34. CADTH Common Drug Reviews. Pharmacoeconomic Review Report: Nusinersen (Spinraza): (Biogen Canada Inc): Indication: Treatment of patients with 5q SMA. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health Copyright © 2018 Canadian Agency for Drugs and Technologies in Health; 2018.
35. Zuluaga-Sanchez S, Teynor M, Knight C, Thompson R, Lundqvist T, Ekelund M, et al. Cost effectiveness of nusinersen in the treatment of patients with infantile-onset and later-onset spinal muscular atrophy in Sweden. PharmacoEconomics. 2019;37(6):845–65.

## Annexe XI. 244th ENMC International Workshop: Newborn screening in Spinal Muscular Atrophy May 10-12, 2019, Hoofdorp, The Netherlands. (Chapitre III, 4)

Dangouloff T, Burghes A, Tizzano EF, Servais L. Neuromuscular Disorders. 2019.

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 30 (2020) 93–103

www.elsevier.com/locate/nmd

# 244th ENMC international workshop: Newborn screening in spinal muscular atrophy May 10–12, 2019, Hoofdorp, The Netherlands

Tamara Dangouloff[a], Arthur Burghes[b], Eduardo F. Tizzano[c,*], Laurent Servais[a,d,**], on behalf of the NBS SMA Study Group[1]

[a] *Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, 4000 Belgium*
[b] *Department of Biological Chemistry and Pharmacology, The Ohio State University, Columbus, OH, USA*
[c] *Department of Clinical and Molecular Genetics, University Hospital Valle Hebron, Medicine Genetics Group VHIR, Pso. Vall d' Hebron, 119-129, 08035 Barcelona, Spain*
[d] *MDUK Neuromuscular Center, Paediatric Department, University of Oxford, Oxford OX1 2JD, UK*

© 2019 Elsevier B.V. All rights reserved.

*Keywords:* Newborn screening; Spinal muscular atrophy; Pre-symptomatic.

## 1. Introduction and overview

A total of 19 participants including clinicians, newborn screening specialists, economists, geneticists, patients and patient advocates, and industry representatives from 12 countries convened from the May 12–14, 2019 in Hoofdorp, The Netherlands, for the 244th ENMC International Workshop, on the topic newborn screening (NBS) for spinal muscular atrophy.

Following a welcome from Alexandra Breukel, ENMC representative, and the chairpersons of the workshop, Eduardo Tizzano and Laurent Servais, Professor Tizzano gave an overview of the topic.

Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by abnormally low levels of functional survival of Motor Neuron (SMN) protein [1], which leads to early death of motor neurons. SMN is coded by *SMN1* gene, and 95% of patients present with homozygous absence of exon 7 of *SMN1*, whereas 5% present with the absence in one allele and a point mutation in the other allele [2]. Patients with SMA fall on a continuous spectrum of weakness: At one end are patients who present as neonates with rapid decrease in muscle strength that progresses to paralysis and to respiratory insufficiency; at the other are patients with adult onset SMA who have minor disabilities. The most severe form is called SMA type 0; it starts in utero, and patients are symptomatic at birth. SMA type 1 typically starts before the age of 6 months, and patients never acquire the ability to sit. SMA type 2 symptoms begin between 6 and 18 months, and these patients never gain the ability to walk. SMA type 3 starts after 18 months; patients walk initially but ambulation is lost in a high proportion of patients. In addition to this basic classification according to age and maximal ability achieved, groups may be further divided into many more subgroups, from 1.1 to 1.9, 2.1 to 2.9…adding more granularity in the classification and underlying the broad uninterrupted phenotypic spectrum from type 0 to type 4 [3]. All SMA types are associated with significant motor disability, a burden for caregivers, and substantial costs [4,5]. The main predictive factor for severity is the number of copies of *SMN2*, a paralogous gene, from which a small amount of functional SMN protein is produced [6].

Recently, several therapeutic agents for treatment of SMA have been approved for clinical use or are in

* Corresponding author.
** Correspondence to: CRMN Liège, CHR de la Citadelle, Boulevard du 12ème de Ligne, 4000 Liège, Belgium.
*E-mail addresses:* etizzano@vhebron.net (E.F. Tizzano), lservais@chuliege.be (L. Servais).
[1] NBS SMA Study Group are listed at the end of the Article.

https://doi.org/10.1016/j.nmd.2019.11.002
0960-8966/© 2019 Elsevier B.V. All rights reserved.

late-stage development. Spinraza (Nusinersen), an antisense oligonucleotide alters splicing of the *SMN2* pre-mRNA to cause expression of the full-length SMN protein. Spinraza was approved by the Food and Drug Administration (FDA) in December 2016 and by the European Medicines Agency in June 2017 as the first tailored therapy for SMA [7]. The benefit of therapeutic intervention soon after onset of symptoms has been demonstrated in double-blind, placebo-controlled study as well as during the real-world data collection [8–10]. Anecdotal cases of success in treatment of pre-symptomatic patients have been presented or published [11], and it has been reported that outcomes for 25 pre-symptomatic patients treated during an open-label study were dramatically more positive than for patients treated post-symptomatically [12]. Other approaches, including gene therapy and oral splicing modifiers currently in the late phase of clinical trial development [13–15], have also shown promising results [16]. The gene replacement therapy, known as Zolgensma, was approved by the FDA in May 2019 for treatment of patients with SMA below the age of 2 years [17], The benefit of early treatment with these agents in patients with SMA type 1 has also been suggested during ongoing studies.

Results from clinical trials indicate that early diagnosis should be facilitated. NBS for SMA meets the modified criteria proposed by Wilson and Jungner [18,19] which are widely used to determine whether screening for a disease should be included in an NBS panel. These criteria include 10 different items:

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

The recent availability of new treatments for SMA has provided impetuous to include screening for SMA in NBS programs [20–22]. Indeed, in the USA a number of states have implemented NBS and others are rapidly implementing it. (https://www.babysfirsttest.org/newborn-screening/rusp-conditions#spinal-muscular-atrophy) The aim of this workshop was to synthetize the currently available information on technical, ethical, economic, and practical aspects of NBS and to identify gaps in our current knowledge of patient identification and communication of diagnosis and treatment following NBS.

## 2. Biomarkers and predictors

**Arthur Burghes** gave an overview of the current SMA predictors. The first key modifier of the SMA phenotype is *SMN2* copy number. The second is the type of *SMN2* present; specific variants such as c.859G>C in exon 7 and the intron 6 variant A-44 G both alter the amount of full-length SMN produced from *SMN2* [23–26]. In general, there is strong correlation between the number of *SMN2* copies and SMA phenotype [6]. However, there are exceptions and only some of these are explained by variants in *SMN2* [25,26]. Other modifiers of SMA have been suggested, but there are no validated genetic markers yet that can be readily used in follow-up analysis to obtain a more accurate genotype versus phenotype correlation. In addition, it has been reported by several experts that the precise quantification of *SMN2* number varies from one lab to another, especially for the highest number of copies. Indeed Schorling et al. [27] reported that on re-testing SMA patient samples, 9 out of 20 samples had a discrepant copy number determination. In experience of other expert labs, the observed discrepant copy number on retesting are usually consistent with phenotype. Issues concerning DNA quality and methodologies may underlie these discrepancies [6,27]. One particular concern is the rare occurrence of type 1 SMA cases with 4 or more copies of *SMN2*. Samples from these patients should be further analyzed to determine whether these diagnoses result from inaccurate copy number tests. In large collections of patients in laboratories with experience in *SMN2* determination, 4 copies of *SMN2* in type 1 has not been seen so it must be rare finding albeit its exact frequency is not known [6]. It would seem important to re-test these discordant samples to determine whether any patient with high *SMN2* copy number have severe illness as this is critical in risk assessment. It can be assumed that historical *SMN2* copy number data and phenotype gives a reasonable indication that the genotype versus phenotype correlation can be used to calculate practical risk estimates [6].

Information on natural history and clinical evolution is crucial to facilitate decisions on benefits of early treatment. The main question after a newborn screen that is positive for *SMN1* deletion and a given copy number of *SMN2* is the probability of developing a particular form of SMA or of being asymptomatic for a long period of time [19]. The calculations for this risk use a multinomial logistic regression model. In this model both the *SMN2* copy number and the type of SMA can be included and additional modifiers or factors such as *SMN2* variants (i.e., c.859G>C and A-44G) and gender can be included. Depending on the nature of the

studies and the specifics of the dataset, a Bayesian calculation to determine posterior probability may be required, [6,28] which gives a more accurate probability of developing a specific phenotype. The known *SMN2* variants account for some cases where phenotype is milder than would be expected based strictly on *SMN2* copy number [6,25,26]; however, there are a large number of cases that are milder than expected without these variants, and these are under active investigation to identify additional modifiers at the DNA level. It is likely that a number of these modifiers lie outside the *SMN* gene region. The identification of additional modifiers will improve prediction of phenotype by genotype and can be incorporated in the model.

**Wildon Farwell** discussed recent findings regarding neurofilaments in the context of NBS. Neurofilaments are intermediate filaments uniquely expressed in neuronal cells that, together with microtubules and microfilaments, make up the neuronal cytoskeleton [29,30]. Neurofilaments are composed of three proteins differentiated by molecular weight — light, medium, and heavy — that are released into the extracellular fluid during axonal degeneration [29,30]. Neurofilaments heavy and neurofilaments light have been proposed as biomarkers of disorders characterized by axonal injury and degeneration, and their clinical utility in diseases such as multiple sclerosis and amyotrophic lateral sclerosis is being explored [30]. Axonal neurofilaments are predominately phosphorylated, conferring resistance to protein degradation [29].

The natural disease course of SMA can now be significantly altered with treatment [7,31,32], and therefore strategies to assess disease activity and monitor treatment response are needed. Biogen has investigated plasma levels of phosphorylated neurofilaments heavy (pNF-H) in children with and without SMA using blood samples collected at baseline from participants in Spinraza clinical trials (with pre-symptomatic, infantile-onset or later-onset SMA [$n = 302$]) and from children without SMA ($n = 34$), as well as change in pNF-H with treatment. The levels of pNF-H were measured using the ProteinSimple® enzyme-linked lectin assay [33]. In children without SMA, pNF-H levels were highest in the youngest infants and appeared to decline with age: median (range) in those aged < 1 year was 1510 pg/mL (579–7030; $n = 6$) compared with 124.5 pg/mL (below the limit of quantification–395; $n = 28$) in those aged 1 to 18 years ($p = 0.0002$) [34]. In children with SMA, baseline plasma pNF-H levels were higher than levels in children without SMA, and were highest in the youngest affected individuals; these individuals were pre-symptomatic and generally had two *SMN2* copies [35]. In individuals with pre-symptomatic or infantile-onset SMA who received Spinraza treatment, pNF-H levels declined during the loading period of Spinraza and then remained relatively stable over the course of the study [34,35]. In contrast, participants who received sham treatment experienced a steady, gradual decline in pNF-H over the course of the study [34]. Results from additional analyses demonstrated the potential of pNF-H levels after initiation of treatment with Spinraza to predict future motor function improvement. Taken together, the results suggest that pNF-H may be a useful biomarker for predicting motor function outcomes in SMA. The utility of additional markers in cerebrospinal fluid of treated SMA patients is also matter of active research [36,37].

## 3. Techniques of NBS

**François Boemer** presented the validation of an in-house technique for NBS designed to specifically recognize homozygous deletions of exon 7 in the *SMN1* gene [22,38]. To ensure the specificity for *SMN1* and to avoid any *SMN2* gene detection, qPCR screening assay was designed with a specific locked nucleic acid probe. The newborn screening center in Liege, Belgium, initiated a 3-year pilot study to screen all newborns in its area on March 5, 2018. Thereafter, several improvements allowed shortening of the turnaround time. The technical refinements, the acquisition a new qPCR instrument, the hiring of a dedicated lab technician, and the extension of the project to all Southern Belgium allowed the delay between birth and results availability from 14.2 days when screening was initiated to the current 8.5 days.

**Mikael Hjort** presented PerkinElmer's objectives for NBS. Panel expansion to include screening for additional diseases, like SMA, and introduction of new technologies will present challenges to NBS laboratories. Use of liquid handlers, automation, and dedicated software solutions will become routine in NBS workflows.

SMA NBS assays detect *SMN1* exon 7 deletion in a qualitative manner and carrier detection should be avoided. To ensure specificity of the SMA assay, modified nucleotides such as locked nucleic acid probes can be used to ensure specificity for *SMN1*. *SMN2* copy number determination can be part of the NBS workflow as a second-tier testing utilizing droplet digital Polymerase Chain Reaction (PCR) technology; however, this should not be considered as a critical part of the NBS program as it can be also done outside the NBS laboratory during the confirmation stage.

The SMA NBS assay can be multiplexed together with the severe combined immunodeficiency screening assay. Furthermore, multiplexing of T-cell receptor excision circles, kappa-deleting recombination excision circles, and *SMN1* can be done in one assay utilizing real-time PCR technology without increasing daily hands-on workload and complexity. The combination of simple DNA extraction, multiplexing, and automation allows maximum efficiency in the workflow.

During discussion, it was noted that none of the methods currently employed in NBS for SMA allows detection of point mutations in *SMN1*. Thus, about 5% of cases will remain undiagnosed until manifestations of the disease occur and specific genetic tests are performed.

## 4. NBS programs

Programs from the USA and several European countries were discussed, with the aims of comparing costs,

Table 1
Ongoing SMA screening projects in Europe.

| | Germany | Italy | Belgium | Spain |
|---|---|---|---|---|
| Type of consent | Information of the parents, additional Informed consent | Consent (information during pregnancy, flyer, social media camping, consent signature) | No consent (as for other NBS), informed consent for confirming | Proposal of Information flyer, informed consent for confirming positive cases |
| Type of assay | Real-time PCR | Real-time PCR (dedicated DBS) | Real time PCR + MLPA for positive cases | Real-time PCR coupled with severe combined immunodeficiency +MLPA for positive cases |
| Multi-site or single site test | Central for Bavaria | 1 central lab | 1 central lab | 1 central lab |
| Budget per infant screened | Non-available | 2.35–3.35 euros | 2.5 euros/sample + tech | |
| Starting date | 15/01/2018 | 15/03/2019 | 05/03/2018 | Not yet |
| Expected births per year (pilot duration) | 150,000/year (3 years) | 70–80,000/ years (2 years) | 60,000/year (3 years) | 60–70,000/year |
| Number of patients screened so far | 178,000 | >7000 | 42,000 | 0 |
| Number of positives cases | 25 (1/7100) | 0 | 6 (1/7000) | 0 |
| Treatment | 2 and 3 copies | 2 and 3 copies | 2, 3 and 4 copies | |
| Number of copies per patients | 11 with 2 copies,<br>5 with 3 copies,<br>9 with 4 copies | / | 2 with 2 copies<br>2 with 3 copies<br>2 with 4 copies | |

organization, attitude towards informed consent, and techniques (Table 1).

**Arthur Burghes** gave a general overview of the status of SMA NBS in the USA. A number of states have started NBS for SMA, for instance Minnesota, Indiana, Utah and other states have legislation mandating this screening and some states such as Ohio are implementing it in pilot studies. A number of these states are using the real-time PCR assay developed by the Centers for Disease and Control to detect the loss of *SMN1* exon 7. This assay was developed to be used in combination with the assay for detection of severe combined immunodeficiency (the TREC assay), which is also a DNA-based test. This allows rapid and inexpensive implementation of the assay as all states are performing severe combined immunodeficiency screening. The assay described above that was developed by PerkinElmer is very similar but the exact differences between the two cannot be determined due to lack of information concerning the primers and probes in the PerkinElmer assay. In the case of New York [21], the lack of *SMN1* is first determined and then the copy number of *SMN2* is determined concurrently with confirmatory tests. The aim is rapid reporting of the results to the physician to allow rapid treatment. To date, there are no data available on the number of babies screened or the number of patients identified.

**Francesco Danilo Tiziano** described the status of the Italian NBS for SMA. The pilot project that is ongoing in Italy was designed as an epidemiologic study with the goal of establishing the incidence of SMA in two regions: Lazio and Tuscany. Informed consent is required. Due to the duration of the study (two years) and the limited estimated number of patients (about 20), no formal analysis of treatment efficacy is planned. The pilot project is aligned to the extended metabolic NBS that is mandatory by law, and exploits the same infrastructure for the management of samples. In contrast with the US and Belgian organization, a dedicated dried blood spot (DBS) is used for SMA. The diagnostic testing is centralized in a single center, the Catholic University in Roma. The genetic test is performed using an in-house assay based on real time PCR. The assay has been validated for carrier testing and *SMN2* copy number assessment, has been adapted for an automatic analytic pipeline in small reaction volumes, and co-amplifies *SMN1* and *SMN2* exon 7, which are differentiated by different Taqman MGB probes. *SMN2* is amplified as a PCR positive control. Positive samples are confirmed by a second DNA extraction from the same DBS. Subsequently, the family is invited for genetic counselling to explain the condition, prognosis, and therapeutic opportunities. On that occasion, a fresh blood sample is collected from the child, and an appointment is made for the neonate at a tertiary neuromuscular center, which will be kept assuming that confirmatory testing is positive. An official report, which includes the *SMN2* copy number, is provided to the family in order to obtain the reimbursement of the treatment by the National Health System. The pilot project started in the single center for the exploratory phase on March 15, 2019: So far, over 7000 newborns have been screened, and no patients have been reported. The screening was extended to all newborn centers in July.

**François Boemer** described the implementation of the Belgian NBS. A 3-year pilot study was initiated on March 5, 2018 in a Belgian neonatal screening laboratory to cover 17,000 newborns per year [22]. The extension of the program's coverage to the whole of southern Belgium (French-speaking Belgium: Wallonia-Brussels federation), extending the population's coverage to 55,000 babies per year, was carried out 9 months after the launch of the pilot study. The SMA NBS follows the general NBS process, using the same DBS. Similarly, to any screening in Southern Belgium, parents are informed of the existence of a screening for several diseases and have the option to opt out; parents rarely choose not to have the screening. Formal signed consent is not required. After more than one year of screening,

42,000 newborns have been tested for SMA. Six cases of SMA were identified: two children with two copies of *SMN2*, two children with three copies, and two with four copies. This corresponds to an incidence of 1 in 7000. All identified patients have received treatment with Spinraza or have been included in a gene or oral therapy trial and are being monitored by clinical and physical therapy tests including the CHOP-intend and the Bayley test (motor and cognition). A medical-economic analysis of the project is being carried out, with questionnaires on quality of life and cost caused by the disease. Over the course of the project, public engagement through mainstream media and Facebook (http://facebook/sunmayariseonsma) are ensuring visibility.

**Wolfgang Müller-Felber** reported on the German pilot project based on PCR of DBS samples [39]. Starting in January 2018 the project, which is still going on in three centers in the southern and western part of Germany (Munich, Essen, and Münster) and which was started as a collaboration project with the Cystinosis Foundation, had screened 178,000 newborns through by the end of March 2019. Twenty-five children with homozygous mutations in the *SMN1* gene were identified for an incidence of 1 in 7120. Sixteen children (64%) had two or three copies of *SMN2*, and the remaining four and more copies. Treatment was offered to all children with two or three *SMN2* copies. In 12 children treatment with Spinraza was started immediately after confirmation of the diagnosis. All children are undergoing regular clinical and physiotherapeutic tests. HINE and CHOP-Intend scores show near normal development in all children who began treatment prior to onset of symptoms. In one child with four copies of *SMN2* symptoms appeared at 10 months of age. NBS was well accepted by the parents. The project will be continued until NBS is part of the general NBS program in Germany.

**Eduardo Tizzano** presented a proposal for a NBS project in Catalonia. Among the different programs of NBS in Spain there is a large heterogeneity in the 17 autonomous regions that are responsible for new program implementation, with screening for 7 to up to 30 diseases depending on the region. Catalonia has approximately 7,500,000 inhabitants and between 60,000 and 70,000 births per year. NBS screening in Catalonia started in 1968 and includes 24 diseases. Catalonia was the first region in Europe to include severe combined immunodeficiency by T-cell receptor excision circles determination, to which the SMA NBS could be coupled. Initial guidance to run a pilot project is under review by health authorities responsible for the regional NBS program. The proposal is to initially conduct SMA screening through the overall process of NBS, and the analysis will be centrally performed. A flyer about the purpose of this pilot study will be included in the initial information that is given to the families during the collection of blood, and families may choose not to participate. Informed consent will be collected at the stage of diagnosis confirmation, which will be performed in the reference center. Communication of diagnosis is considered to be a crucial issue in the project and is expected to be provided by an expert team of genetic counselors and pediatric neurologists with psychological support for decision making.

