BELGIAN ADVISORY COMMITTEE ON
Bioethics

Opinion by letter No 12 on informed consent by parents when extending neonatal screening to include detection of spinal muscular atrophy (SMA)

Request for opinion dated 22 September 2021 from the Flemish Minister of Welfare, Health, Family and Poverty Reduction

Adoption of the opinion by letter: Committee plenary session of 14 March 2022

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The committee's opinions are drafted in Dutch and French. Please consider these two language versions as official, even if translations in other languages are available.

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BELGIAN ADVISORY COMMITTEE ON
Bioethics

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Your request for an opinion dated 22 September 2021 regarding informed consent by parents when extending neonatal screening to include detection of spinal muscular atrophy (SMA)

Minister,

By letter dated 22 September 2021, you, as Flemish Minister of Welfare, Health, Family and Poverty Reduction, requested the opinion of the Advisory Committee on Bioethics in the context of extending neonatal screening to include detection of spinal muscular atrophy (SMA). The question is whether separate informed consent is needed in this regard, as it is a genetic test and because there is no long-term data on the effectiveness of the treatment. In this opinion, we first discuss the disorder and its treatment, as well as the organisation of neonatal screening for SMA at the global level. The way neonatal screening is currently organised in Belgium, the current informed consent procedure and the follow-up of an abnormal result are also discussed.

1) Spinal muscular atrophy or spinal muscular atrophy (SMA)

Spinal muscular atrophy is a rare genetic disorder characterised by progressive muscular atrophy, with varying degrees of severity which can lead to disability and respiratory failure. This is caused by the degeneration of nerve cells which are essential for transmitting nerve impulses necessary for muscle contraction. These cells, the motor neurons, are located in the anterior portion of the spinal cord.

Spinal atrophy is caused by a mutation in the *SMN1* gene (SMN stands for Survival of Motor Neuron); this gene is located on chromosome 5 and is responsible for producing the protein (i.e. protein synthesis) which is necessary for maintaining the integrity and normal function of motor neurons. The defect in the SMN protein can be partially compensated for by the *SMN2* gene, but the degree of compensation varies from individual to individual. The disease presents as progressive paralysis, including of the respiratory muscles. Depending on the age at which the first symptoms appear and the severity, and related to the number of copies of *SMN2*, several different types of SMA can be identified. SMA type I is the earliest and most severe form of SMA that can be observed during the first six months of life. The child is

never able to take a sitting position, and without respiratory support, usually dies within the first two years. SMA type II presents between the ages of 6 and 18 months. Without treatment, the child cannot learn to walk and has a shorter life expectancy than the general population. The first symptoms of SMA type III appear after 18 months but before the age of 6 years; the child can learn to walk. SMA type IV begins in adulthood.[1]

Until recently, care was primarily focused on compensating for the disabilities caused by the disease. In recent years, treatments have been approved[2] by the various Medicines agencies, and some of these have already been reimbursed in Belgium. These treatments aim to increase *SMN2* gene expression or restore SMN1 activity. Starting these treatments early appears to provide real benefit. For the earliest forms of the disease, and provided treatment is given before the onset of the first symptoms, this means that the onset of the first symptoms is delayed longer and the symptoms are attenuated.[3] Current data show that when treatment is started before the onset of symptoms, the child actually experiences (almost) normal development. The longer-term consequences are currently not known.

2) State of play as regards screening for SMA

When there was still no treatment available for SMA, it seemed unethical to offer neonatal screening. Patients with SMA were diagnosed based on a family history or the occurrence of suggestive symptoms. Since the emergence of innovative therapies, this position has been revised internationally.

To gain more insight, the team at the *Université de Liège* launched a global questionnaire on the subject.[4] The evolution of the implementation of neonatal screening for SMA can also be followed on the website of the *European Alliance for Newborn Screening in Spinal Muscular Atrophy*.[5]
Neonatal screening of SMA has already been implemented:

- at the national level: Austria (06/2021), Germany (10/2021), Norway (09/2021), Taiwan (2016);
- at the local level, national implementation pending approval: Australia (2 regions), Canada (2 provinces), Italy (3 regions), US (38/50 states) and Belgium (*Fédération Wallonie-Bruxelles*);
- in pilot project: Moscow (2019), St. Petersburg (2021), Lithuania (2021), Japan (2021)[6], Spain (2021), United Kingdom (2021).

In addition, neonatal screening of SMA will be implemented:

- at country level (2022): Croatia[7], Czech Republic (implementation started), Poland (implementation 85% complete), Portugal, Slovenia[7] and Belgium (expansion with Flemish Community);
- at country level (date still uncertain): Denmark, Netherlands, Sweden;
- in pilot project: France (2022), North Macedonia.