**Kacper Rucinski** described the ongoing efforts to initiate pilot projects of SMA NBS in Central and Eastern Europe. Pilot projects in Hungary and Poland were outlined. The Polish project aims to screen 120,000 newborns over two years and is in a more advanced stage of planning than is the Hungarian program.

## 5. Treatments

**Enrico Bertini** presented the data from the Biogen-sponsored NURTURE study (NCT02386553) of Spinraza efficacy. Spinraza was the first approved treatment for SMA. Interim results were presented as of May 2018. Treatment was initiated prior to symptom onset in infants with two or three *SMN2* copies. Enrolled infants were aged ≤6 weeks at first dose, clinically pre-symptomatic, had a compound muscle action potential (CMAP) above 1 mV and were genetically diagnosed with SMA. The primary endpoint is time to death or respiratory intervention (≥6 h/day continuously for ≥7 days or tracheostomy). A total of 25 infants (2 copies *SMN2*, $n=15$; 3 copies, $n=10$) were enrolled with a median age at last visit of 26.0 months (range 14.0–34.3 months). As of May 2018, all infants were alive, and none required permanent ventilation. Four infants (all with 2 *SMN2* copies) required respiratory intervention for ≥6 h/day continuously for ≥7 days during acute, reversible illness. All infants achieved the WHO motor milestone sitting without support, 22 of 25 (88%) achieved walking with assistance, and 17 of 22 (77%) were walking alone [12]. pNF-H levels rapidly declined during the Spinraza loading phase and then stabilized. At baseline, pNF-H were considerably elevated in individuals with two copies of *SMN2*. Adverse events occurred in all infants; 20 of 25 had adverse events that were mild or moderate in severity; nine had severe adverse events. No new safety concerns were identified. There was continued benefit to infants who initiated Spinraza before symptom onset, emphasizing the value of early treatment made possible by NBS. This open ongoing trial will also identify biomarkers to use in the pre-symptomatic treatment approach.

**Imran Kausar** presented data on the AveXis AAV9-based gene therapy Zolgensma (previously known as AVXS-101) pre-symptomatic clinical trial (SPR1NT, NCT03505099) in SMA. The data are the most recent data cut from the ongoing SPR1NT trial and were recently presented at the American Association of Neurology meeting in Philadelphia, PA, USA. SPR1NT is a Phase 3, open-label, single-arm, multi-center trial designed to evaluate the safety and efficacy of a one-time intravenous infusion of Zolgensma in pre-symptomatic patients with SMA and two or three copies of *SMN2* who began treatment at ≤6 weeks of age. The primary outcome measure for patients with two copies of *SMN2* is independent sitting for ≥30 s by 18 months. The primary outcome measure for patients with three copies of *SMN2* is standing without support for at least three seconds by 24 months.

As of March 8, 2019, all patients (18/18) were alive and event-free. One patient was enrolled into SPR1NT with four copies of SMN2 and was assessed for safety but not efficacy as this patient did not meet the intent-to-treat criteria. The median duration of follow-up was 5.4 months, and the median age was 6.1 months. Among patients with two copies of *SMN2* ($n=8$), a mean 8.9-point improvement from baseline in CHOP-INTEND was achieved 1 month post dosing, and a mean score of 8.4 points in Bayley-III Gross Motor was achieved by 2 months after dosing. All patients achieved or maintained a CHOP-INTEND score of 50 points, with four patients achieving a score of 60 points and three patients achieving the maximum score of 64.

Patients with two copies of *SMN2* reached age-appropriate motor milestones, including four patients who could sit without support for at least 30 s according to Bayley-III Gross Motor criteria, and one patient who could stand with assistance for ≥2 s. Untreated natural history indicates that most patients with two copies of *SMN2* never sit without assistance.

Serious adverse events were cases of croup ($n=1$), lethargy ($n=1$), and hypercalcemia ($n=1$), all of which resolved and were considered unrelated to treatment by investigators. Other observed adverse events included elevated transaminases, elevated blood creatine phosphokinase-muscle/brain, and elevated troponin.

**Ksenija Gorni** presented the study design and the inclusion/exclusion criteria of the RAINBOWFISH trial (NCT03779334) designed to evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics of Risdiplam. Risdiplam is a small-molecule splicing modulator that will be given orally. Infants with one to four copies of *SMN2* will be included in the study, and the primary analysis will be performed considering at least 10 babies with two *SMN2* copies. Similar, to other studies in pre-symptomatic infants with SMA, the inclusion age will be ≤6 weeks at time of first dose. Enrollment into this study has just begun and no data are available.

The use of NBS modalities has been discussed for RAINBOWFISH, considering the global nature of the study, which involves geographies with differing standard of care. NBS that is being utilized will follow an ad hoc approach using existing NBS programs when present and supporting ongoing pilots and starting new efforts where NBS is not readily available.

## 6. Alternatives to NBS

**Eduardo Tizzano** presented the carrier screening concept as an alternative to NBS. NBS is considered a reasonable initial approach to prevent and modify the trajectory of SMA, given the movement from treating patients with manifesting disease, which constitutes a tertiary prevention in patients with early symptoms, to a secondary prevention in asymptomatic patients. However, it is envisaged that in the future there will be consolidation of carrier screening programs in the population for primary prevention of SMA [19]. The final result will be a decrease of the incidence and prevalence of the disease with a potential positive impact on the health system considering the burden of the disease and the high cost of new treatments [40]. Carrier screening in SMA may be triggered by a family history of SMA or as part of a general screening programs. These programs could be SMA specific, as are the geography- or population-based screenings conducted for carriers of recessive conditions that are observed in limited locations or ethnic groups (e.g., Tay Sachs [41], cystic fibrosis [42,43], thalassemia [44]), or as part of expanded (commercially available) carrier screening next generation sequencing genetic panels that are offered for several autosomal recessive conditions. This type of screening is done in potential gamete donors in some fertility and reproduction clinics [45].

Parents of SMA patients are not always carriers since a small proportion of patients have pathogenic variants that occurred de novo or that resulted from germinal/somatic mosaicism [46]. Thus, even a universal carrier screening program will not make SMA disappear. SMA carrier detection should be a quantitative method that detects one copy of *SMN1* in classical 1/0 carriers. A small proportion of carriers have two *SMN1* copies in *cis* and none on the other allele (2/0 carriers). The current carrier diagnosis methods based on the *SMN1* dosage do not allow discrimination between 1/1 non-carriers and 2/0 carriers when an individual shows two *SMN1* copies. Although the presence of some polymorphisms in *SMN1* can aid in categorization of a risk group of 2/0 carriers [47], its absence in a person with two *SMN1* copies does not preclude 2/0 carrier status limiting the utility of this analysis to some populations [48]. Testing of parents to exclude the presence of a chromosome with more than one *SMN1* copy is usually confirmatory to interpret the case under study as 1/1 non-carrier [46,48].

There was an overall agreement that NBS and carrier screening programs are two complementary approaches to SMA prevention. Carrier screening by next generation sequencing has the potential to detect *SMN1* point mutations that are false negative in the NBS programs. By contrast a carrier screening program will not cover homogenously and universally the whole population, the 2/0 carriers, de novo mutations as well as non-biological filiation will contribute with cases that would be detected by universal NBS.

## 7. Economic and psychological cost of NBS and parental views

**Mickaël Hiligsmann** provided the rationale and background for the economic evaluation of NBS for SMA**.** Considering the limited healthcare resources available, it is important for decision makers to efficiently allocate scarce healthcare resources [49]. As part of a health technology assessment, economic evaluations provide a framework to identify and compare the costs and effects of potential interventions. These evaluations inform efficient healthcare allocation and play an increasing role in pricing and

reimbursement decisions and are formally requested in many countries [50].

An economic evaluation can be defined as a comparative analysis between two or more interventions in terms of costs and outcomes [51]. The most common type of economic evaluation is a cost-utility analysis where the outcomes are expressed in quality-adjusted life years (QALYs) that correspond to the number of years in good health and allow capture of the effects of health interventions on both mortality and morbidity. The results of an economic evaluation are typically expressed in terms of an incremental cost-effectiveness ratio defined as the difference in terms of costs between two interventions divided by their difference in effectiveness. An incremental cost-effectiveness ratio represents the additional cost of an intervention per effectiveness unit (e.g., QALY gained) versus the comparator. To qualify an intervention as cost-effective, the incremental cost-effectiveness ratio is compared to a cost-effectiveness threshold representing the decision makers' willingness to pay per effect unit. If the incremental cost-effectiveness ratio falls below the cost-effectiveness threshold, the intervention is considered as cost-effective. Cost-effective thresholds are estimated, for example, at $100,000 to $150,000 per QALY gained in the USA [52] and are commonly higher for orphan drugs, end of life diseases, and very severe diseases.

Few economic evaluations have been conducted in the field of SMA although there have been some reports about the cost-effectiveness of Spinraza for reimbursement decisions [53], a report of the Institute for Clinical and Economic Review in the USA [54], and one scientific article to assess the cost-effectiveness of Spinraza in Sweden [55]. These studies reported a high incremental cost-effectiveness ratio of an SMA drug (by example estimated at €551,300 and €311,800 for Spinraza for the infantile-onset model and later-onset model, respectively) [55] suggesting that, at current prices, SMA drugs are not cost-effective at common thresholds for cost-effectiveness. However, alongside economic considerations, other criteria are important for drug value assessment including the lack of alternative treatment, the societal impact, ethical considerations, and budget impact. The Institute for Clinical and Economic Review in the USA has recognized the high benefits of Spinraza and Zolgensma and the need to consider contextual issues and broader benefits for patients and families in the judgment of overall drug value [54]. A value framework developed specifically for SMA should take into account, in addition to QALY and net costs, factors such as equity, real option value, value of hope, and severity of disease [56].

The one economic evaluation of screening for SMA conducted to date suggested that screening for SMA is not cost-effective [57]. This study was, however, conducted several years ago when drug treatments were not yet available and thus needs to be updated. Given the increasing use of NBS for SMA worldwide and effective treatment options, alongside the importance of economic considerations, investigating the cost-effectiveness of NBS for SMA is needed. As pre-symptomatic treatment of SMA has been shown to be associated with improved treatment benefits compared to post-symptomatic treatment [11,12], we anticipate that an economic evaluation comparing NBS followed by pre-symptomatic treatment could represent a high economic value compared to no screening followed by post-symptomatic treatment. In summary, given the increasing importance of economic evaluations and increasing interest and use of NBS for SMA, it will be important to investigate the cost-effectiveness of NBS for SMA. This analysis will provide relevant information for policy makers.

**Philip Young** presented data on the views of the general population and SMA community on NBS in the UK. This project was coordinated by Dr. Felicity Boardman [58] (Warwick Medical School) as part of the Imagining Futures Project and was conducted before the availability of innovative medication. This mixed model study involved qualitative (interviews with the SMA community members) and quantitative (survey-based) analyses. Even in absence of disease-modifying treatment, the majority of participants supported NBS (70% for the SMA community; 84% for the general population). The most common reasons cited were (1) it would increase support for children and families; (2) it would facilitate enrolment in clinical trials; and (3) it would allow parents to make informed decisions about future pregnancies. Finally, the data highlighted that participants believed the diagnosis of SMA in newborns was important even if the SMA type could not be definitively determined and even in the absence of effective treatment.

**Mencia de Lemus** pointed out that NBS is a tool that can help provide the SMA community with the best available options to tackle their disease. There is increasing evidence that the earlier SMA patients are treated, the better the prognosis. SMA is a fatal or, at the very least, a highly debilitating disease that if untreated leads to inevitable and constant decline, and all possible efforts to change that road should be pursued. It was emphasized that NBS should not be viewed as a way to limit innovative medication to only pre-symptomatic patients. Data from NBS should not preclude access to therapy by patients who are symptomatic.

**Laetitia Ouillade** gave an overview of the situation in France, where Spinraza is now reimbursed for all patients. She underlined the importance of the medical communication during the diagnosis process, which is even more important in the context of a NBS, as the absence of clinical signs can make a diagnosis difficult to accept for parents. She insisted on the standardized follow up of patients with four copies of *SMN2* if no treatment is offered. In all cases, the physician should present and explain the different approved and investigational treatments, clearly balancing expectations and unknown long-term effects, and give parents time to make a choice.

**Olga Germanenko** explained that families with children with SMA now have high expectations about treatment outcomes that sometimes overpass the actual treatment effect. It is therefore very important to communicate the diagnosis and treatment options, possible outcomes, and limitations of

treatments, as well as the importance of lifelong monitoring. Communication in the NBS screening process has a high impact and should be clear and transparent and reflect the current level of understanding of SMA and the expected effect of potential treatments.

Although NBS for SMA is not yet widely implemented, especially in countries with gaps in access to treatment, it is necessary to gather best practices on different aspects of NBS (e.g., technical, communication, implementation, clinical, legal, advocacy) into guidelines or recommendations that will be useful for countries where NBS is not yet implemented in order to speed up the worldwide process.

**Kacper Rucinski** stated that SMA patient organizations are supportive of universal NBS for SMA. However, they are also mindful of a range of issues related to early diagnostics and treatment. Experience shows that neuromuscular centers of excellence are usually able to provide a good standard of care but that there is insufficient expertise available in smaller hospitals (e.g., local neonatal and pediatric wards), and these facilities will play an important role in NBS and in decisions on the provision of care to newly diagnosed newborns. Future deliverables of the working group should include the development of universal recommendations to be issued as a Consensus Statement on standards for SMA NBS programs. Such a reference document, containing guidance on the topics ranging from diagnostic methods to timelines, parent communication, clinician training, and performance monitoring, would be of immense help in the design and introduction of SMA pilots and national screening programs worldwide.

**Kristin Stephenson** provided an overview of how NBS for neuromuscular disorders is moving forward in the USA, with Pompe disease and SMA both added to the US Recommended Uniform Screening Panel by the US Secretary of Health and Human Services and additional disorders such as Duchenne muscular dystrophy in process for nomination to the Recommended Uniform Screening Panel. Implementation of NBS in the USA is determined on a state-by-state basis. An overview of the mechanisms for adding disorders and policy considerations that impact the inclusion of additional disorders to the individual state testing panels was provided. The Muscular Dystrophy Association's recent interest in NBS is in part due to the nationwide network of multidisciplinary medical clinics across the USA that the Muscular Dystrophy Association supports and that serve as the infrastructure to provide expert clinical care and support to babies with SMA and other neuromuscular diseases and their families who are identified and diagnosed through NBS. Ensuring that uniform screening is implemented across all of the USA and that families have access to the care and support available takes the coordinated activities of multiple stakeholders and collaboration across organizations and entities. In the USA, there has been a significant amount of collaboration among clinicians, researchers, state health laboratory personnel, and patient advocacy groups that is allowing NBS for neuromuscular disease to move forward.

## 8. Toward a collaborative effort for data-based decision making for treatment

There is today a growing data set from Spinraza and Zolgensma studies that demonstrate the benefits of early pre-symptomatic treatment in patients with two or with three copies of *SMN2* in comparison with post-symptomatic treatments. The question of treating or not treating patients as a function of *SMN2* copy number was initially assessed using a Delphi methodology, and the results led to strong consensus for treating patients with two copies, but results were not clear for patients with three or four copies [59]. Although the benefit of treating patients with more than three copies of *SMN2* at birth is not established, and the overall feeling of the attendees was that these patients should be treated, the questions of whether or not patients with four copies of SMN2 should be treated at birth is highly debated [60].

It was unanimously agreed that a better standardization of copy number quantification is needed and that the natural history of the disease in patients with three or four copies of *SMN2* must be understood before strongly recommending treatment of these patients. This is particularly true in the context of the not-yet-fully-understood short- and long-term safety profiles of the currently used medications. There was a strong agreement that recommendations should be evidence-based.

## 9. Workshop key deliverables

The attendees defined a working plan (WP) divided into seven work packages in order to provide the data for an evidence-based and data-grounded decision making. To take into consideration a strong request issued by the patients and patient advocates, a WP aimed at establishing best practice and training for NBS was added. Attendees volunteered to participate in the different WPs. The attendees agreed that participation of physicians and scientists outside the group of workshop attendees should be encouraged.

It is likely that data issued from these different WPs will not be available for four to five years and during that time patients with a single or with more than three copies will be detected by NBS. For these subjects, the recommendation of the working group is to carefully evaluate the safety of the available treatments and to individually asses the benefit to risk ratios in these patients taking into account familial background and clinical information. If available, the exploratory evaluation of CMAP, pNF-H and/or other potential biomarkers should be taken into account. The group emphasizes that decision making should be a shared process including clinicians and the patient or patient advocates.

WP1: Best practice for *SMN2* copy number quantification including the minimal quality standard for DNA samples for reliable assessment (A. Burghes, E. Bertini, F. Boemer, E. Tizzano, F. D. Tiziano).

WP2: Identification and re-testing with up-to-date methods samples from patients who have reportedly with four copies of *SMN2* and presented with a severe phenotype or with type 1 or 2 SMA or who are asymptomatic, and identification of potential *SMN2*-related or unrelated modifiers (E. Tizzano, E. Bertini, A. Burghes, F. D. Tiziano).

WP3: Identification in the published literature of patient series with two, three, and four copies of *SMN2* matching the best practices as defined in WP1, in order to define the major milestones and timelines for different genotypes (E. Tizzano).

WP4: Establish patient milestones (date at first symptoms, date at diagnosis, and date at death) for patients with four copies using best practice as defined by WP1 and locally assessed (L. Servais).

WP5: Assess the prevalence of patients identified with *SMN1* loss in the elder general population (A. Burghes, E. Bertini, E. Tizzano, F. D. Tiziano).

WP6: Develop a European Registry of patients identified by NBS (W. Mueller-Felber, E. Bertini, L. Servais).

WP7: Train physicians in best practices for NBS for SMA; the aim of this working plan is to welcome physicians and scientists committed to gathering strong data to support evidence-based recommendations to join different working groups (W. Mueller-Felber, E. Tizzano, M. de Lemus, L. Servais, F. D. Tiziano).

L. Servais will be responsible for overall coordination of the work plan.

## 10. Conclusions

Several studies have demonstrated the benefits of early treatment of patients with SMA and newborn screening for SMA has been initiated in a number of countries. The workshop provided an overview of the current state of the art of different aspects of NBS and SMA including but not limited to scientific, economic, psychological, and ethical perspectives. The attendees did not try to reach a consensus on recommendations for treatment or NBS best practice, which would reflect the opinion only of workshop attendees, but rather defined a working methodology to move forward on critical questions.

## SMA Study Group

SMA Study Group authors:

Tamara Dangouloff, University of Liege, Belgium

Arthur Burghes, Ohio State University, Columbus OH

Enrico Bertini, Bambino Gesù Children's Hospital, Rome, Italy

François Boemer, University of Liege, Belgium

Mickaël Hiligsmann, Maastricht University, Maastricht, The Netherlands

Wolfgang Mueller-Felber, Ludwig-Maximilian University of Munich, Germany

Francesco Danilo Tiziano, Catholic University of Sacred Heart, Rome, Italy

Philip Young, University of Warwick, Coventry, UK

Eduardo F. Tizzano, University Hospital Valle Hebron, Barcelona, Spain

Laurent Servais, MDUK Neuromuscular Center, University of Oxford, UK & University of Liege, Belgium.

SMA Study Group patient representatives:

Olga Germanenko, Patient Advocacy Group, SMA Moscow, Russia

Mencia de Lemus, Patient Advocacy Group, SMA Spain, Madrid, Spain

Laetitia Ouillade, Patient Advocacy Group, SMA France, Pessac, France

Kasper Rucinski, Patient Advocacy Group, SMA Poland, Poland

Kristin Stephenson, Muscular Dystrophy Association, Washington, D.C., USA

SMA Study Group pharmaceutical company representatives:

Wildon Farwell, Biogen, Boston, MA, USA

Ksenija Gorni, Roche Pharma Research and Early Development, F. Hoffmann –

La Roche Ltd, Basel, Switzerland

Mikael Hjort, PerkinElmer Finland, Turku, Finland

Imran Kausar, Medical Affairs, London, UK and AveXis, (a division of Novartis, Bannockburn, IL, USA)

## Acknowledgments

The organizers warmly acknowledge the staff of ENMC: Alexandra Breukel, Managing Director and Annelies Zittersteijn, Operational Manager. This Workshop was made possible thanks to the financial support of the European Neuromuscular Centre (ENMC) and ENMC main sponsors: Association Française contre les Myopathies (France), Deutsche Gesellschaft für Muskelkranke (Germany), Muscular Dystrophy Campaign (UK), Muskelsvindfonden (Denmark), Prinses Beatrix Spierfonds (The Netherlands), Schweizerische Stiftung für die Erforschung der Muskelkrankheiten (Switzerland), Telethon Foundation (Italy), Spierziekten Nederland (The Netherlands) and Associated members: Finnish Neuromuscular Association (Finland) and Österreichische Muskelforschung (Austria).