In the context of a pilot project in the French-speaking Community (*Fédération Wallonie-Bruxelles*), coordinated by the *Université de Liège*, the first Belgian babies could undergo neonatal screening for SMA in 2018, via a genetic test (qPCR or quantitative polymerase

chain reaction). Since March 2021, this screening has been included in the official neonatal screening programme for congenital diseases (population screening) of the *Fédération Wallonie-Bruxelles*.
Although the technique (qPCR) involves analysing a small part of the patient's DNA, it consists of specific and targeted multiplication of the *SMN1* gene, thereby eliminating the possibility of incidental findings.
As with neonatal screening for other diseases (such as cystic fibrosis), a positive test requires both a repeat of the test and confirmation of the test result using another testing technique. Communication of the test result (after repeating the test) and collection for the confirmation test take place during a consultation with a specialist.
Over a period of 3 years, the pilot project resulted in 136,339 tests being carried out and SMA being diagnosed in 9 patients. These 9 patients received access to treatment, most of them in pre-symptomatic stage.[8]

3) Current informed consent procedure for neonatal screening

The heel prick (Guthrie test) is offered free and routinely in Belgium, but is not mandatory. According to Art. 8 of the Law on Patient's Rights, parents have the right to informed consent and can also refuse the heel prick. In the Flemish Community, verbal consent (opting-in principle) is sufficient for performing the heel prick (art. 5 of the Order of the Government of Flanders of 12 December 2008 on population screening in the context of disease prevention); in the *Fédération Wallonie-Bruxelles*, not verbally refusing (opting-out principle) is sufficient (art. 11 *of the Order of the Government of the French Community of 9 January 2020 on the screening of congenital disorders in the French Community*).
Parents are asked by a midwife or doctor if they agree that their newborn child receives a heel prick. In general, it is neither realistic nor desirable to provide detailed information about every disease detected and the relevant treatment at that time, but it is explained that the test is taken in the context of detecting rare diseases that can be treated before severe and/or irreversible symptoms occur. To further inform parents, the Government provides posters, leaflets, a short video and a Web page (https://www.aangeborenaandoeningen.be/wij-doen-het-en-wat-doe-jij;https://www.depistageneonatal.be/familles_anomalies_congenita-les/index.htm). The information also states that parents can feel free to ask the doctor or midwife for more explanations about the diseases detected and the advantages and disadvantages of screening.

If a positive result on the Guthrie test is abnormal even after repeating it, there will be a second blood sample taken to confirm, with the parents specifically informed by a specialist.

The informed consent for participation in neonatal screening is an overarching consent for screening all diseases in the programme. Choosing to screen for some diseases and not others is not possible. It is not practically feasible to split up the analytical tests and therefore "choose" which analytical tests you wish to have performed for which blood sample cards. In addition, it would not be desirable from an ethical perspective for parents to be able to choose which results they want to be informed about and which not, since the results of the

neonatal screening are always relevant to the child's health. Consequently, informed consent means accepting the total package.

4) Informed consent when including SMA in neonatal screening

Neonatal screening for SMA differs from most tests on the current panel because it is not a biochemical test, but requires a targeted genetic detection test. However, SMA is detected through the same blood sample as the other diseases in the screening. This procedure is similar to neonatal screening for cystic fibrosis, which also involves targeted genetic testing. The implications of the different testing methods are however limited. First, this always involves hereditary diseases, for which early diagnosis and treatment are advisable for the health of the newborn. Second, the genetic test used is targeted and excludes these incidental findings.

As a result, there is little basis to modify the informed consent procedure after SMA has been included in the neonatal screening. SMA can be included in the screening panel, where consent to screening implies consent for the entire panel, including SMA. It should also be recalled here that refusal to screen for SMA implies refusing all analysis tests in the context of the heel prick.
Conversely, seeking specific written informed consent for screening for SMA is not without risk. For example, taking a different approach to SMA compared to other diseases may lead to mistrust, which is sometimes difficult for healthcare providers (obstetricians, midwives, etc.) to overcome.

It can therefore be decided that the current information about the Guthrie test, the fact that it detects rare diseases for which there is effective treatment and that early detection is important (as well as the possibility of refusing the Guthrie test or further processing of the data) is also sufficient when SMA is included in the screening panel.

5) Recommendations of the Advisory Committee on Bioethics.

As for the other diseases, neonatal screening of SMA is relevant given the rare and severe nature of the disorder and the possibility of early treatment, for which the initial outcomes appear to be favourable.

Although the analytical test for SMA is genetic and not biochemical, as is the case for most other diseases detected via heel prick, it is a targeted detection test (qPCR) that eliminates the possibility of incidental findings, which means it can be included in the current neonatal screening programme without specific informed consent, as is the case for screening for cystic fibrosis. The Committee recommends having a specific focus on good information (as described in point 3) but taking into account the sometimes limited digital literacy of parents. In the event of a repeat positive test result, parents should be offered a consultation with a neuromuscular and/or genetic specialist who will ask for their separate informed consent for a confirmatory test during the consultation.

The Committee also recommends that health authorities organise a follow-up of the results of this screening programme.

Given the advances in medicine and the likely emergence of new screening tests in the coming years and new targeted treatments for certain rare diseases, the Advisory Committee on Bioethics considers expanding this debate to include the modalities of neonatal screening in a broader context and not limited to a particular disease or condition.

Yours sincerely,

Jan De Lepeleire, President

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This letter opinion was drawn up by the select committee "neonatal screening" consisting of: Veerle Labarque (co-chair), Laurent Houtekie (co-chair), Nathalie Bernheim, Patrick Cras, Jan De Lepeleire (Bureau representative), Vera De Vleesschauwer, Charlotte Lambert, Ingrid Morales, Wim Pinxten.