The ENMC is also grateful for the support of MDA USA and SMA Europe.

Special thanks are extended to the members of the ENMC Company Forum: Amicus Therapeutics, AveXis, Biogen, CSL Behring, Ionis Pharmaceuticals, PerkinElmer, Roche, Sanofi Genzyme, Sanquin Plasma Products, Santhera Pharmaceuticals, and other partner organizations for their support of the ENMC workshops.

## Abbreviations

| | |
|---|---|
| CMAP | Compound Muscle Action Potential |
| DBS | Dried Blood Spot |

| | |
|---|---|
| DNA | Deoxyribonucleic Acid |
| FDA | Food and Drug Administration |
| NBS | Newborn Screening |
| PCR | Polymerase Chain Reaction |
| QALY | Quality-Adjusted Life Years |
| qPCR | Quantitative Polymerase Chain Reaction |
| SMA | Spinal Muscular Atrophy |
| SMN | Survival of Motor Neuron |

## References

[1] Lefebvre S, Burglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell 1995;80(1):155–65.
[2] Alias L, Bernal S, Fuentes-Prior P, Barcelo MJ, Also E, Martinez-Hernandez R, et al. Mutation update of spinal muscular atrophy in Spain: molecular characterization of 745 unrelated patients and identification of four novel mutations in the SMN1 gene. Hum genet. 2009;125(1):29–39.
[3] Dubowitz V. Sixty years of spinal muscular atrophy: a personal odyssey. Spinal muscular atrophy. Sumner CJ, Paushkin S, Ko C-P, editors. Academic Press; 2017. xvii–xxxi.
[4] Klug C, Schreiber-Katz O, Thiele S, Schorling E, Zowe J, Reilich P, et al. Disease burden of spinal muscular atrophy in Germany. Orphanet J Rare Dis. 2016;11(1):58.
[5] Chabanon A, Seferian AM, Daron A, Pereon Y, Cances C, Vuillerot C, et al. Prospective and longitudinal natural history study of patients with type 2 and 3 spinal muscular atrophy: baseline data Nathis-Sma study. PLoS ONE 2018;13(7):e0201004.
[6] Calucho M, Bernal S, Alias L, March F, Vencesla A, Rodriguez-Alvarez FJ, et al. Correlation between SMA type and SMN2 copy number revisited: an analysis of 625 unrelated spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord. 2018;28(3):208–15.
[7] Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. New Engl J Med. 2017;377(18):1723–32.
[8] Pechmann A, Konig K, Bernert G, Schachtrup K, Schara U, Schorling D, et al. SMArtCARE – a platform to collect real-life outcome data of patients with spinal muscular atrophy. Orphanet J Rare Dis. 2019;14(1):18.
[9] Aragon-Gawinska K, Seferian AM, Daron A, Gargaun E, Vuillerot C, Cances C, et al. Nusinersen in patients older than 7 months with spinal muscular atrophy type 1: a cohort study. Neurology 2018;91(14):e1312–e13e8.
[10] Pane M, Palermo C, Messina S, Sansone VA, Bruno C, Catteruccia M, et al. Nusinersen in type 1 sma infants, children and young adults: preliminary results on motor function. Neuromuscul Disord. 2018;28(7):582–5.
[11] Gidaro T, Servais L. Nusinersen treatment of spinal muscular atrophy: current knowledge and existing gaps. Dev Med Child Neurol. 2019;61(1):19–24.
[12] De Vivo D, Bertini E, Swoboda KJ, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromusc Disord 2019;29(11):842–56.
[13] Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl Journal Med. 2017;377(18):1713–22.
[14] Dabbous O., Sproule D., Feltner D.E., Ogrinc F.G., Menier M., Droege M., et al. Event-Free survival and motor milestone achievement following AVXS-101 and nusinersen interventions contrasted to natural history for type I spinal muscular atrophy patients. AAN: S25: Child Neurology: Spinal Muscular Atrophy: Treatments and Outcomes. 2019.
[15] Servais L., Baranello G., Day J.W., Deconinck N., Mercuri E., A. K., et al. FIREFISH part 1: survival, ventilation and swallowing ability in infants with type 1 SMA receiving Risdiplam (RG7916). AAN: S25: Child Neurology: Spinal Muscular Atrophy: Treatments and Outcomes. 2019.
[16] Dangouloff T, Servais L. Clinical evidence supporting early treatment in SMA. Ther Clin Risk Manag. 2019;15:1153–61.
[17] FDA. FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality: 05/24/2019; 2019 [Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease.
[18] Wilson JMG, Jungner G. Principles and practice of screening for disease. Public health paper, 34. World Health Organization; 1968.
[19] Serra-Juhe C, Tizzano EF. Perspectives in genetic counseling for spinal muscular atrophy in the new therapeutic era: early pre-symptomatic intervention and test in minors. Eur J Human Genet. 2019;27(12):1774–82.
[20] Chien YH, Chiang SC, Weng WC, Lee NC, Lin CJ, Hsieh WS, et al. Presymptomatic diagnosis of spinal muscular atrophy through newborn screening. J Pediatr. 2017;190 124-9.e1.
[21] Kraszewski JN, Kay DM, Stevens CF, Koval C, Haser B, Ortiz V, et al. Pilot study of population-based newborn screening for spinal muscular atrophy in new york state. Genet Med. 2018;20(6):608–13.
[22] Boemer F, Caberg JH, Dideberg V, Dardenne D, Bours V, Hiligsmann M, et al. Newborn screening for SMA in Southern Belgium. Neuromuscul Disord. 2019;29(5):343–9.
[23] Prior TW, Krainer AR, Hua Y, Swoboda KJ, Snyder PC, Bridgeman SJ, et al. A positive modifier of spinal muscular atrophy in the SMN2 gene. Am J Hum Genet. 2009;85(3):408–13.
[24] Wu X, Wang SH, Sun J, Krainer AR, Hua Y, Prior TW. A-44G transition in SMN2 intron 6 protects patients with spinal muscular atrophy. Hum Mol Genet. 2017;26(14):2768–80.
[25] Ruhno C, McGovern VL, Avenarius MR, Snyder PJ, Prior TW, Nery FC, et al. Complete sequencing of the SMN2 gene in SMA patients detects SMN gene deletion junctions and variants in SMN2 that modify the SMA phenotype. Hum Genet. 2019;138(3):241–56.
[26] Bernal S, Alias L, Barcelo MJ, Also-Rallo E, Martinez-Hernandez R, Gamez J, et al. The c.859G>C variant in the SMN2 gene is associated with types II and III sma and originates from a common ancestor. J Med Genet. 2010;47(9):640–2.
[27] Schorling DC, Becker J, Pechmann A, Langer T, Wirth B, Kirschner J. Discrepancy in redetermination of SMN2 copy numbers in children with SMA. Neurology 2019;93(6):267–9.
[28] Feldkotter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet. 2002;70(2):358–68.
[29] Yuan A, Rao MV, Veeranna, Nixon RA. Neurofilaments and neurofilament proteins in health and disease. Cold Spring Harb Perspect Biol 2017;9:a018309.
[30] Petzold A. Neurofilament phosphoforms: surrogate markers for axonal injury, degeneration and loss. J Neurol Sci. 2005;233(1–2):183–98.
[31] Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med. 2018;378(7):625–35.
[32] Darras BT, Chiriboga CA, Iannaccone ST, Swoboda KJ, Montes J, Mignon L, et al. Nusinersen in later-onset spinal muscular atrophy: long-term results from the phase 1/2 studies. Neurology 2019;92(21):e2492–ee506.
[33] Human N.F.-H. Simple plex assay for the detection of human neurofilament heavy (NF-H) in serum pEH, and cerebrospinal fluid (CSF) [ProteinSimple assay specification sheet]. Available at: https://www.proteinsimple.com/documents/NF-H_Specification_Sheet_Rev_B.pdf. Accessed 20 May 2019.

[34] Darras BT, Crawford TO, Finkel RS, Mercuri E, De Vivo DC, Oskoui M, et al. Neurofilament as a potential biomarker for spinal muscular atrophy. Ann Clin Transl Neurol. 2019;6(5):932–44.
[35] Sumner CJ D.B., Muntoni F., Crawford T.O., Finkel R.S., Mercuri E., De Vivo D.C., et al. Association of phosphorylated neurofilament heavy chain (pNF-H) levels with motor function achievement in individuals with spinal muscular atrophy (SMA) treated with nusinersen. Proceedings of the AAN 2019 – Seventy-first Annual Meeting, May 4–10, 2019, Philadelphia, PA, USA.
[36] Olsson B, Alberg L, Cullen NC, Michael E, Wahlgren L, Kroksmark AK, et al. NFL is a marker of treatment response in children with SMA treated with nusinersen. J Neurol 2019;266:2129–36.
[37] Winter B, Guenther R, Ludolph AC, Hermann A, Otto M, Wurster CD. Neurofilaments and tau in CSF in an infant with SMA type 1 treated with nusinersen. J Neurol Neurosurg Psychiatry 2019;90:1068–9.
[38] Boemer F, Caberg J, Dideberg V, Beckers P, Marie S, Marcelis L, et al. (S)un (M)ay (A)rise on SMA: l’espoir d’une région sans amyotrophie spinale [(S)un (M)ay (A)rise on SMA: the hope of a region without spinal muscular atrophy]. Rev Med Liege 2019;74(9):461–4.
[39] Czibere L, Burggraf S, Fleige T, Gluck B, Keitel LM, Landt O, et al. High-throughput genetic newborn screening for spinal muscular atrophy by rapid nucleic acid extraction from dried blood spots and 384-well qPCR. Eur J Hum Genet. 2019;90:1068–9.
[40] Wurster CD, Ludolph AC. Nusinersen for spinal muscular atrophy. Ther Adv Neurol Disord. 2018;11:1756285618754459.
[41] Mokhtariye A, Hagh-Nazari L, Varasteh A-R, Keyfi F. Diagnostic methods for Lysosomal storage disease. Rep Biochem Mol Biol. 2019;7(2):119–28.
[42] Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: cystic fibrosis foundation consensus report. J Pediatr. 2008;153(2):S4–S14.
[43] Tridello G, Castellani C, Meneghelli I, Tamanini A, Assael BM. Early diagnosis from newborn screening maximises survival in severe cystic fibrosis. ERJ Open Res. 2018;4(2):00109–2017.
[44] Amato A, Giordano PC. Screening and genetic diagnosis of hemoglobinopathies in southern and northern europe: two examples. Mediterr J Hematol Infect Dis. 2009;1(1):e2009007.
[45] Abuli A, Boada M, Rodriguez-Santiago B, Coroleu B, Veiga A, Armengol L, et al. NGS-Based assay for the identification of individuals carrying recessive genetic mutations in reproductive medicine. Hum Mutat. 2016;37(6):516–23.
[46] Alias L, Barcelo MJ, Bernal S, Martinez-Hernandez R, Also-Rallo E, Vazquez C, et al. Improving detection and genetic counseling in carriers of spinal muscular atrophy with two copies of the SMN1 gene. Clin Genet. 2014;85(5):470–5.
[47] Luo M, Liu L, Peter I, Zhu J, Scott SA, Zhao G, et al. An Ashkenazi Jewish SMN1 haplotype specific to duplication alleles improves pan-ethnic carrier screening for spinal muscular atrophy. Genet Med. 2014;16(2):149–56.
[48] Alias L, Bernal S, Calucho M, Martinez E, March F, Gallano P, et al. Utility of two SMN1 variants to improve spinal muscular atrophy carrier diagnosis and genetic counselling. Eur J Hum Genet. 2018;26(10):1554–7.
[49] Jonsson E, Banta D. Treatments that fail to prove their worth. interview by Judy Jones. BMJ 1999;319(7220):1293.
[50] Drummond M, Jonsson B, Rutten F. The role of economic evaluation in the pricing and reimbursement of medicines. Health Policy (New York) 1997;40(3):199–215.
[51] Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 4th ed Oxford: Oxford: Oxford University Press; 2015.
[52] Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. N Engl J Med. 2014;371(9):796–7.
[53] CADTH Common Drug Reviews. Pharmacoeconomic review report: Nusinersen (Spinraza): (Biogen Canada Inc): Indication: Treatment of patients with 5q SMA. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018.
[54] ICER. Spinraza® and zolgensma® for spinal muscular atrophy: effectiveness and value. 2019. Institute for Clinical and Economic Review, www.icer.org 0403192019 i–iii.
[55] Zuluaga-Sanchez S, Teynor M, Knight C, Thompson R, Lundqvist T, Ekelund M, et al. Cost effectiveness of nusinersen in the treatment of patients with infantile-onset and later-onset spinal muscular atrophy in Sweden. PharmacoEcon. 2019;37(6):845–65.
[56] Garrison LP, Jackson T, Paul D, Kenston M. Value-Based pricing for emerging gene therapies: the economic case for a higher cost-effectiveness threshold. J Manag Care Spec Pharm 2019;27:795–9.
[57] Little SE, Janakiraman V, Kaimal A, Musci T, Ecker J, Caughey AB. The cost-effectiveness of prenatal screening for spinal muscular atrophy. Am J Obstet Gynecol 2010;202(3):253.e1–253.e7.
[58] Boardman FK, Young PJ, Griffiths FE. Population screening for spinal muscular atrophy: a mixed methods study of the views of affected families. Am J Med Genet A 2017;173(2):421–34.
[59] Glascock J, Sampson J, Haidet-Phillips A, Connolly A, Darras B, Day J, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. J Neuromuscul Dis 2018;5(2):145–58.
[60] Darras BT, De Vivo DC. Precious SMA natural history data: a benchmark to measure future treatment successes. Neurology 2018;91(8):337–9.

## Annexe XII. Correspondence on: “Discrepancy in Spinal Muscular Atrophy Incidence findings in newborn screening programs: the influence of carrier screening?” by Kay et al. (Chapitre III, 4)

Dangouloff T, Boemer F, Caberg J-H, Servais L. Genetics in Medicine. 2020.

© American College of Medical Genetics and Genomics

CORRESPONDENCE | Genetics inMedicine

# Correspondence on: "Discrepancy in Spinal Muscular Atrophy Incidence findings in newborn screening programs: the influence of carrier screening?" by Kay et al

**To the Editor:**

We would like to congratulate Kay et al. for their article[1] on the implementation of newborn screening (NBS) for spinal muscular atrophy (SMA) in New York State (NYS), and also salute their pioneering work in NBS for SMA.[2]

In this paper, the authors review one year of NBS implementation in NYS. Of 225,093 infants, 8 were identified with SMA. All newborns were asymptomatic at diagnosis and promptly received disease-modifying treatment for the most severe forms. The authors noticed an incidence significantly lower than expected, and propose two hypotheses to explain this particularly low prevalence:

- Part of their population has been previously screened for SMA through preconceptional carrier screening, genetic counseling, cascade testing, prenatal diagnosis, or advanced reproductive technologies.
- Previous studies overestimated the incidence of SMA in the general population.

We believe it is crucial to differentiate between the two hypotheses given the public health implications and the cost of drug reimbursement, since many drug reimbursement models are linked to the exact incidence of the disease. The suggestion of a lower incidence of SMA could have considerable consequences for the reimbursement process of disease-modifying therapies in several countries, as well as for NBS funding decisions. Therefore, trying to better identify the causes of the finding is of primary importance for existing and future patients.

We could reasonably consider that the second hypothesis of a previously overestimated incidence is not valid. Indeed, other studies have demonstrated that the incidence of SMA at birth appears to be fairly comparable with that reported in the literature. Pilot studies for neonatal screening of SMA are currently underway in several countries,[3] and data of incidence are available from Germany, Belgium, and Australia. These three programs found relatively similar and close figures to the initial studies that estimated the incidence at 1 in 10,000, with higher figures in Europe. The Australian study[4] reported an incidence of 1 in 11,545, the German study[5] returned an incidence of 1 in 7096, and finally our pilot study in Belgium[6] shows an incidence of 1 in 8398. The unique studies announcing lower SMA incidence are in New York State during the pilot study (1 in 16,712) and after the first year of experience (1 in 28,137), and in Taiwan (1 in 17,181).[7]

If we consider that the low incidence reported from NYS results from a better awareness of the risks of genetic disease transmission and the concurrent implementation of carrier screening, and that a "normal" incidence would have resulted in about 22 cases in 225,093 infants, it means that about 14 potential cases of 22 (about 64%) have been avoided by carrier or prenatal screening. This heartening uptake could be the result of increased communication regarding SMA in recent years, the pioneer work conducted in NYS, the addition of SMA to the Recommended Uniform Screening Panel (RUSP) in 2018, the marketing of drugs, and polemics against the prices of these drugs in mainstream media and on social networks. All of these efforts may have encouraged future parents to ask for genetic counseling and carrier screening, which has until now remained very rare in some regions such as Southern Belgium. Nevertheless, such a lowering in incidence should normally be suggested by the number of tests carried on in the same region.

We hope that future data from NYS and from other regions in the United States and around the world will help to further reinforce and contextualize the findings of Professor Kay and her colleagues.

## DISCLOSURE

T.D. has given lectures sponsored by Biogen and Roche. L.S. has given lectures and has served as a consultant for Roche, Biogen, Avexis, and Cytokinetics. L.S. is the project leader of the NBS in Southern Belgium, funded by Avexis, Roche, and Biogen. The other authors declare no conflicts of interest.

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

*Tamara Dangouloff, RN*[1], *François Boemer, PhD*[2], *Jean-Hubert Caberg, PhD*[3] *and Laurent Servais, MD, PhD*[1,4]

[1]Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, Liège, Belgium; [2]Biochemical Genetics Laboratory, Human Genetics Department, University Hospital Liège & University of Liège, Liège, Belgium; [3]Molecular Genetics Laboratory, Human Genetics Department, University Hospital Liège & University of Liège, Liège, Belgium; [4]MDUK Neuromuscular Centre, Department of Paediatrics, University of Oxford, Oxford, UK. Correspondence: Laurent Servais (laurent.servais@paediatrics.ox.ac.uk)

## REFERENCES

1. Kay DM, et al. Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy. Genet Med. 2020 May 18; https://doi.org/10.1038/s41436-020-0824-3 [Epub ahead of print].

Submitted 29 May 2020; accepted: 17 June 2020
Published online: 30 June 2020

# CORRESPONDENCE



2. Kraszewski JN, et al. Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. Genet Med. 2018;20: 608–613.
3. Dangouloff T, Burghes A, Tizzano EF, Servais L, NBS SMA Study Group. 244th ENMC international workshop: Newborn screening in spinal muscular atrophy May 10–12, 2019, Hoofdorp, The Netherlands. Neuromuscul Disord. 2020;30:93–103.
4. Kariyawasam DST, Russell JS, Wiley V, et al. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. Genet Med. 2020;22:557–565.
5. Vill K, et al. One year of newborn screening for SMA—results of a German pilot project. J Neuromuscul Dis. 2019;6:503–515.
6. Boemer F, et al. Newborn screening for SMA in Southern Belgium. Neuromuscul Disord. 2019;29:343–349.
7. Chien YH, et al. Presymptomatic diagnosis of spinal muscular atrophy through newborn screening. J Pediatr. 2017;190:124–129.e1.



Advance online publication 30 June 2020. doi:10.1038/s41436-020-0887-1

## Annexe XIII. Newborn screening programs for spinal muscular atrophy worldwide: where we stand and where to go. (Chapitre III, 4)

Dangouloff T*, Vrščaj E*, Servais L#, Osredkar D#, and the SMA NBS World Study Group. Neuromuscular Disorders. 2021.

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 31 (2021) 574–582

www.elsevier.com/locate/nmd

# Newborn screening programs for spinal muscular atrophy worldwide: Where we stand and where to go

Tamara Dangouloff[a,1], Eva Vrščaj[b,1], Laurent Servais[a,c,*], Damjan Osredkar[b,d,*], the SMA NBS World Study Group[#]

[a] *Division of Child Neurology, Reference Center for Neuromuscular Diseases, Department of Pediatrics, University Hospital Liège & University of Liège, CRMN Liège, CHR de la Citadelle, Boulevard du 12ème de Ligne, 4000 Liège, Belgium*

[b] *Department of Pediatric Neurology, University Children's Hospital, University Medical Centre Ljubljana, Bohoričeva 20, 1525 Ljubljana, Slovenia*

[c] *MDUK Neuromuscular Centre, Department of Paediatrics, University of Oxford, United Kingdom*

[d] *Medical Faculty, University of Ljubljana, Slovenia*

Received 14 February 2021; received in revised form 10 March 2021; accepted 16 March 2021

**Abstract**

Spinal muscular atrophy (SMA) is a rare and devastating disease. New disease-modifying treatments have recently been approved and early treatment has been related to a better outcome. In this context, several newborn screening (NBS) programs have been implemented. The aim of the study was to obtain a global overview on the current situation and perspectives on SMA NBS. We conducted a survey and contacted experts from 152 countries, from which we gathered 87 responses. We identified 9 SMA NBS programs that have so far detected 288 newborns with SMA out of 3,674,277 newborns screened. Funding, screening methods, organisation, and consent process were variable between SMA NBS programs. Many respondents pointed the lack of cost/benefit data as a major obstacle to SMA NBS implementation. In the next four years, our data suggest a 24% coverage of newborns from countries where a disease-modifying drug is available and 8,5% coverage in countries with no diseases-modifying drugs. The annual proportion of newborns to be screened in the coming years is expected to increase steadily. The experts expressed a strong need for the implementation of SMA NBS as means to improve care for patients with SMA.

© 2021 Elsevier B.V. All rights reserved.

*Keywords:* Newborn screening; Spinal muscular atrophy; Pre-symptomatic; Nusinersen; Risdiplam; Onasemnogene abeparvovec.

## 1. Introduction and context

5q Spinal muscular atrophy (SMA) is an autosomal recessive disease, caused by lack of functional survival motor neuron (SMN) protein. The incidence is approximately 1 in 10,000–12,000 live births [1],[2]. Despite a broad phenotypic spectrum, with symptoms onset from birth to adulthood, 95% of patients present with a homozygous deletion of *SMN1* gene, and 5% with a single allelic deletion and a point mutation on the other allele [3].

Three disease-modifying drugs have been approved by the U.S. Food and Drug Administration (FDA), and around the world over the last four years [4]: nusinersen in December 2016 [5], onasemnogene abeparvovec in May 2019 [6],[7], and risdiplam in August 2020 [8]. Disease duration has been demonstrated to be a consistent prognostic factor across the different clinical trials [9]. The most significant treatment effect has been observed in pre-symptomatic patients [10].

In this context, several newborn screening (NBS) programs have been implemented [11] in Australia [12], Belgium [13], Canada [14], Germany [15], Italy, Japan [16], and Taiwan [17]. In the United States [18], SMA was included in the

* Corresponding authors.
*E-mail addresses:* laurent.servais@paediatrics.ox.ac.uk (L. Servais), damjan.osredkar@kclj.si (D. Osredkar).

[1] The authors have contributed equally.

[#] The SMA NBS world study group listed at the end.

https://doi.org/10.1016/j.nmd.2021.03.007
0960-8966/© 2021 Elsevier B.V. All rights reserved.

Recommended Uniform Screening Panel (RUSP) on July 2, 2018.

Several technical, financial, organisational or ethical considerations may block or slow down NBS implementation throughout the world. To better appreciate the current global situation, and to foresee the development in the coming years, we launched a survey that was distributed to SMA and NBS key leaders in most countries around the world.

## 2. Methods

We contacted experts in the fields of SMA and NBS in as many countries around the world as possible to obtain a global overview on the availability of disease-modifying drugs for SMA and the current state of SMA NBS in their countries. We also gathered expert opinions on technical and organisational issues related to actual or coming SMA NBS as well as their predictions of how SMA NBS will be implemented in their respective countries in the next ten years. The experts were invited to reply to a questionnaire, which was accessible via a web link that was sent in the invitational e-mail. Queries were sent to clarify any inconsistent data entered in the survey.

### *2.1. The questionnaire*

Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University Medical Centre Ljubljana, Slovenia [19]. Surveys were completed between November 26 and December 29, 2020. The questionnaire comprised of four sections:

1. Basic information, such as name and surname, profession or speciality, email, country/region (C/R) for which the expert provided data, and the number of births in that C/R.
2. Questions related to the availability of disease-modifying drugs for SMA in the respective C/R.
3. Questions related to SMA NBS in the respective C/R.
4. Questions related to the existence of NBS for other diseases than SMA and SMA carrier screening in the respective C/R. The respondents could also share other unlisted information in this final part.

The questionnaire is available in Appendix 1, and at the following link: http://sma.pedkl.si.

### *2.2. Identifying experts with knowledge in the fields of SMA NBS*

To establish a list of the contacts, we addressed experts in as many countries around the world as possible from the following fields of expertise: paediatric or adult neurology, paediatrics, genetics, clinical research, newborn screening programs, patient advocacy groups, or other relevant specialties. The list of contacts was compiled using various resources: professional connections (including through Researchgate and LinkedIn), the details given for corresponding authors of relevant peer-reviewed articles, and web searching using the keywords “newborn screening” and “spinal muscular atrophy”.

For each country, one expert was invited to participate in the survey and in case of no response, one or more substitutes were identified. In countries which had two regions that significantly differed regarding SMA NBS, we invited one expert from each region with and without NBS programs.

### *2.3. Statistical analysis*

For answers regarding disease-modifying drugs and implemented SMA NBS, we have combined the responses where two experts have given an answer for two different regions of a particular country. All statistics reported here are descriptive.

The median for continuous variables, or mode for categorical variables, was calculated. A categorical variable (0–10%, 10–20%, etc.) was proposed to estimate the percentage of newborns screened. Statistical analyses were performed using SPSS version 27 (SPSS Inc., Chicago, USA). World maps were designed in Microsoft Excel (2019) for Mac (Microsoft, Redmond, USA), while other images were designed with Prism version 7 for Mac (GraphPad Software, La Jolla California, USA).

### *2.4. Study group*

The respondents were invited to join the SMA NBS World Study Group. The group met on January 15, 2021 on two video calls to discuss the findings. Following the calls, we gathered more precise information on false positives and false negatives encountered in the pilot programs. The draft of the paper was sent to the group for double-checking of the provided data.

## 3. Results

According to information from the United Nations [20], there are currently 197 countries in the world. The questionnaire was sent to experts in 152 countries. We obtained responses from 87 experts from 82 different countries (54% of contacted countries) in 6 continents (Appendix 2). Altogether, these countries count 8,434,000 newborns per year, which account for 57% of the total number of newborns born per year in the world.

Of 87 respondents, 61 identified themselves (with more than one option possible) as paediatric neurologists, 13 as adult neurologists, 11 as geneticists, 4 as paediatricians, 4 as newborn screening specialists, 2 as patient advocacy group members, and 8 as researchers. For four countries (Australia, Belgium, Canada, Colombia), two independent respondents have provided data for the two distinct regions of their country and the data were combined accordingly for the purpose of analysis; for China, three respondents responded on this basis for the mainland People’s Republic of China, the Hong Kong

Table 1
Availability of SMA disease-modifying drugs in the 53/82 countries where at least one disease-modifying drug was reported to be available.

| Drug | Nusinersen | Onasemnogene abeparvovec | Risdiplam |
|---|---|---|---|
| Countries ($n=53$) | 53 | 24 | 26 |
| Access | | | |
| Reimbursement | 48 | 14 | 6 |
| Compassionate use | 1 | 5 | 18 |
| Patient charge | 4 | 5 | 2 |
| Indication (symptoms) | | | |
| Symptomatic | 53 | 22 | 25 |
| Pre-symptomatic | 32 | 15 | 3 |
| Indication pre-sympto (*SMN2* copies) | | | |
| 1 copy | 18 | 9 | 0 |
| 2 copies | 30 | 13 | 1 |
| 3 copies | 29 | 12 | 1 |
| 4 copies | 14 | 5 | 1 |
| 5+ copies | 7 | 1 | 0 |
| Do not know | 1 | 0 | 1 |
| No criteria (case/case) | 2 | 2 | 1 |

SAR and Taiwan respectively. Sixty respondents attended the SMA NBS study group meeting.

### *3.1. Availability of SMA disease-Modifying drugs*

The availability of treatments according to the number of copies and the time of disease onset is reported in Table 1.

The availability of disease-modifying drugs around the world, and the relationship between the availability of disease-modifying drugs and implemented SMA NBS, is illustrated in Figs. 1A and B.

### *3.2. Countries with implemented SMA NBS*

We obtained responses from 82 countries regarding their newborn screening program, except for Mexico where we only received information on disease-modifying drugs. Newborn screening for SMA was implemented in 9 countries, 11% of all responding countries (Fig 1B, Table 2).

Ethical committee approval was required for implementing SMA NBS in all countries, although it was not required in specific regions in Canada with active NBS.

Altogether, the respondents have reported 288 newborns with diagnosed SMA out of 3,674,277 screened newborns in the above mentioned 9 countries with SMA NBS program. This represented an incidence of 1 in 12,757 (Table 2).

False positives in Taiwan and Italy were reported only at the beginning of the program and no new cases were reported after the change of primers. False positives in the US were generally reported to be due to low white blood cell counts resulting in false positive or an unsatisfactory result for SMA.

Patients with the deletions of one allele and point mutations on the other allele in the *SMN1* gene were not considered as false negatives as they are not supposed to be identified by the current methods. Nevertheless, at least 3 such cases were identified (2 in Taiwan, 1 in Belgium).

Respondents from countries with an opt-out consent process reported a much better acceptability rate (99%) than those with an opt-in process (80–87%). The fact that the U.S. has only a 61–70% rate is because not all states have yet included SMA in their NBS.

In countries with an implemented SMA NBS program, when asked about how important they believe it is to have the SMA NBS implemented in their country, all but one expert rated 100, and one rated 90 (on a 0–100 scale). Obstacles faced by the respondents in their respective countries and measures that could be helpful for improving the current SMA NBS are listed in Table 3.

The main obstacles mentioned ($n=5$) related to cost/effectiveness issues and long-term data availability ($n=4$). Other mentioned obstacles were uncertainties about patients with higher *SMN2* copy numbers ($\geq 4$), reimbursement of treatment, and carrier testing. COVID-19 was also a significant present concern, as it has had a considerable impact on the ability of the national standing committees to meet and has also had a worldwide economic impact.

Each respondent from countries where an SMA NBS program is ongoing highlighted the following points as important for initiating NBS at the national or regional level: (i) to start by pilot project; (ii) to identify the process for implementation of SMA NBS in the country (typical steps include developing the screening assay, identifying the staff need to carry out testing and follow up, identifying funding for the NBS work, completing the regulatory requirements for implementation, identify the speciality healthcare referral centres); (iii) to educate colleagues in NBS and provincial government officials about the importance of pre-symptomatic treatment initiation; (iv) to present long-term efficacy of treatment; (v) to share the experience in the NBS-SMA implementation process; (vi) to use the whole of health systems approach and partnering with patient organisations.

Table 2
Details on SMA NBS program. W: Whole country P: Part of country, NB: newborns, Pilot: pilot program, Official: official program, Cases: number of SMA cases identified; pos: positive, neg: negative, Cons Proc: Consent process, H: funds by hospital, P: funds by parents, G: funds by government, HI: fund by Health insurance, Ph: funds by pharmaceutical companies, Gr: funds by grants, US NBS: usual NBS laboratories, Gen lab: genetic laboratory, qPCR: quantitative Polymerase Chain Reaction, dPCR: droplet digital polymerase chain reaction, MLPA: multiplex ligation dependant probe amplification, var methods: various methods.

| Country (W/P) | NB/y | % NB Screened | Year NBS SMA implemented | | Cases | NB screened | False Pos | False neg | Cons Proc | Fund | Site test | Genetic method | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Pilot | Official | | | | | | | | Tier 1 | Tier 2 |
| Taiwan (W) | 170,000 | 81–90% | 11/14 | 01/18 | 20 | 419,102 | 8 | 0 | Opt-in | H/P | Us NBS | qPCR | MLPA |
| USA (P) | 3,745,540 | 61–70% | 01/16 | 07/18 | 180 | 2,395,718 | 10 | 0 | Opt-out | G | Us NBS | Var meth. | dPCR/ qPCR |
| Germany (P) | 780,000 (305,000) | 11–20% (87%) | 01/18 | <1y | 43 | 297,163 | 0 | 0 | Opt-in | HI | Us NBS | qPCR | MLPA |
| Belgium (P) | 120,000 (55,000) | 45% (99%) | 03/18 | 03/21 | 9 | 127,329 | 0 | 0 | Opt-out | Ph/G/Gr | 1 Us NBS | qPCR | MLPA |
| Australia (P) | 300,000 (100,000) | 21–40% (99%) | 08/18 | >2y | 19 | 202,388 | 1 | 0 | Opt-out | Gr/G | 1 Us NBS | qPCR | dPCR |
| Italy (P) | 435,000 (68,000) | 11–20% (86%) | 09/19 | NA | 12 | 58,558 | 0 | 0 | Opt-in | Ph | 1 gen lab | qPCR | qPCR |
| Russia (P) | 1,373,550 (15,000) | < 10% (80%) | 08/19 | 3y | 0 | 12,000 | 0 | 0 | Opt-in | Ph | 1 gen lab | qPCR | MLPA |
| Canada (P) | 377,000 (140,000) | 31–40% (99%) | 01/20 | 06/20 | 5 | 139,810 | 0 | 0 | Opt-out | G/Ph | 1 Us NBS | Mass | MLPA |
| Japan (P) | 864,000 (1 district) | < 10% | 05/20 | 3 y | 0 | 22,209 | 0 | 0 | Opt-in | Ph/P | 1 gen lab | qPCR | MLPA |
| **All** | **8,100,090** | **3,081,839** | | | **288** | **3,674,277** | **19** | **0** | | | | | |

Table 3
Actual or foreseen obstacles and measures for help for establishing SMA NBS.

| Obstacles | Countries with SMA NBS ($N=9$) | Countries without SMA NBS ($N=76$) |
|---|---|---|
| Lack of professional consensus on an international level | | 13% (10) |
| Lack of professional consensus on a national level | 11% (1) | 17% (13) |
| Lack of long-term follow-up data | 11% (1) | 16% (12) |
| Lack of financial resources | 55% (5) | 68% (52) |
| Lack of human resources | 11% (1) | 29% (22) |
| Lack of equipment | 22% (2) | 29% (22) |
| Organisational issues | 33% (3) | 21% (16) |
| Too difficult to be implemented in practice | 11% (1) | 11% (8) |
| Lack of support from the hospitals involved | 33% (3) | 14% (11) |
| Lack of governmental support | 44% (4) | 30% (23) |
| Not a healthcare priority in our country | 11% (1) | 29% (22) |
| Ethical issues | 0 | 6% (5) |
| Other | 33% (3) | 12% (9) |
| Measures | | |
| Clear professional consensus on an international level | 11% (1) | 39% (30) |
| Clear professional consensus on a national level | 22% (2) | 32% (24) |
| Clear professional guidelines / recommendations | 22% (2) | 45% (34) |
| Health-economic data | 44% (4) | 54% (41) |
| Cost-benefit analysis | 55% (5) | 70% (53) |
| Long term follow-up data on treatment of pre-symptomatic patients | 55% (5) | 53% (40) |
| Resources and support by institution | 0 | 32% (24) |
| Resources and support by government | 66% (6) | 67% (51) |
| Assistance with implementation practicalities | 22% (2) | 20% (15) |
| Measures against genetic discrimination of patients | 0 | 12% (9) |
| Support from patient advocacy organizations | 11% (1) | 28% (21) |
| Other | 11% (1) | 0 |

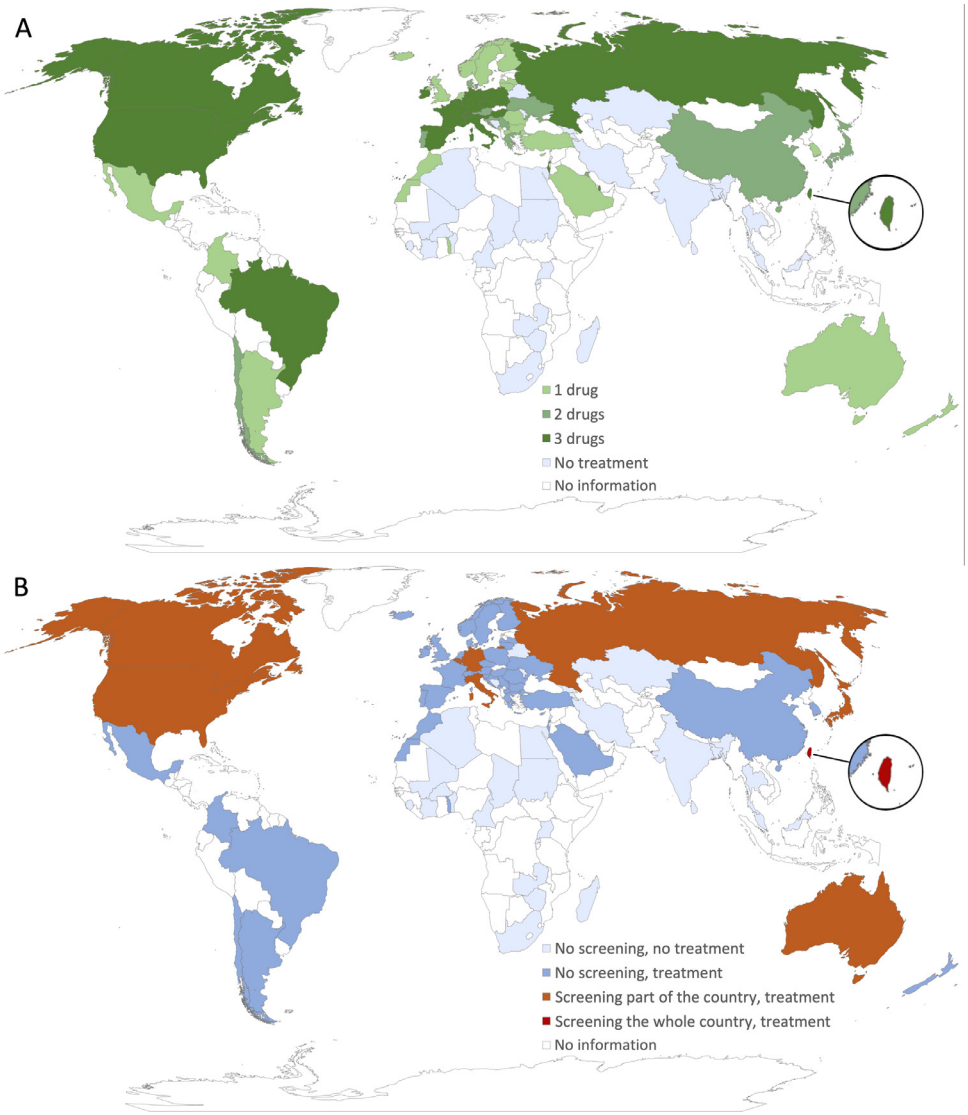



Fig. 1. Availability of treatments and NBS around the world. A: Availability of treatment. B. Availability of treatment related to the status of SMA NBS. We could not gather responses from or identify experts in 115 countries and assumed no NBS.

### *3.3. Countries without NBS for SMA*

We obtained 76 responses regarding SMA NBS from 74 countries that do not yet have an SMA NBS program implemented (the additional two responses were from the regional respondents for Bogota in Colombia and the Hong Kong SAR in China). In countries without an implemented SMA NBS, the average score (on a 0–100 scale) the respondents gave when asked about how important they believed it would be to implement the SMA NBS in their country was 94.5 (range: 10 – 100). Out of 76 respondents from countries without implemented SMA NBS, 37 reported plans for establishing SMA NBS and 39 declared no plan. Ethical committee approval specific to the SMA NBS will be required in 45/76 C/R; ethical committee approval for previously implemented NBS will also cover SMA NBS in 11/76 C/R; and no ethical committee approval will be needed for establishing SMA NBS in 10/76 C/R. The remaining 10 respondents replied that their need for ethical committee approval still needs to be determined.

The respondents predicted that qPCR will be used as a first-tier test in 30/75 C/R; MLPA in 18 C/R; NGS in 1 C/R; multiplex PCR in 1 C/R; and 26 respondents were not sure.

The respondents anticipated that the financial burden for the future SMA NBS will be covered by the government health funds in 36 C/R; public health insurance in 34 C/R; pharmaceutical research funds or grants in 15 C/R; academic research funds or grants in 14 C/R; parents in 11 C/R; regional health funds in 7 C/R; private health insurance in 6 C/R; hospital funds in 1 C/R; and 10 indicated the answer ‘other’.

The respondents described the obstacles they might encounter in establishing SMA NBS and the measures that might be useful in launching SMA NBS in their respective countries in Table 3. Other mentioned obstacles were the need to modify the law to introduce

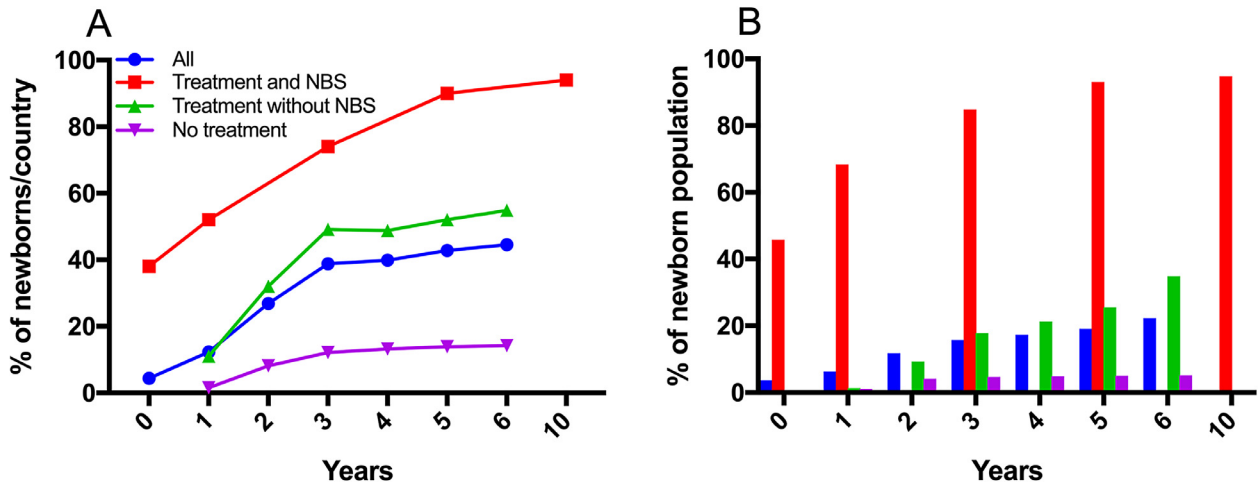



Fig. 2. (A) Current and predicted percentage of newborns screened for SMA in countries for all respondents (blue), respondents from countries with NBS already in place (red), respondents from countries with treatment available but no NBS in place (green) and countries with no treatment and no NBS available (purple). (B) Idem, expressed in% of newborn population screened for the different groups . (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the possibility of genetic screening, the need to ask for parental consent, and a lack of consensus about treatments, especially for patients with 4 copies of *SMN2* gene.

### *3.4. Prediction of future developments of SMA NBS*

We have asked the respondents about the current and predicted percentage of newborns screened for SMA in countries with SMA NBS ($N=9$ countries) and predicted percentage in countries without SMA NBS ($N=76$ C/R) in the coming years. The results are depicted in Fig. 2.

### *3.5. Carrier screening and other NBS programs*

There was no implemented SMA carrier screening (CS) in 42 C/R; there was CS for anybody who request it (covered by health insurance) in 9 C/R; CS for a limited number of parents (covered by health insurance) in 10 C/R; CS for a limited number of parents (covered by parents) in 16 C/R; and CS for families with a previously affected member with SMA in 4 C/R. Six respondents did not know whether there was CS in their respective countries. CS outside detection of familial cases was available in 5 of the 9 C/R where NBS is available. CS outside detection of familial cases was available in 20 of the 46 C/R with no NBS and treatment available.

## 4. Discussion

In this paper, we present a survey of the current situation of NBS for SMA and the perspective for the coming years.

In most European countries and the United States, the existence of SMA NBS was related to the presence of reimbursed disease-modifying treatments and after scientific data proved that early treatment is related to a better outcome.

Taiwan, which has been pioneering in most aspects of SMA NBS [21–23], is currently the only place in the world in which the whole population of newborns is being screened for SMA. Outside Taiwan, several countries have started with a regional pilot before SMA became included in the official NBS programs. Several programs are already planning to transition to official programs in 2021, such as in Germany and Belgium.

We could not gather responses from or identify experts in 115 countries. Nevertheless, it is fair to assume that there is currently no SMA NBS in these countries. We can thus reasonably assume that in 2021, about 2% of the newborns population of the world is currently being screened for SMA. This proportion of newborns screened across the world is low in spite of accumulative evidence of the importance of early [9] and especially pre-symptomatic treatment of patients with SMA [10].

Several obstacles are reported by respondents. The absence of health economic data or cost/effectiveness of SMA NBS was almost unanimously identified by experts as an important obstacle. Indeed, very preliminary data have recently been presented or modelized [24], but important information is still missing. It could be hypothesised that given the very high cost related to SMA, NBS offers the opportunity to decrease the societal cost of SMA by relatively cheap early detection in patients, however this remains to be demonstrated or anchored to unequivocal data. Ethical issues are reported only by 5 respondents, which seems to indicate a global acceptance and understanding of the need of a genetic method for NBS.

Interestingly, no respondent reported the absence of approval/reimbursement of disease-modifying treatment in pre-symptomatic as a potential issue. It is likely that even if the benefit of pre-symptomatic treatment has been clearly established, the initiation of treatments when the very first symptoms occur rather than after a long diagnostic journey appears to be anyways a significant benefit.

In 7 of the 9 countries where NBS is available, carrier screening is also offered, but only for families with a family genetic history ($n=4$), or covered by parents (3), or more broadly, parents may decide based on health insurance coverage as in the United States. Intuitively, carrier screening offers the possibility to avoid a substantial number of SMA cases, but its impact on actual SMA incidence in regions or countries where it is performed remains controversial [25],[26].

In countries where NBS is available, no false negative data have been reported. False negative cases are difficult to clearly identify, except in well-defined regions with well-structured reference centres and case reporting. In addition, false negatives with SMA type 3 may show up later, which means that the proportion of false negatives will still remain approximate in the coming years. The identification of heterozygous deletion/point mutation cases in Taiwan and in Belgium, with an incidence of 10% of the total number of cases, strongly suggests that the reporting process of cases identified in these two countries outside the NBS program has been efficient, and thus that the number of non-identified false negative cases must be very low.

False positive results seem to be mostly commonly related to process and methods. Identification of false positive cases in Taiwan was resolved by the change of primers; in the USA, most false positive cases were due to low white blood cell count. Altogether, the incidence of false positive cases with current methods appears to be extremely low. In comparison, NBS for cystic fibrosis can yield up to 19% of false positives [27],[28]. Benchmarked with other diseases, SMA NBS thus seems to be extremely reliable.

According to respondents' responses, the prediction of the number of countries where at least half of the children will be screened in 1, 2 and 4 years' time was 11, 24 and 39 respectively*. In comparison with the generalization of NBS for SCID, a treatable condition if diagnosed early, this would represent a much faster rate of implementation. Indeed, the first SCID screening programs were initiated in 2006 and SCID is part of the RUSP since 2010 [29]. However, only 20 countries are currently screening for SCID [30].

Our study has several limitations. Firstly, the survey was filled by different types of stakeholders, such as child neurologists, patient advocacy individuals, and geneticists. Also, we opted for asking the stakeholders involved in SMA in their own country rather than national experts responsible for NBS in the respective country, as people deeply involved in SMA care might have a better view of future pilots and SMA specificity. Furthermore, despite an inclusive and systematic approach to all countries, including countries with no treatment and no standard of care available for SMA, we could not identify respondents for 43 countries. We were therefore only able to attempt to contact experts from 78% of countries identified by the UN, and we only received responses from 42% of all countries. Nevertheless, we obtained an answer from almost all European countries and a total of 78% of countries with advanced economies [31]. Of the 114 countries in which we could not identify a respondent, 105 (92%) were from countries with emerging and developing economies, which could indicate that SMA NBS is understandably not considered to be an available option or a priority in these countries. We were able to get responses from only 32% of countries with emerging and developing economies. We believe that the present work has the potential in the near future to increase awareness about SMA NBS including in developing countries.

We plan to follow up with respondents in 1, 3, 5, and 10 years in order to compare the actual evolution of NBS with the projected evolution. This could help to demonstrate how such methods could be used to project NBS implementation of other diseases in the near future.

## 5. Conclusion

Within the world population of children, today there are still a low proportion who are screened for SMA at birth. This survey has established a clear need for SMA NBS and projects a moderately optimistic view for the development of SMA NBS. Nevertheless, we should be cautious given the different obstacles that need to be tackled in order to organise and implement future NBS programs.

## Contributors, SMA NBS study group

The SMA NBS world study group is composed of academics from the following countries and regions, listed alphabetically by family name:

Thierry Adoukonou (Benin), Omid Aryani (Iran), Nina Barisic (Croatia), Fahad Bashiri (Saudi Arabia), Laila Bastaki (Kuwait), Afaf Benitto (Morocco), Tawfeg Ben Omran (Qatar), Guenther Bernert (Austria), Enrico Bertini (Italy), Patricia Borde (Luxembourg), Peter Born (Denmark), Rose-Mary Boustani (Lebanon), Nina Butoianu (Romania), Claudia Castiglioni (Chile), Feriha Catibusic (Bosnia), Sophelia Chan (Hong Kong, China), Yin Hsiu Chien (Taiwan, China), Kyproula Christodoulou (Cyprus), Donniphat Dejsuphong (Thailand), Michelle Farrar (Australia), Duma Filip (Macedonia), Nathalie Goemans (Flanders, Belgium), Kokou Guinhouya (Togo), Jana Haberlova (Czech Republic), Kinga Hadzsiev (Hungary), Kristine Hovhannesyan (Armenia), Pirjo Isohanni (Finland), Nelica Ivanovic Radovic (Montenegro), David Jacquier (Switzerland), Alusine Jalloh (Sierra Leone), Maria Jedrzejowska (Poland), Gwen Kandawasvika (Zimbabwe), Celestin Kaputu (Democratic Republic of the Congo), Nfwama Kawatu (Zambia), Kristin Kernohan (Canada), Jan Kirschner (Germany), Barbara Klink (Luxembourg), Sherry Kodsy (Egypt), Ange-Eric Kouame-Assouan (Ivory Coast), Ruzica Kravljanac (Serbia), Madara Kreile (Latvia), Ivan Litvinenko (Bulgaria), Hugh McMillan (Ontario, Canada), Sandra Mesa (Colombia), Inaam Mohamed (Sudan), Liljana Muaremoska Kanzoska (Macedonia), Yoram Nevo (Israel), Seraphin Nguefack (Cameroon), Kafula Nkole

* Regional NBS is planned to start this year in Poland and Spain.

(Zambia), Gina O'Grady (New Zealand), Declan O'Rourke (Republic of Ireland), Maryam Oskoui (Canada), Flavia Piazzon (Brazil), Dimitri Poddighe (Kazakhstan), Audrone Prasauskiene (Lithuania), Juan Prieto (Chile), Magnhild Rasmussen (Norway), Santara Razafindrasata (Madagascar), Narayan Saha (Bangladesh), Kayoko Saito (Japan), Foksouna Sakadi (Chad), Modibo Sangare (Mali), Mary Schroth (USA), Leanid Shalkevich (Belarus), Andriy Shatillo (Ukraine), Renu Suthar (India), Lena Szabo (Hungary), Nana Tatishvili (Georgia), Meriem Tazir (Algeria), Eduardo Tizzano (Spain), Haluk Topaloglu (Turkey), Mar Tulinius (Sweden), Ludo van der Pol (Netherlands), Gabriel Vazquez (Argentina), Dimitry Vlodavets (Russia), Jithangi Wanigasinghe (Sri Lanka), Jo Wilmshurst (South Africa), Hui Xiong (People's Republic of China), Dimitrios Zafeiriou (Greece), Eleni Zamba (Cyprus).

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of Competing Interest

TD has given lectures sponsored by Biogen and Roche.

EV has served as a consultant for Biogen.

LS has given lectures and has served as a consultant for Roche, Biogen, Avexis, and Cytokinetics. LS is the project leader of the newborn screening in Southern Belgium funded by Avexis, Roche, and Biogen.

DO has given lectures and has served as a consultant for Biogen, Avexis, and Roche.

## Acknowledgements

The authors thank Dom Tromans for language editing.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2021.03.007.

## References

[1] Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis 2017;12:124. doi:10.1186/s13023-017-0671-8.

[2] D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. Orphanet J Rare Dis 2011;6:71. doi:10.1186/1750-1172-6-71.

[3] Wirth B. An update of the mutation spectrum of the survival motor neuron gene (*SMN1*) in autosomal recessive spinal muscular atrophy (SMA). Hum Mutat 2000;15:228–37 10.1002/(sici)1098-1004(200003)15:3<228::Aid−humu3>3.0.Co;2-9.

[4] Ramdas S, Servais L. New treatments in spinal muscular atrophy: an overview of currently available data. Expert Opin Pharmacother 2020;21:307–15. doi:10.1080/14656566.2019.1704732.

[5] Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017;377:1723–32. doi:10.1056/NEJMoa1702752.

[6] Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med 2017;377:1713–22. doi:10.1056/NEJMoa1706198.

[7] Lowes L, Al-Zaidy S, Shell R, Arnold W, Rodino-Klapac L, Prior T, et al. AVXS-101 phase 1 gene therapy clinical trial in SMA Type 1: patients treated early with the proposed therapeutic dose were able to sit unassisted at a younger age. Neuromuscul Disord 2017;27:S208–9. doi:10.1016/j.nmd.2017.06.414.

[8] Baranello G., Darras B., Day J., Deconinck N., Klein A., Masson R., et al. Risdiplam in type 1 spinal muscular atrophy. N Engl J Med, in Press

[9] Dangouloff T, Servais L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: current perspectives. Ther Clin Risk Manag 2019;15:1153–61. doi:10.2147/tcrm.S172291.

[10] De Vivo D.C., Topaloglu H., Swoboda K.J., Bertini E., Hwu W.-L., Crawford T.O., et al. Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy (SMA): interim efficacy and safety results from the phase 2 Nurture study (S25.001). Am Acad Neurol 2019 - 71st Annu Meet, n.d.

[11] Dangouloff T, Burghes A, Tizzano EF, Servais L. 244th ENMC International Workshop: newborn screening in spinal muscular atrophy May 10-12, 2019, Hoofdorp, The Netherlands. Neuromuscul Disord 2020;30:93–103. doi:10.1016/j.nmd.2019.11.002.

[12] Kariyawasam DST, Russell JS, Wiley V, Alexander IE, Farrar MA. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. Genet Med 2019;22:557–65. doi:10.1038/s41436-019-0673-0.

[13] Boemer F, Caberg J-H, Dideberg V, Dardenne D, Bours V, Hiligsmann M, et al. Newborn screening for SMA in Southern Belgium. Neuromuscul Disord 2019;29:343–9. doi:10.1016/j.nmd.2019.02.003.

[14] McMillan HJ, Kernohan KD, Yeh E, Amburgey K, Boyd J, Campbell C, et al. Newborn screening for spinal muscular atrophy: ontario testing & follow-up recommendations. Can J Neurol Sci Le J Can Des Sci Neurol 2020:1–24. doi:10.1017/cjn.2020.229.

[15] Vill K, Kolbel H, Schwartz O, Blaschek A, Olgemoller B, Harms E, et al. One year of newborn screening for SMA - results of a german pilot project. J Neuromuscul Dis 2019;6:503–15. doi:10.3233/jnd-190428.

[16] Shinohara M, Niba ETE, Wijaya YOS, Takayama I, Mitsuishi C, Kumasaka S, et al. A novel system for spinal muscular atrophy screening in newborns: Japanese pilot study. Int J Neonatal Screen 2019;5:41. doi:10.3390/ijns5040041.

[17] Chien YH, Chiang SC, Weng WC, Lee NC, Lin CJ, Hsieh WS, et al. Presymptomatic diagnosis of spinal muscular atrophy through newborn screening. J Pediatr 2017;190:124–9 e1. doi:10.1016/j.jpeds.2017.06.042.

[18] Kraszewski JN, Kay DM, Stevens CF, Koval C, Haser B, Ortiz V, et al. Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. Genet Med 2017;10.1038/gim.2017.152. doi:10.1038/gim.2017.152.

[19] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208. doi:10.1016/j.jbi.2019.103208.

[20] Nations U. Welcome to the United Nations. https://www.un.org/en/sections/about-un/overview/index.html (accessed December 1, 2020).

[21] Chien Y-H, Hwu W-L, Lee N-C. Newborn screening: Taiwanese experience. Ann Transl Med 2019;7:281. doi:10.21037/atm.2019.05.47.

[22] Chan M-J, Liao H-C, Gelb MH, Chuang C-K, Liu M-Y, Chen H-J, et al. Taiwan National newborn screening program by tandem mass spectrometry for mucopolysaccharidoses types I, II, and VI. J Pediatr 2019;205:176–82. doi:10.1016/j.jpeds.2018.09.063.

[23] Hwu W-L, Chien Y-H, Lee N-C, Chiang S-C, Dobrovolny R, Huang A-C, et al. Newborn screening for Fabry disease in Taiwan reveals a high incidence of the later-onset GLA mutation c.936+919G>A (IVS4+919G>A). Hum Mutat 2009;30:1397–405. doi:10.1002/humu.21074.

[24] Dangouloff T, Botty C, Beaudart C, Servais L, Hiligsmann M. Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments. Orphanet J Rare Dis 2021;16:47. doi:10.1186/s13023-021-01695-7.

[25] Aharoni S, Nevo Y, Orenstein N, Basel-Salmon L, Ben-Shachar S, Mussaffi H, et al. Impact of a national population-based carrier-screening program on spinal muscular atrophy births. Neuromuscul Disord 2020;30:970–4. doi:10.1016/j.nmd.2020.10.005.

[26] Kay DM, Stevens CF, Parker A, Saavedra-Matiz CA, Sack V, Chung WK, et al. Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy. Genet Med 2020;8:1296–302. doi:10.1038/s41436-020-0824-3.

[27] Edmondson C, Grime C, Prasad A, Cowlard J, Nwokoro CEC, Ruiz G, et al. Cystic fibrosis newborn screening: outcome of infants with normal sweat tests. Arch Dis Child 2018;103:753–6. doi:10.1136/archdischild-2017-313290.

[28] Kay DM, Maloney B, Hamel R, Pearce M, DeMartino L, McMahon R, et al. Screening for cystic fibrosis in New York State: considerations for algorithm improvements. Eur J Pediatr 2016;175:181–93. doi:10.1007/s00431-015-2616-3.

[29] Buckley RH. The long quest for neonatal screening for severe combined immunodeficiency. J Allergy Clin Immunol 2012;129:597–606. doi:10.1016/j.jaci.2011.12.964.

[30] Quinn J, Orange JS, Modell V, Modell F. The case for severe combined immunodeficiency (SCID) and T cell lymphopenia newborn screening: saving lives…one at a time. Immunol Res 2020;68:48–53. doi:10.1007/s12026-020-09117-9.

[31] International Monetary Fund. Country Composition of World Economic Outlook Groups 2020. https://www.imf.org/external/pubs/ft/weo/2020/02/weodata/groups.htm.

## Annexe XIV. Newborn screening of neuromuscular disease. (Chapiter III, 4)

Dangouloff T, Boemer F, Servais L. Neuromuscular disorder. 2021.

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 31 (2021) 1070–1080

www.elsevier.com/locate/nmd

Review

# Newborn screening of neuromuscular diseases

Tamara Dangouloff[a], François Boemer[b], Laurent Servais[a,c,*]

[a] *Division of Child Neurology, Reference Center for Neuromuscular Diseases, Department of Pediatrics, University Hospital Liège & University of Liège, Belgium*

[b] *Biochemical Genetics Lab, Department of Human Genetics, CHU of Liège, University of Liège, Liège, Belgium*

[c] *MDUK Neuromuscular Centre, Department of Paediatrics, University of Oxford, UK*

Received 30 June 2021; received in revised form 7 July 2021; accepted 13 July 2021

**Abstract**

Neuromuscular diseases represent an heterogenous group of more than 400 diseases, with a very broad phenotypic spectrum. Given their rarity and complexity, neuromuscular diseases are often diagnosed with a very significant delay after which irreversible muscle damage may limit the efficacy of treatments when available. In this context, neonatal screening could constitute a solution for early detection and treatment. A systematic review of the literature in PubMed up to May 1, 2021, was conducted according to PRISMA guidelines, including classical neuromuscular diseases and diseases with a clear peripheral nervous system involvement (including central nervous system disease with severe neuropathy). We found seven diseases for which newborn screening data were reported: spinal muscular atrophy (9), Duchenne muscular dystrophy (9), Pompe disease (8), X-linked adrenoleukodystrophy (5), Krabbe disease (4), myotonic dystrophy type 1 (1), metachromatic leukodystrophy (1). The future of newborn screening for neuromuscular disorders pass through a global technological switch, from a biochemical to a genetic-based approach. The rapid development of therapy also requires the possibility to quickly adapt the list of treated conditions, to allow innovative therapies to achieve their best efficacy.
© 2021 Elsevier B.V. All rights reserved.

*Keywords:* Newborn screening; Neuromuscular disorder; Pompe disease; Spinal muscular atrophy; Duchenne muscular dystrophy.

This paper is an invited review for the special issue of Neuromuscular Disorders to celebrate Professor Victor Dubowitz's 90th birthday.

## 1. Introduction and context

Forty-five years ago, a *stricto sensu* mid-career 45-year-old myologist proposed Creatine Kinase (CK) dosage as a valid approach for Duchenne muscular dystrophy (DMD) and introduced the concept of screening newborns for neuromuscular disorders [1]. At that time, phenylketonuria newborn screening (NBS) had only been recently implemented in most developed countries. This paper is a tribute to this former mid-career myologist who celebrates today his 90th birthday.

Forty-five years later, the Dubowitz disease (not to be confounded with Dubowitz syndrome...) [2], also inappropriately called 'spinal muscular atrophy type 2′ by a very limited number of physicians, has become the stereotype of the perfect indication for NBS in the neuromuscular field.

Neuromuscular diseases represent an heterogenous group of more than 400 diseases, with a very broad phenotypic spectrum. Until very recently, few disease-modifying treatments were available for most of them. However, with a growing understanding of pathophysiology and preclinical research, several transformative treatments have had dramatic effects on not only inflammatory diseases, but also genetic diseases such as congenital myasthenia (CMS), spinal muscular atrophy (SMA), Pompe disease, or Brown-Vialetto-Van Laere syndrome (BVVL). Promising preliminary data have also been reported in limb girdle muscular dystrophy, X-linked myotubular myopathy or in DMD, for which five drugs have so far reached regulatory approval.

Given their rarity and complexity, neuromuscular diseases are often diagnosed after a very significant delay [3–6] during

* Corresponding author at: CRMN Liège, CHR de la Citadelle, Boulevard du 12ème de Ligne, 4000 Liège, Belgium.

*E-mail addresses:* tamara.dangouloff@uliege.be (T. Dangouloff), laurent.servais@paediatrics.ox.ac.uk (L. Servais).

https://doi.org/10.1016/j.nmd.2021.07.008

0960-8966/© 2021 Elsevier B.V. All rights reserved.

which irreversible muscle damage may limit the dramatic efficacy of early treatment administered patients [7,8]. Even in the absence of a muscle destruction process, such as in some form of CMS, the long diagnostic journey can cause decades of limitation in quality of life [9] before a correct diagnosis is established and the appropriate treatment is prescribed.

Neonatal screening is generally governed worldwide by the modified criteria proposed by Wilson and Jungner [10] which are widely used to determine whether screening for a disease should be included in an NBS panel. This list consists of the following ten items:

1 The condition sought should be an important health problem.
2 There should be an accepted treatment for patients with recognized disease.
3 Facilities for diagnosis and treatment should be available.
4 There should be a recognizable latent or early symptomatic stage.
5 There should be a suitable test or examination.
6 The test should be acceptable to the population.
7 The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8 There should be an agreed policy on whom to treat as patients.
9 The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10 Case-finding should be a continuing process and not a "once and for all" project.

These criteria are broadly applied across the world, with a much more conservative approach in European Union (EU) and UK in comparison with the US. As a consequence, the number of diseases screened in different countries, or even in different regions of a same country, varies significantly [11]. In line with these criteria, our mid-career myologist had already noticed in 1976 that "*the stage does not yet seem set for a [UK] nationwide program of screening for preclinical Duchenne muscular dystrophy, but when the time is ripe for it the techniques will hopefully be sufficiently standardized for immediate application.*"[1]

NBS has been organized for the last 60 years as a metabolic and endocrine screening process, but many treatable genetic neuromuscular diseases in children, such as BVVL, CMS or SMA have no metabolic or endocrine marker, which causes additional challenges in implementation of screening.

Nevertheless, the dramatic difference observed between pre-symptomatic and post-symptomatic treated patients with SMA, the successful implementation of NBS for SMA across the world, and the pipeline of potential therapy, all suggest that several neuromuscular diseases could be targeted by NBS before our previous mid-career myologist celebrate his 100th birthday. In this context, we conducted a review of the existing pilot or official NBS programs in the area of neuromuscular disease.

## 2. Methods

### 2.1. Literature search

A literature search was conducted using Medline (PubMed) following the PRISMA checklist [12]. We searched for original, full-text articles reporting NBS program in neuromuscular disease published after the 70th birthday of Prof. Victor Dubowitz (i.e., August 06th 2001). To identify relevant articles, key terms related to NBS (e.g., 'neonatal screening', 'dried blood spot testing', 'dried blood', and 'guthrie') were combined with key terms for neuromuscular disease. The detailed search strategy is shown schematically in Supplementary file 1. The literature search was conducted until May 1, 2021.

### 2.2. Selection of studies

Two researchers (TD, LS) first screened titles and abstracts independently for eligibility and then evaluated the full text. To be included, the articles had to be published original research, in English or French, and had to report NBS program for at least one neuromuscular disease, or a disease with a clear peripheral nervous system involvement (mostly peripheral neuropathy). The two reviewers compared their findings, and a list of studies for full-text screening was created. Reasons for article exclusion were recorded, and potential disagreements were specified to be resolved by consensus.

### 2.3. Data extraction and presentation

Studies were classified by disease screened: SMA, DMD, myotonic dystrophy type 1 (MD1), Pompe disease, X-linked adrenoleukodystrophy (X-ALD), metachromatic leukodystrophy (MLD) and Krabbe disease.

Study characteristics related to publication (e.g., authors, year of publication, journal name) and study design (e.g., country, sample size…) were extracted.

## 3. Results

### 3.1. Study selection process

The initial searches identified 405 articles that describe NBS for neuromuscular diseases. After removing 108 duplicates, and screening by title and abstract, 84 articles were identified for full-text screening; 36 full-text studies were validated as eligible and 8 identified by bibliography were added. Supplementary file 2 shows the flowchart based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines used for the identification of these studies.

Articles concerning the same pilot project were disregarded and only the most recent update was considered. We retained studies demonstrating the efficacy of NBS on deidentified

Guthries cards only if pilot projects with identified patients had not taken place.

### 3.2. Spinal muscular atrophy

SMA is a recessive disorder caused by a homozygous loss of function mutation (mostly a deletion of exon 7) of *SMN1*. There are three drugs approved for treatment [13] (nusinersen [14], onasemnogene abeparvovec [15] and risdiplam [16]), and three pre-symptomatic trials published or ongoing (Nurture: NCT02386553, SPR1NT: NCT03505099, Rainbowfish: NCT03779334). Several other drugs are in pre-clinical or early clinical development [17].

NBS for SMA has been reported in nine countries / subnational regions [18–25]. The first pilots were implemented in 2014 in Taiwan [18], and in New-York in 2016 [19]. Interestingly, these pilots were implemented prior to the approval of any medications, and some of the patients identified through these pilots could be included in pre-symptomatic studies [26]. The incidence found in these screening programs ranges from 1 in 5,000 in Italy to 1 in 28,000 in Ontario [27]. One of the lowest rates of incidence was found in New York [28], which may be explained by an increase in the use of preconception screening as a result of increased communication about the disease [29]. An additional reason of variability from study to study resides in the small number of cases in some reports, which over-weight the influence of a single case on the prevalence.

In most programs, the first tier of screening is done by quantitative real-time polymerase chain reaction (qPCR), while the second is done by MLPA. In the USA and Italy, qPCR is also used for the second tier.

Even if this remains to be confirmed in the next few years for SMA with later onset, no false negatives have yet been found in countries that have developed NBS programs. False positives were only encountered at the beginning of the pilot programs [27].

A recent survey has demonstrated that several countries anticipate to initiate a NBS program in the coming months and years, so that the number of newborn screened for SMA, today approximately 2% of the world population, should progressively climb to 24% of the total world population and 88% of the population of countries where a disease modifying treatment is available [27].

The characteristics of NBS programs in SMA are reported in Table 1.

### 3.3. Pompe disease

Pompe disease, also known as glycogenosis type 2, is an autosomal recessive inherited lysosomal storage disease caused by a deficiency of acid alpha-glucosidase.

Pompe disease has a wide clinical spectrum ranging from the infantile form, beginning in the first months of life, to adult forms. In the absence of treatment, the infantile form always leads to early death by cardiorespiratory failure or respiratory infection, usually before the age of one year. Symptoms can appear at any age in the later forms and are related to progressive skeletal muscle dysfunction.

Enzyme replacement therapy (ERT) using alglucosidase alfa (Myozyme) was approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2006. Early treatment has been associated with better outcome [30,31].

The first NBS pilot was initiated in Taiwan in 2005 and has been regularly documented since then [31–35]. In the USA, since 2015, Pompe Disease is part of the Recommended Uniformed Screening Panel (RUSP) program and is implemented in almost half of the states [36–39]. Other projects were conducted in Mexico [40], Japan [41] and Brazil [42]. The rate of incidence reported across all screening program was extremely variable: 1 in 10,600 in Brazil, 1 in 20,000 in Mexico, Taiwan and in the US, and 1 in 38,000 in Japan.

The characteristics of NBS programs in Pompe disease are reported in Table 2.

### 3.4. Duchenne muscular dystrophy

DMD is the most common inherited muscular dystrophy in childhood and is characterized by progressive muscle weakness. It is caused by an out-of-frame mutation of the *Dystrophin* gene located on the X chromosome. The incidence is around 1 in 4,700 [43] of young males. The first symptoms most commonly appear at as early as two years of age; the disease manifests as a proximal weakness leading to a rapid loss of walking between the ages of seven and fifteen. The delay between the appearance of symptoms and diagnosis is on average two years [3]; this diagnostic errancy, which causes parental distress, can also create a delay in the child's care.

Five drugs have achieved US FDA approval: Deflazacort, a corticosteroid; and Eteplirsen, Casimersen and Golodirsen for exon skipping 51, 45 and 53, respectively. Vitolarsen has also been approved for exon 53 skipping. In the EU, only Ataluren has been conditionally approved [44]. The clinical efficacy of these different drugs remains modest.

We found nine pilot projects or official implementations for DMD [45–54] between 1974 and 2017. The aim of these screening programs, as there was no treatment approved when they were initiated, was most often to establish recommendations for the following-up of patients. An early follow-up seemed preferable, not only to avoid diagnostic delay, but also to prevent a recurrence in the family through genetic counselling.

The characteristics of NBS programs in DMD are reported in Table 3.

### 3.5. Myotonic dystrophy 1

MD1 is an autosomal dominant disorder characterized by muscle weakness, myotonia, early onset cataracts, and systemic manifestations (cerebral, endocrine, cardiac, gastrointestinal tract, uterus, skin, and immunologic involvement) that vary depending on the age of onset.

Table 1
Newborn screening programs in SMA.

| | Country [ref] | Date | Pop | Total number | Scr First-tier | Scr 2nd-tier | Conf | Cons | First result | N° cases | Prev | Aim of study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SMA** | Taiwan [18] | 2014–2016 | NB | 419,102 | qPCR | ddPCR | MLPA | Opt-in | 28 | 20 | 1/21,000 | Explore NBS SMA feasibility |
| | USA [19,20] | 2016–2017 | NB | 2,395,718 | qPCR | ddPCR | MLPA | Opt-out | 190 | 180 | 1/13,300 | Report on NBS SMA |
| | Germany [21] | 2018–2019 | NB | 297,163 | qPCR | / | MLPA | Opt-in | 43 | 43 | 1/7,000 | Report on 2 years pilot |
| | Belgium (FWB) [22] | 2018–2021 | NB | 153,728 | qPCR | MLPA | MLPA | Opt-out | 12 | 12 | 1/12,800 | Explain start of NBS SMA |
| | Australia (NSW, ACT) [23] | 2018–2019 | NB | 202,388 | qPCR | ddPCR | ddPCR | Opt-out | 19 | 19 | 1/10,600 | Evaluate implementation |
| | Italy (Tuscany, Lazio) | 2019–2021 | NB | 58,558 | qPCR | qPCR | qPCR | Opt-in | 12 | 12 | 1/5,000 | Evaluate NBS |
| | Russia (Moscow) | 2019–2021 | NB | 12,000 | qPCR | MLPA | MLPA | Opt-in | 0 | 0 | | Evaluate NBS |
| | Canada (Ontario) [24] | 2020–2021 | NB | 139,810 | Mass Array | MLPA | / | Opt-out | 5 | 5 | 1/28,000 | Report on beginning of NBS |
| | Japan [25] | 2020–2021 | NB | 22,209 | qPCR | MLPA | MLPA | Opt-in | 0 | 0 | | Evaluate NBS |
| | **Total World** [27] | | **NB** | **3,674,277** | | | | | **307** | **288** | | **NBS SMA in the world** |

List of abbreviations: Conf: Confirmatory assay; Cons: parents' method of consent; ddPCR: digital droplet PCR; First result: Positive first result or inconclusive; FWB: Federation Wallonia-Brussels (Region of Belgium); MLPA: multiplex ligation-dependent probe amplification; NB: Newborn; N° cases: Number of confirmed cases; NSW/ACT: New South Wales and Australian Capital Territory (region of Australia); Pop: description of population screened; Prev: Prevalence; Ref: references used; Scr: Screening assay.

Table 2
Newborn screening programs in Pompe disease.

| | Country [ref] | Date | Pop | Total number | Scr First-tier | Scr 2nd-tier | Conf | Cons | First result | N° cases | Prev | Aim of study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Pompe disease** | Taiwan [31,32] | 2005-2014 | NB | 669,797 | Fluor assay | / | Leukocytes Enzymatic assay | Opt-in | 4184 | 13 IOPD >19 LOPD | IOPD: 1/51,500 LOPD: 1/35,300 All: 1/21,000 | Demonstrate advantage of early treatment, even for LOPD |
| | Mexico [40] | 2012-2016 | NB | 20,018 | LC-MS-MS | / | Enzymatic + Molecular testing | Opt-in | 19 | 1 | 1/20,000 | Evaluate the results of a lysosomal NBS |
| | USA (MO) [36] | 2013-2018 | NB | 467,000 | Fluor Digital Micro-fluidics | / | Enzymatic + Molecular testing + Urinary GAGs analysis + CK | Opt-out | 274 | 10 IOPD 36 LOPD | IOPD: 1/46,700 LOPD: 1/13,000 All: 1/10,200 | Report on 6-year NBS |
| | Japan [41] | 2013-2016 | NB | 103,204 | Fluor assay | / | Molecular testing | Opt-in | 225 | 0 IOPD 3 LOPD | LOPD: 1/34,000 All: 1/34,000 | Summary of NBS program + results |
| | USA (IL) [37] | 2015-2019 | NB | 684,290 | LC-MS-MS | 2-tiered cutoff system | Enzymatic + Molecular testing + Urinary GAGs analysis | Opt-out | 397 | 3 IOPD 26 LOPD | IOPD: 1/228,100 LOPD: 1/26,300 All: 1/23,600 | Description of experience of NBS |
| | USA (PA) [38] | 2016-2019 | NB | 531,139 | FIA-MS-MS | / | Enzymatic + Molecular testing | Opt-out | 115 | 2 IOPD 31 LOPD | IOPD: 1/265,500 LOPD: 1/17,100 All: 1/16,100 | Evaluation of benefits + challenges of NBS |
| | USA (CA) [39] | 2018-2019 | NB | 453,152 | FIA-MS-MS | Molecular testing | Molecular testing | Opt-out | 88 | 2 IOPD 16 LOPD | IOPD: 1/226,600 LOPD: 1/28,300 All: 1/25,200 | Report on 1-year NBS program |
| | Brazil [42] | 2016 | NB | 10,567 | Fluor assays | | Enzymatic + Molecular testing + Urinary GAGs analysis | Opt-out | 4 | 1 | 1/10,600 | Evaluation of challenges of NBS |

List of abbreviations: CA: California; Conf: Confirmatory assay; Cons: parents' method of consent; FIA-MS-MS: flow-injection mass spectrometry; First result: Positive first result or inconclusive; Fluor: Fluorometric; IL: Illinois; IOPD: infantile onset Pompe disease; LC-MS-MS: liquid-chromatography mass spectrometry; LOPD: late onset Pompe disease; MO: Missouri; NB: Newborn; N° cases: Number of confirmed cases; PA: Pennsylvania; Pop: description of population screened; Prev: Prevalence; Ref: references used; Scr: Screening assay.

Table 3
Newborn screening programs in DMD and MD1.

| | Country [ref] | Date | Pop | Total number | Scr First-tier | Scr 2nd-tier | Conf | Cons | First result | N° cases | Prev | Aim of study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **DMD** | Germany [51,54] | 1974-2011 | NB (M) | 537,000 | CK assay | / | | Opt-in | | 155 | 1/3,500 | Evaluation of opportunity of NBS for DMD |
| | France [53] | 1975-1986 | NB (M) | 218,851 | CK assay | / | Clinical assessment | ? | | 48 | 1/4,600 | Report on course of NBS |
| | New Zealand [52] | 1979 | NB (M) | 10,000 | CK assay | / | Clinical assessment | ? | | 2 | 1/5,000 | Report on course of NBS |
| | Canada (Man) [50,51] | 1986-2007 | NB (M) | 172,860 | CK assay | / | DMD molecular testing | Opt-out | | 18 | 1/9,600 | Reduction of the number of 2nd$^{s}$ DMD children born. Observation of development. |
| | USA (PA) [49] | 1987-1995 | NB (M) | 403,576 | CK assay | CK isozyme | DMD molecular testing / muscle biopsy | Opt-out, verbal consent | | 39 | 1/10,300 | Description of attitude of patients + parents diagnosed with or without NBS toward NBS |
| | UK (Wales) [48] | 1990-2011 | NB (M) | 369,780 | CK assay | / | DMD molecular testing / plasma CK | Opt-in | 145 | 56 | 1/6,600 | Report on 21-year NBS pilot program |
| | Cyprus [47] | 1992-1997 | NB (M) | 30,014 | CK assay | / | DMD molecular testing / muscle biopsy | Opt-out | 43 | 5 | 1/6,000 | Evaluation of the method + implementation of NBS pilot |
| | USA (OH) [46] | 2007-2010 | NB (M) | 17,865 | CK assay | / | DMD molecular testing | Opt-in | 168 | 3 | 1/6,000 | Evaluate of method + feasibility of NBS |
| | China (Zhejiang) [45] | 2017 | NB (M) | 18,424 | CK-MM assay | / | DMD molecular testing | Opt-in | 13 | 4 | 1/4,600 | Recommendations for follow-up care |
| **MD1** | USA (NY) [57] | 2013 | DBS | 51,341 | triplet primed-PCR + melt curve analysis | | Molecular testing | no | 143 | 24 | 1/2,100 | Determination of prevalence |

List of abbreviations: CK-MM: Creatine kinase muscle; Conf: Confirmatory assay; Cons: parents' method of consent; DBS: DBS deidentified; First result: Positive first result or inconclusive; M: Male; Man: Manitoba; NB: Newborn; N° cases: Number of confirmed cases; NY: New York state; OH: Ohio; PCR: polymerase chain reaction; PA: Pennsylvania; Pop: description of population screened; Prev: Prevalence; Ref: references used; Scr: Screening assay.

MD1 is caused by a pathological (>50) CTG repeat in the *DMPK* gene. Anticipation, a phenomenon in which the age of onset of an autosomal dominant disease becomes earlier with each successive generation, typically occurs in maternal transmission of the disease. The most severe form is the congenital form (15% of cases) which includes severe generalized weakness at birth with respiratory distress, hypotonia and feeding difficulties. Patients subsequently develop delayed cognitive and motor milestones, intellectual disability, and autism spectrum disorder with the physical symptoms taking a potentially fatal course. The incidence is extremely variable from 0.5 to 1.8 per 100,000 [55].

Despite several pre-clinical developments [56], no specific disease-modifying therapy is currently available. Management consists primarily of monitoring for complications and standard of care (assistive devices, hormone therapy, pain medication).

We found one pilot project for MD1 in 2013, in the USA, using deidentified dried blood spot (DBS), with the aim of determining prevalence [57]. This was found to be 1 in 21,100.

The characteristics of NBS program in MD1 are reported in Table 3.

### *3.6. Krabbe disease*

Krabbe disease is an autosomal recessive lysosomal disease affecting the white matter of the central and peripheral nervous systems, characterized by neurodegeneration whose severity depends on the age of onset. Krabbe disease is caused by a loss of function mutation in both alleles of the *GALC* gene leading to a deficit in galactosylceramidase.

Historically, 85–90% of patients were diagnosed with the infantile form, which is the most severe and manifests in the first six years of life. In those in whom the disease begins in the first year, a rapid neurological deterioration is observed, leading to death before the age of two years. Late-onset Krabbe disease is much more variable in its presentation and

course [58]. The incidence of both forms of Krabbe disease is estimated to 1 in 100,000 [59].

The low incidence of the disease is an obstacle for the observation of the effectiveness of a pre-symptomatic treatment. Post-symptomatic treatment, presently limited to hematopoietic stem cell transplantation, slows disease progression. However, this is far from being transformative [60]. Pre-symptomatic treatment was initially presented as being much more efficient, but a recent report has demonstrated that only 1 of 18 patients treated before the onset of symptoms presented with mild disability; 13 of the other patients presented with severe disability, and four died [60–62].

We found four pilot projects for Krabbe disease as part of the introduction of NBS for a range of lysosomal diseases. The five-year NBS program in Mexico [40], with 20,000 newborn babies screened, found zero cases. The first US program in New York States screened more than two millions newborns and identified five case [63], the second, in Kentucky with 55,000 newborns, identified one case [64], and the third in Illinois, with almost 500,000 babies, identified eight cases: two infantile Krabbe disease and six probable late-onset Krabbe infants [65]. This NBS is a recommended disease in the RUSP but is now implemented in seven states in the USA. Recent publications have questioned the ethical basis of such screening [66].

The characteristics of NBS programs in Krabbe disease are reported in Table 4.

### 3.7. X-linked adrenoleukodystrophy

X-ALD is a peroxisomal genetic disease caused by a loss of function mutation in *ABCD1* gene. It is a devastating metabolic disorder affecting the adrenal glands, brain, and spinal cord. X-ALD affects hemizygous boys more severely than heterozygous girls (60%). If untreated, X-ALD is most often fatal.

Corticosteroid treatment for adrenal insufficiency, hematopoietic stem cell transplantation, and gene therapy for neurologically devastating brain adrenoleukodystrophy administered at the very beginning of brain inflammation, have been associated with improved survival and functional outcomes [67].

The RUSP included X-ALD as a secondary condition in 2016. Only eight states in the US were conducting X-ALD NBS in 2019, rising to twenty in 2021 [68,69]. Several articles reported on the implementation of X-ALD NBS in their states [69–71]. The Ministry of Health of the Netherlands added ALD in the NBS panel in 2015, but only for males [72]. A prospective pilot study was first implemented to assess feasibility and establish the algorithm that identifies only males. Broad implementation began on January 1, 2021.

Another NBS pilot project is currently underway in Taiwan for X-ALD. Started in 2016, it has already screened 45,796 newborns. Results have not yet been published (NCT02952482) [73].

The characteristics of NBS programs in X-ALD are reported in Table 4.

### 3.8. Metachromatic leukodystrophy

MLD is an autosomal recessively-inherited metabolic disease characterized by accumulation of sulfatides in the central and peripheral nervous system due to deficiency of the enzyme arylsulfatase A, which leads to demyelination. The main characteristics of the disease are a deterioration of motor or cognitive functions, depending on the subtype, leading to severe disability and death after a very variable evolution and duration of the disease.

Gene therapy has recently been approved in the US and the EU (OTL-200). Pre-symptomatic patients have presented much better outcome [74,75].

To our knowledge, only one pilot project aimed at demonstrating the feasibility of MLD NBS took place in the USA in 2020, screening 27,335 de-identified DBS [76].

The characteristics of NBS program in MLD are reported in Table 4.

## 4. Discussion

We identified seven diseases with a clear peripheral neurologic system component that have been targeted by NBS over the last twenty years. SMA is certainly the disease for which NBS has the greatest consensus, given the importance of early intervention demonstrated or suggested in all clinical developments, and the dramatic efficacy of pre-symptomatic treatments [26,77]. Interestingly, SMA NBS programs were initiated before the approval of disease modifying treatments but have contributed to demonstrating the dramatic efficacy of early treatment. The low cost of screening [78] which contrasts with the very high societal cost of untreated disease, or post-symptomatic diseases [79] also suggests that the NBS program is highly cost-effective, even if this remains to be formally demonstrated. The treatment algorithm, including the difficult question of patients with symptoms at birth and on the other hand of the spectrum patients with four copies of *SMN2* remains to be established [80,81]. Although an agreement was revised in favour of early treatment of patients with four copies, there is no clear and unanimous attitude today towards the choice of the treatment of these patients.

NBS of Pompe disease brings different technical and prognostic consideration, the most significant of which is the proportion at birth of late onset forms, for which there is today no indication of early treatment, compared to the infantile form, for which a treatment certainly should be initiated. A recent study in Pennsylvania has illustrated that the earlier form is less prevalent than later forms with a ratio of 1:15 [38]; this situation is completely different to that of SMA in which the more severe form represents about 60% of all forms [82]. As it is the case for other the other neuromuscular diseases with metabolic origin (i.e., Krabbe,

Table 4
Newborn screening programs in Krabbe disease, X-ALD and MLD.

| | Country [ref] | Date | Pop | Total number | Scr First-tier | Scr 2nd-tier | Conf | Cons | First result | N° cases | Prev | Aim of study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Krabbe** | USA (NY) [63] | 2006-2014 | NB | 2,090,910 | LC-MS-MS | Molecular testing | Enzymatic testing | Opt-out | 620 | 5 | 1/418,000 | Report on experience of NBS |
| | Mexico [40] | 2012-2016 | NB | 20,018 | LC-MS-MS | / | Enzymatic and Molecular testing | Opt-in | 38 | 0 | | Evaluation of the results of a lysosomal NBS |
| | USA (KY) [64] | 2016-2017 | NB | 55,161 | FIA-MS-MS | CLIR tools | | Opt-out | 181 | 1 | 1/55,000 | Report on experience of NBS |
| | USA (IL) [65] | 2017-2020 | NB | 494,147 | LC-MS-MS | Molecular testing + psychosine levels | Follow-up | Opt-out | 288 | 2 IOKD 6 LOKD | IOKD: 1/250,000 LOKD: 1/82,400 All: 1/61,800 | Report on experience of NBS and role of psychosine in disease diagnosis |
| **X-ALD** | USA (NY) [69] | 2013-2019 | NB | 1,039,000 | NA | NA | NA | Opt-out | | | 1/18,783 | Update on NBS, explanation of diagnosis and treatment |
| | USA (MN) [70] | 2017-2018 | NB | 67,836 | FIA-MS-MS | / | Molecular testing + Very-Long Chain Fatty Acids analysis | Opt-out | 56 | 14 (9 M, 5F) | All: 1/4,845 Male: 1/3,878 | Report on experience of NBS |
| | USA (NC) [71] | 2018(6 m) | NB | 52,301 | FIA-MS-MS | Molecular testing | / | Opt-out | 12 | 6 | 1/18,717 | Evaluation of the performance of a single-tier NBS assay |
| | Taiwan [73] | 2016-2018 | NB | 45,796 | FIA-MS-MS | / | / | Opt-in | | | | Evaluation of routine NBS method |
| | The Netherlands [72] | 2015/2020 | DBS (M) | 250 | FIA-MS-MS | LC-MS-MS and Molecular testing | / | Opt-out | | | | Assessment of feasibility of NBS only for male |
| **MLD** | USA (WA) [76] | | DBS | 27,335 | LC-MS-MS | Enzymatic assay | Molecular testing | no | 195 | 2 | | Assessment of feasibility |

List of abbreviations: Conf: Confirmatory assay; Cons: parents' method of consent; DBS: DBS deidentified; FIA-MS-MS: flow-injection mass spectrometry; F: Female; First result: Positive first result or inconclusive; IL: Illinois; IOKD: infantile onset Krabbe disease; KY: Kentucky; LC-MS-MS: liquid-chromatography mass spectrometry; LOKD: late onset Krabbe disease; M: Male; m: months; NA: not available; MN: Minnesota; NB: Newborn; NY: New York state; NC: North Carolina; N° cases: Number of confirmed cases; Pop: description of population screened; Prev: Prevalence; Ref: references used; Scr: Screening assay; WA: Washington.

X-ALD and MLD), the setup of specific and laborious assays tends to hamper the implementation of corresponding NBS programs.

Aside from deflazacort, which is usually not prescribed before the age of three years, all approved treatments for DMD are mutation-specific, which raises questions as to the utility of broadly screening for CK or CK-MM levels at birth. Indeed, only about 30% of patients could potentially benefit from early detection, however this remains hypothetical as it has not yet been demonstrated. Recently, an assay has been proposed for identifying only the patients with a mutation eligible for exon [83]. The lack of specificity of CK level also makes the use of this test difficult to use at a population level.

As discussed in the present review, some neuromuscular diseases are currently amenable to NBS as they are identifiable either by a sensitive biochemical assay or by a specific hotspot mutation (e.g., deletion of SMN1 exon 7 in SMA). However, most NMDs have neither a specific biomarker nor a prevalent molecular defect. Screening for these disorders is therefore not suitable for current technological NBS platforms, which are biochemically driven. Two clear examples can be found in CMS and BVVL. To date, 34 genes are described as being involved in CMS [84]. Low-cost treatments such as salbutamol or pyridostigmine can avoid sudden death or disability in the course of a long diagnostic journey. BVVL, a recessive disorder caused by a loss of function mutation in one of

the three different intestinal riboflavin transporter genes, can be managed with a high dose of riboflavin [85], and leads to severe bulbospinal atrophy in absence of treatment. Unfortunately, neither CMS not BVVL can be identified by any sensitive biomarker and are thus not amenable to NBS; identification of such disorders at birth should therefore be carried out through whole exome or targeted sequencing.

The same will apply for conditions for which transformative clinical or pre-clinical results have been reported recently. One example is X-linked myotubular myopathy, a rare congenital myopathy caused by a loss of function mutation in the X chromosome located *myotubularin* protein, which leads to early death in the most severe form and to severe disability in the milder forms [86,87]. X-linked myotubular myopathy patients treated with gene therapy have initially demonstrated dramatic improvement [88] and although severe safety concerns have been raised [89], it is very likely that a drug will be approved for the condition, as several other therapeutic approaches are in development [90].

Taken as a whole, we should expect the future for NBS for neuromuscular disorders globally to pass through a technological paradigm shift, from a biochemical to a genetic-based approach. The rapid development of therapies also requires the prospect of promptly adapting the list of treated conditions in order to allow innovative therapies to achieve utmost efficacy.

NBS and carrier screening (explored in another review of this issue), should be simultaneously implemented. Carrier screening has the potential to decrease the incidence of diseases in a population, but fails to address the whole population, and is obviously socially oriented. It fails to identify neo-mutations, a situation in which both variants are on the same allele (which is not rare in SMA) and of course cannot fully cover babies with an unknown father or with one or both parents absent. NBS is universal, addresses all children regardless of parents' conditions, and allows both patient and society to obtain the maximal benefit of innovative medications.

Let's hope that in 45 years, our 135-year-old dear myologist, wherever his rambling of child neurologist has led him, could list 90 diseases that we have happily blown out as we wish him to happily blow out his 90 candles today.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

The authors thank Dominic Tromans for language editing.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2021.07.008.

## References

[1] Dubowitz V. Screening for Duchenne muscular dystrophy. Arch Dis Child 1976;51:249–51. doi:10.1136/adc.51.4.249.
[2] Dubowitz V. Familial low birthweight dwarfism with an unusual facies and a skin eruption. J Med Genet 1965;2:12–17. doi:10.1136/jmg.2.1.12.
[3] Ciafaloni E, Fox DJ, Pandya S, Westfield CP, Puzhankara S, Romitti PA, et al. Delayed diagnosis in duchenne muscular dystrophy: data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). J Pediatr 2009;155:380–5. doi:10.1016/j.jpeds.2009.02.007.
[4] Lin CW, Kalb SJ, Yeh WS. Delay in diagnosis of spinal muscular atrophy: a systematic literature review. Pediatr Neurol 2015;53:293–300. doi:10.1016/j.pediatrneurol.2015.06.002.
[5] Kishnani PS, Amartino HM, Lindberg C, Miller TM, Wilson A, Keutzer J. Timing of diagnosis of patients with Pompe disease: data from the Pompe registry. Am J Med Genet A 2013;161A:2431–43 https://doi.org/10.1002/ajmg.a.36110.
[6] van Geel BM, Assies J, Haverkort EB, Barth PG, Wanders RJ, Schutgens RB, et al. Delay in diagnosis of X-linked adrenoleukodystrophy. Clin Neurol Neurosurg 1993;95:115–20. doi:10.1016/0303-8467(93)90004-z.
[7] Dangouloff T, Servais L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: current perspectives. Ther Clin Risk Manag 2019;15:1153–61. doi:10.2147/TCRM.S172291.
[8] Yang C-F, Yang CC, Liao H-C, Huang L-Y, Chiang C-C, Ho H-C, et al. Very early treatment for infantile-onset pompe disease contributes to better outcomes. J Pediatr 2016;169 174-80.e1. https://doi.org/10.1016/j.jpeds.2015.10.078.
[9] Delstanche S, Servais L, Gidaro T. Improved muscular weakness during asthma exacerbation. JAMA Neurol 2017;74:353–4. doi:10.1001/jamaneurol.2016.4069.
[10] Wilson J, Jungner G. Principles and practice of screening. Geneva: WHO; 1968.
[11] Loeber JG, Platis D, Zetterström RH, Almashanu S, Boemer F, Bonham JR, et al. Neonatal screening in europe revisited: an ISNS perspective on the current state and developments since 2010. Int J Neonatal Screen 2021;7. doi:10.3390/ijns7010015.
[12] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097. doi:10.1371/journal.pmed.1000097.
[13] Ramdas S, Servais L. New treatments in spinal muscular atrophy: an overview of currently available data. Expert Opin Pharmacother 2020;21:307–15. doi:10.1080/14656566.2019.1704732.
[14] Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet 2016;388:3017–26. doi:10.1016/s0140-6736(16)31408-8.
[15] Day JW, Finkel RS, Chiriboga CA, Connolly AM, Crawford TO, Darras BT, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol 2021;20:284–93. doi:10.1016/S1474-4422(21)00001-6.

[16] Baranello G, Darras B, Day J, Deconinck N, Klein A, Masson R, et al. Risdiplam in Type 1 spinal muscular atrophy. N Engl J Med 2021;384(10):915–23 https://doi.org/10.1056/NEJMoa2009965.

[17] Servais L, Baranello G, Scoto M, Daron A, Oskoui M. Therapeutic interventions for spinal muscular atrophy: preclinical and early clinical development opportunities. Expert Opin Investig Drugs 2021;30:519–27. doi:10.1080/13543784.2021.1904889.

[18] Chien YH, Chiang SC, Weng WC, Lee NC, Lin CJ, Hsieh WS, et al. Presymptomatic diagnosis of spinal muscular atrophy through newborn screening. J Pediatr 2017;190 124-9.e1. https://doi.org/10.1016/j.jpeds.2017.06.042.

[19] Kraszewski JN, Kay DM, Stevens CF, Koval C, Haser B, Ortiz V, et al. Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. Genet Med 2018;20:608–13 https://doi.org/10.1038/gim.2017.152.

[20] Kucera KS, Taylor JL, Robles VR, Clinard K, Migliore B, Boyea BL, et al. A voluntary statewide newborn screening pilot for spinal muscular atrophy: results from early check. Int J Neonatal Screen 2021;7(1):20 https://doi.org/https://dx.doi.org/10.3390/ijns7010020.

[21] Vill K, Schwartz O, Blaschek A, Glaser D, Nennstiel U, Wirth B, et al. Newborn screening for spinal muscular atrophy in Germany: clinical results after 2 years. Orphanet J Rare Dis 2021;16(1):153 https://doi.org/https://dx.doi.org/10.1186/s13023-021-01783-8.

[22] Boemer F, Caberg JH, Dideberg V, Dardenne D, Bours V, Hiligsmann M, et al. Newborn screening for SMA in Southern Belgium. Neuromuscul Disord 2019;29:343–9. doi:10.1016/j.nmd.2019.02.003.

[23] Kariyawasam DST, Russell JS, Wiley V, Alexander IE, Farrar MA. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. Genet Med 2019;22:557–65 https://doi.org/10.1038/s41436-019-0673-0.

[24] McMillan HJ, Kernohan KD, Yeh E, Amburgey K, Boyd J, Campbell C, et al. Newborn screening for spinal muscular atrophy: Ontario testing and follow-up recommendations. Can J Neurol Sci 2020:1–8. doi:10.1017/cjn.2020.229.

[25] Shinohara M, Niba ETE, Wijaya YOS, Takayama I, Mitsuishi C, Kumasaka S, et al. A novel system for spinal muscular atrophy screening in newborns: Japanese pilot study. Int J Neonatal Screen 2019;5:41. doi:10.3390/ijns5040041.

[26] De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscul Disord 2019;29:842–56. doi:10.1016/j.nmd.2019.09.007.

[27] Dangouloff T, Vrščaj E, Servais L, Osredkar D. Newborn screening programs for spinal muscular atrophy worldwide: where we stand and where to go. Neuromuscul Disord 2021;31:574–82. doi:10.1016/j.nmd.2021.03.007.

[28] Kay DM, Stevens CF, Parker A, Saavedra-Matiz CA, Sack V, Chung WK, et al. Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy. Genet Med 2020;22:1296–302. doi:10.1038/s41436-020-0824-3.

[29] Dangouloff T, Boemer F, Caberg JH, Servais L. Correspondence on: "Discrepancy in Spinal Muscular Atrophy Incidence findings in newborn screening programs: the influence of carrier screening?" by Kay et al. Genet Med 2020;22:1913–14. doi:10.1038/s41436-020-0887-1.

[30] Li C, Desai AK, Gupta P, Dempsey K, Bhambhani V, Hopkin RJ, et al. Transforming the clinical outcome in CRIM-negative infantile Pompe disease identified via newborn screening: the benefits of early treatment with enzyme replacement therapy and immune tolerance induction. Genet Med 2021;23:845–55. doi:10.1038/s41436-020-01080-y.

[31] Lai C-J, Hsu T-R, Yang C-F, Chen S-J, Chuang Y-C, Niu D-M. Cognitive development in infantile-onset pompe disease under very early enzyme replacement therapy. J Child Neurol 2016;31:1617–21. doi:10.1177/0883073816665549.

[32] Chien Y-H, Chiang S-C, Zhang XK, Keutzer J, Lee N-C, Huang A-C, et al. Early detection of Pompe disease by newborn screening is feasible: results from the Taiwan screening program. Pediatrics 2008;122:e39–45 https://doi.org/https://dx.doi.org/10.1542/peds.2007-2222.

[33] Labrousse P, Chien Y-H, Pomponio RJ, Keutzer J, Lee N-C, Akmaev VR, et al. Genetic heterozygosity and pseudodeficiency in the Pompe disease newborn screening pilot program. Mol Genet Metab 2010;99:379–83 https://doi.org/https://dx.doi.org/10.1016/j.ymgme.2009.12.014.

[34] Chiang S-C, Hwu W-L, Lee N-C, Hsu L-W, Chien Y-H. Algorithm for Pompe disease newborn screening: results from the Taiwan screening program. Mol Genet Metab 2012;106:281–6. doi:10.1016/j.ymgme.2012.04.013.

[35] Yang C-F, Liu H-C, Hsu T-R, Tsai F-C, Chiang S-F, Chiang C-C, et al. A large-scale nationwide newborn screening program for Pompe disease in Taiwan: towards effective diagnosis and treatment. Am J Med Genet A 2014;164A:54–61 https://doi.org/https://dx.doi.org/10.1002/ajmg.a.36197.

[36] Klug TL, Swartz LB, Washburn J, Brannen C, Kiesling JL. Lessons learned from Pompe disease newborn screening and follow-up. Int J Neonatal Screen 2020;6(1):11 https://doi.org/https://dx.doi.org/10.3390/ijns6010011.

[37] Burton BK, Charrow J, Hoganson GE, Fleischer J, Grange DK, Braddock SR, et al. Newborn screening for Pompe disease in Illinois: experience with 684,290 infants. Int J Neonatal Screen 2020;6:8–12 https://doi.org/https://dx.doi.org/10.3390/ijns6010004.

[38] Ficicioglu C, Ahrens-Nicklas RC, Barch J, Cuddapah SR, DiBoscio BS, DiPerna JC, et al. Newborn screening for Pompe disease: Pennsylvania experience. Int J Neonatal Screen 2020;6:89 https://doi.org/https://dx.doi.org/10.3390/ijns6040089.

[39] Tang H, Feuchtbaum L, Sciortino S, Matteson J, Mathur D, Bishop T, et al. The first year experience of newborn screening for Pompe disease in California. Int J Neonatal Screen 2020;6(1):9 https://doi.org/https://dx.doi.org/10.3390/ijns6010009.

[40] Navarrete-Martinez JI, Limon-Rojas AE, Gaytan-Garcia M de J, Reyna-Figueroa J, Wakida-Kusunoki G, Delgado-Calvillo MDR, et al. Newborn screening for six lysosomal storage disorders in a cohort of Mexican patients: three-year findings from a screening program in a closed Mexican health system. Mol Genet Metab 2017;121:16–21 https://doi.org/https://dx.doi.org/10.1016/j.ymgme.2017.03.001.

[41] Momosaki K, Kido J, Yoshida S, Sugawara K, Miyamoto T, Inoue T, et al. Newborn screening for Pompe disease in Japan: report and literature review of mutations in the GAA gene in Japanese and Asian patients. J Hum Genet 2019;64:741–55. doi:10.1038/s10038-019-0603-7.

[42] Bravo H, Neto EC, Schulte J, Pereira J, Filho CS, Bittencourt F, et al. Investigation of newborns with abnormal results in a newborn screening program for four lysosomal storage diseases in Brazil. Mol Genet Metab Reports 2017;12:92–7 https://doi.org/https://dx.doi.org/10.1016/j.ymgmr.2017.06.006.

[43] Dooley J, Gordon KE, Dodds L, MacSween J. Duchenne muscular dystrophy: a 30-year population-based incidence study. Clin Pediatr (Phila) 2010;49:177–9. doi:10.1177/0009922809347777.

[44] Shimizu-Motohashi Y, Komaki H, Motohashi N, Takeda S, Yokota T, Aoki Y. Restoring dystrophin expression in Duchenne muscular dystrophy: current status of therapeutic approaches. J Pers Med 2019;9(1). doi:10.3390/jpm9010001.

[45] Ke Q, Zhao Z-Y, Griggs R, Wiley V, Connolly A, Kwon J, et al. Newborn screening for Duchenne muscular dystrophy in China: follow-up diagnosis and subsequent treatment. World J Pediatr 2017;13:197–201 https://doi.org/https://dx.doi.org/10.1007/s12519-017-0036-3.

[46] Mendell JR, Shilling C, Leslie ND, Flanigan KM, Dahhak R, Gastier-Foster J, et al. Evidence-based path to newborn screening for Duchenne muscular dystrophy. Ann Neurol 2012;71:304–13. doi:10.1002/ana.23528.

[47] Drousiotou A, Ioannou P, Georgiou T, Mavrikiou E, Christopoulos G, Kyriakides T, et al. Neonatal screening for Duchenne muscular dystrophy: a novel semiquantitative application of the bioluminescence test for creatine kinase in a pilot national program in Cyprus. Genet Test 1998;2:55–60. doi:10.1089/gte.1998.2.55.

[48] Moat SJ, Bradley DM, Salmon R, Clarke A, Hartley L. Newborn bloodspot screening for Duchenne muscular dystrophy: 21 years experience in Wales (UK). Eur J Hum Genet 2013;21:1049–53 https://doi.org/https://dx.doi.org/10.1038/ejhg.2012.301.

[49] Chung J, Smith AL, Hughes SC, Niizawa G, Abdel-Hamid HZ, Naylor EW, et al. Twenty-year follow-up of newborn screening for patients with muscular dystrophy. Muscle Nerve 2016;53:570–8 https://doi.org/https://dx.doi.org/10.1002/mus.24880.

[50] Greenberg CR, Rohringer M, Jacobs HK, Averill N, Nylen E, van Ommen GJ, et al. Gene studies in newborn males with Duchenne muscular dystrophy detected by neonatal screening. Lancet 1988;2:425–7. doi:10.1016/s0140-6736(88)90414-x.

[51] Ellis JA, Vroom E, Muntoni F. 195th ENMC International Workshop: newborn screening for Duchenne muscular dystrophy 14-16th December 2012, Naarden, The Netherlands. Neuromuscul Disord 2013;23:682–9. doi:10.1016/j.nmd.2013.05.008.

[52] Drummond LM. Creatine phosphokinase levels in the newborn and their use in screening for Duchenne muscular dystrophy. Arch Dis Child 1979;54:362–6. doi:10.1136/adc.54.5.362.

[53] Plauchu H, Dorche C, Cordier MP, Guibaud P, Robert JM. Duchenne muscular dystrophy: neonatal screening and prenatal diagnosis. Lancet 1989;1:669. doi:10.1016/s0140-6736(89)92170-3.

[54] Scheuerbrandt G, Lundin A, Lövgren T, Mortier W. Screening for Duchenne muscular dystrophy: an improved screening test for creatine kinase and its application in an infant screening program. Muscle Nerve 1986;9:11–23. doi:10.1002/mus.880090103.

[55] Theadom A, Rodrigues M, Roxburgh R, Balalla S, Higgins C, Bhattacharjee R, et al. Prevalence of muscular dystrophies: a systematic literature review. Neuroepidemiology 2014;43:259–68. doi:10.1159/000369343.

[56] Pascual-Gilabert M, López-Castel A, Artero R. Myotonic dystrophy type 1 drug development: a pipeline toward the market. Drug Discov Today 2021. doi:10.1016/j.drudis.2021.03.024.

[57] Johnson NE, Butterfield RJ, Mayne K, Newcomb T, Imburgia C, Dunn D, et al. Population-based prevalence of Myotonic dystrophy Type 1 using genetic analysis of statewide blood screening program. Neurology 2021;96:e1045–53 https://doi.org/https://dx.doi.org/10.1212/WNL.0000000000011425.

[58] Orsini JJ, Escolar ML, Wasserstein MP, Caggana M. Krabbe disease. GeneReviews® [Internet]. Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, editors et al., editors, Washington, Seattle: Seattle Univ; 1993. 1993–2020. 2000 Jun 19 [updated 2018 Oct 11]., Seattle (WA).

[59] Wenger DA, Rafi MA, Luzi P, Datto J, Costantino-Ceccarini E. Krabbe disease: genetic aspects and progress toward therapy. Mol Genet Metab 2000;70:1–9. doi:10.1006/mgme.2000.2990.

[60] Graf WD. Stem cell transplantation in Krabbe disease: new truths discovered and opinions change. Neurology 2017;89:1318–19. doi:10.1212/WNL.0000000000004427.

[61] Duffner PK, Caviness VSJ, Erbe RW, Patterson MC, Schultz KR, Wenger DA, et al. The long-term outcomes of presymptomatic infants transplanted for Krabbe disease: report of the workshop held on July 11 and 12, 2008, Holiday Valley, New York. Genet Med 2009;11:450–4. doi:10.1097/GIM.0b013e3181a16e04.

[62] Wasserstein MP, Andriola M, Arnold G, Aron A, Duffner P, Erbe RW, et al. Clinical outcomes of children with abnormal newborn screening results for Krabbe disease in New York State. Genet Med 2016;18:1235–43. doi:10.1038/gim.2016.35.

[63] Orsini JJ, Kay DM, Saavedra-Matiz CA, Wenger DA, Duffner PK, Erbe RW, et al. Newborn screening for Krabbe disease in New York State: the first eight years' experience. Genet Med 2016;18:239–48. doi:10.1038/gim.2015.211.

[64] Minter Baerg MM, Stoway SD, Hart J, Mott L, Peck DS, Nett SL, et al. Precision newborn screening for lysosomal disorders. Genet Med 2018;20:847–54 https://doi.org/https://dx.doi.org/10.1038/gim.2017.194.

[65] Basheeruddin K, Shao R, Balster F, Gardley P, Ashbaugh L. Newborn screening for Krabbe disease-Illinois experience: role of psychosine in diagnosis of the disease. Int J Neonatal Screen 2021;7. doi:10.3390/ijns7020024.

[66] Ehmann P, Lantos JD. Ethical issues with testing and treatment for Krabbe disease. Dev Med Child Neurol 2019;61:1358–61. doi:10.1111/dmcn.14258.

[67] Mallack EJ, Turk B, Yan H, Eichler FS. The landscape of hematopoietic stem cell transplant and gene therapy for X-linked adrenoleukodystrophy. Curr Treat Options Neurol 2019;21:61. doi:10.1007/s11940-019-0605-y.

[68] Health Resources and Services Administration (HRSA). Baby's first test 2020. https://www.babysfirsttest.org.

[69] Eng L, Regelmann MO. Adrenoleukodystrophy in the era of newborn screening. Curr Opin Endocrinol Diabetes Obes 2020;27:47–55. doi:10.1097/MED.0000000000000515.

[70] Wiens K, Berry SA, Choi H, Gaviglio A, Gupta A, Hietala A, et al. A report on state-wide implementation of newborn screening for X-linked Adrenoleukodystrophy. Am J Med Genet A 2019;179:1205–13. doi:10.1002/ajmg.a.61171.

[71] Lee S, Clinard K, Young SP, Rehder CW, Fan Z, Calikoglu AS, et al. Evaluation of X-linked adrenoleukodystrophy newborn screening in North Carolina. JAMA Netw Open 2020;3:e1920356. doi:10.1001/jamanetworkopen.2019.20356.

[72] Barendsen RW, Dijkstra IME, Visser WF, Alders M, Bliek J, Boelen A, et al. Adrenoleukodystrophy newborn screening in the Netherlands (SCAN Study): the X-factor. Front Cell Dev Biol 2020;8:499. doi:10.3389/fcell.2020.00499.

[73] National Librairy of Medicine N. Clinical trial 2021. https://clinicaltrials.gov/ct2/show/NCT02952482?term=NCT02952482&draw=2&rank=1.

[74] Rosenberg JB, Kaminsky SM, Aubourg P, Crystal RG, Sondhi D. Gene therapy for metachromatic leukodystrophy. J Neurosci Res 2016;94:1169–79. doi:10.1002/jnr.23792.

[75] Biffi A, Montini E, Lorioli L, Cesani M, Fumagalli F, Plati T, et al. Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. Science 2013;341:1233158. doi:10.1126/science.1233158.

[76] Hong X, Daiker J, Sadilek M, Ruiz-Schultz N, Kumar AB, Norcross S, et al. Toward newborn screening of metachromatic leukodystrophy: results from analysis of over 27,000 newborn dried blood spots. Genet Med 2021;23:555–61. doi:10.1038/s41436-020-01017-5.

[77] Strauss KA, Swoboda KJ, Farrar M, McMillan HJ, Parsons J, Krueger J, et al. AVXS-101 gene-replacement therapy in presymptomatic spinal muscular atrophy: SPR1NT study update. Am Acad Neurol 2019 2019 - 71st Annu Meet.

[78] Dangouloff T, Burghes A, Tizzano EF, Servais L, Bertini E, Boemer F, et al. 244th ENMC international workshop: newborn screening in spinal muscular atrophy May 10–12, 2019, Hoofdorp, The Netherlands. Neuromuscul. Disord. 2020;30:93–103 Elsevier Ltd. doi:10.1016/j.nmd.2019.11.002.

[79] Dangouloff T, Botty C, Beaudart C, Servais L, Hiligsmann M. Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments. Orphanet J Rare Dis 2021;16:47. doi:10.1186/s13023-021-01695-7.

[80] Glascock J, Sampson J, Haidet-Phillips A, Connolly A, Darras B, Day J, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. J Neuromuscul Dis 2018;5:145–58. doi:10.3233/jnd-180304.

[81] Glascock J, Sampson J, Connolly AM, Darras BT, Day JW, Finkel R, et al. Revised recommendations for the treatment of infants diagnosed with spinal muscular atrophy via newborn screening who have 4 copies of SMN2. J Neuromuscul Dis 2020;7:97–100. doi:10.3233/JND-190468.

[82] Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy—a literature review. Orphanet J Rare Dis 2017;12:124. doi:10.1186/s13023-017-0671-8.

[83] Beckers P, Caberg J-H, Dideberg V, Dangouloff T, den Dunnen JT, Bours V, et al. Newborn screening of duchenne muscular dystrophy specifically targeting deletions amenable to exon-skipping therapy. Sci Rep 2021;11. doi:10.1038/s41598-021-82725-z.

[84] Rodríguez Cruz PM, Cossins J, Beeson D, Vincent A. The neuromuscular junction in health and disease: molecular mechanisms governing synaptic formation and homeostasis. Front Mol Neurosci 2020;13:226. doi:10.3389/fnmol.2020.610964.

[85] Carreau C, Benoit C, Ahle G, Cauquil C, Roubertie A, Lenglet T, et al. Late-onset riboflavin transporter deficiency: a treatable mimic of various motor neuropathy aetiologies. J Neurol Neurosurg Psychiatry 2020. doi:10.1136/jnnp-2020-323304.

[86] Annoussamy M, Lilien C, Gidaro T, Gargaun E, Chê V, Schara U, et al. X-linked myotubular myopathy: a prospective international natural history study. Neurology 2019;92:e1852–67 https://doi.org/10.1212/WNL.0000000000007319.

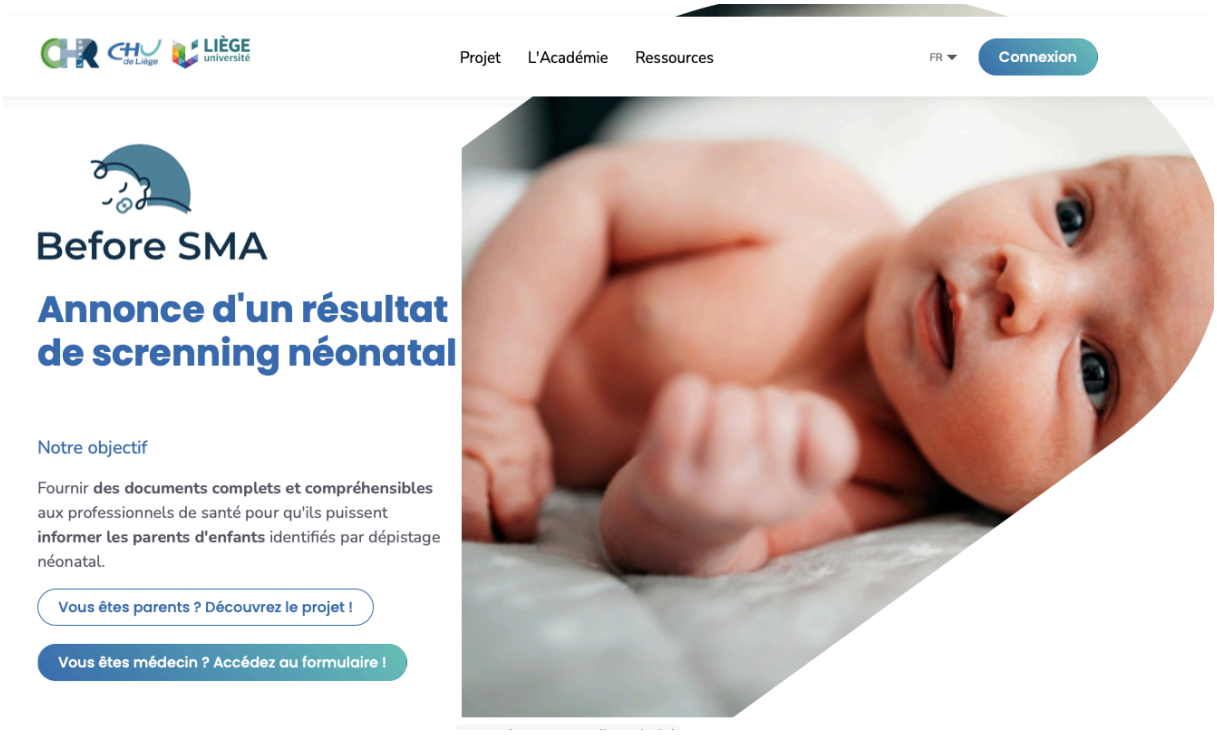
[87] Amburgey K, Tsuchiya E, de Chastonay S, Glueck M, Alverez R, Nguyen C-T, et al. A natural history study of X-linked myotubular myopathy. Neurology 2017;89:1355–64 https://doi.org/10.1212/WNL.0000000000004415.

[88] Duong T, Harding G, Mannix S, Abel C, Phillips D, Alfano LN, et al. Use of the children's hospital of Philadelphia infant test of neuromuscular disorders (CHOP INTEND) in X-linked myotubular myopathy: content validity and psychometric performance. J Neuromuscul Dis 2021;8:63–77. doi:10.3233/JND-200479.

[89] Shieh PB, Bönnemann CG, Müller-Felber W, Blaschek A, Dowling JJ, Kuntz NL, et al. Re: "moving forward after two deaths in a gene therapy trial of myotubular myopathy" by Wilson and Flotte. Hum Gene Ther 2020;31:787. doi:10.1089/hum.2020.217.

[90] Tasfaout H, Cowling BS, Laporte J. Centronuclear myopathies under attack: a plethora of therapeutic targets. J Neuromuscul Dis 2018;5:387–406. doi:10.3233/JND-180309.

## Annexe XV. Page internet Beforesma.com (Chapitre III, 4)




## Annexe XVI. Flyer NBS Academy (Chapitre III, 4)

Before SMA
*The Academy*

# Newborn screening for Spinal Muscular Atrophy: *The academy*

You are a child neurologist, a physician, a geneticist, a screening center manager and you wish to support the development of SMA screening in your country? Join us and discover "Before SMA: The Academy!".

**May, 13-14 2022**

**Registration open**

LIÈGE université

NOVARTIS Roche

Photos © Shutterstock

## What is it?

Two full days interactive training and discussion including lab visit, role play around diagnosis announcement, plenary lectures and round table discussion...
Everything you wanted to know about SMA NBS, but you were afraid to ask.

## Where?

Liège, Belgium. Where SMA NBS is implemented since March 2018.

## For who?

Child neurologists, newborn screeners, geneticists, care/program coordinators... As long as you are/will be/would like to be leading of involved in a SMA NBS program, and have several questions.

## When?

Friday 13th and Saturday 14th May 2022.

## Is it F2F or online?

Both! We want to privilege a F2F interaction with a group of max 20 participants, but all sessions will be filmed, streamed and broadcasted for those who attended online. Anyway, at the end of the day, it's the virus that decides, right?

## Who are the organisers and the speakers?

Organised by Pr Laurent Servais, with a faculty of international Key Opinion Leaders:
- Dr Francois Boemer, CHU Liège, Belgium
- Dr Monika Gos, Institute of Mother and Child, Warsaw, Poland
- Pr Mickael Hiligsmann, University of Maastricht, The Netherlands
- Pr Jan Kirschner, University of Bonn, Germany
- Pr Francesco Muntoni, UCL, London, UK
- Dr Danilo Tiziano, University of Roma, Italy

## How much does it cost?

50€ all included. Residual cost, including housing, travel (up to 600€), inscription... Is covered by grants provided by our generous sponsors. Online attendance is 10€.

## How can I register?

Go to **www.news.uliege.be/beforesma-theacademy** and click on "register". We hope being able to accommodate all requests, but should we not be able, we will prioritise the most diverse audience in terms of origin, specialisation... and we will get a strong incentive to organise a second session.

## When should I register?

Now! And certainly before February 14th (easy to remember isn't?)

**Nice teasing, but I have more questions...**
**Please visit www.news.uliege.be/beforesma-theacademy,**
**beforesma.com or drop us an e-mail tamara.dangouloff@uliege.be**