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Research Report

Newbornscreening SMA – From Pilot Project to Nationwide Screening in Germany

Wolfgang Müller-Felber[a,1,*], Astrid Blaschek[a,1], Oliver Schwartz[b], Dieter Gläser[c], Uta Nennstiel[d], Inken Brockow[d], Brunhilde Wirth[e], Siegfried Burggraf[f], Wulf Röschinger[f], Marc Becker[f], Jürgen Durner[f,g], Katja Eggermann[h], Heike Kölbel[j], Christine Müller[a], Iris Hannibal[a], Bernd Olgemöller[i], Ulrike Schara[j], Arpad von Moers[k], Regina Trollmann[l], Jessika Johannssen[m], Andreas Ziegler[n], Sebahattin Cirak[o], Andreas Hahn[p], Maja von der Hagen[q], Claudia Weiss[r], Gudrun Schreiber[s], Marina Flotats-Bastardas[t], Hans Hartmann[u], Sabine Illsinger[u], Astrid Pechmann[v], Veronka Horber[w], Jan Kirschner[v], Cornelia Köhler[x], Benedikt Winter[y], Johannes Friese[z] and Katharina Vill[a]

[a]*Dr. v. Hauner Children's Hospital, Department of Pediatric Neurology and Developmental Medicine, LMU – University of Munich, Munich, Germany*
[b]*Department of Pediatric Neurology, Muenster University Hospital, Münster, Germany*
[c]*MVZ Genetikum GmbH, Center for Human Genetics, Neu-Ulm, Germany*
[d]*Screening Center of the Bavarian Health and Food Safety Authority, Oberschleissheim, Germany*
[e]*Institute of Human Genetics, Center for Molecular Genetics Cologne and Center for Rare Diseases Cologne, University of Cologne, Cologne, Germany*
[f]*Labor Becker und Kollegen, Munich, Germany*
[g]*Department of Operative/Restorative Dentistry, Periodontology and Pedodontics, Ludwig-Maximilians-Universität München, Munich, Germany*
[h]*Institute of Human Genetics, Medical Faculty, RWTH Aachen University, Aachen, Germany*
[i]*Formerly Labor Becker, Olgemöller und Kollegen, Munich, Germany*
[j]*Department of Pediatric Neurology, Developmental Neurology and Social Pediatrics, University of Essen, Germany*
[k]*Klinik für Kinder- und Jugendmedizin, Neuropädiatrie, DRK Klinikum Westend, Berlin, Germany*
[l]*Department of Pediatrics, Division of Pediatric Neurology, Friedrich-Alexander University of Erlangen-Nürnberg, Erlangen, Germany*
[m]*University Medical Center Hamburg-Eppendorf, Department of Pediatrics, Hamburg, Germany*
[n]*Division of Child Neurology and Metabolic Medicine, Center for Child and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany*

[1]Authors equally contributed to the paper.

*Correspondence to: Prof. Dr. med. Wolfgang Müller-Felber, Department of Pediatrics, Dr. von Hauner Children's Hospital, University Hospital, LMU Munich, Lindwurmstr. 4, 80337 Munich, Germany. E-mail: Wolfgang.mueller-felber@med.uni-muenchen.de.

[o]*Department of Pediatrics, Ulm University, Ulm, Germany*
[p]*Department of Child Neurology, University Hospital, Gießen, Germany*
[q]*Abteilung Neuropädiatrie, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany*
[r]*Department of Pediatric Neurology, Charité–Universitätsmedizin Berlin, Berlin, Germany*
[s]*Department of Pediatric Neurology, Klinikum Kassel, Kassel, Germany*
[t]*Department of Pediatric Neurology, University Hospital Homburg, Homburg, Germany*
[u]*Hannover Medical School, Clinic for Pediatric Kidney-, Liver- and Metabolic Diseases, OE, Hannover, Germany*
[v]*Department of Neuropediatrics and Muscle Disorders, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany*
[w]*Department of Paediatric Neurology, University Children's Hospital, Tübingen, Germany*
[x]*Department of Pediatric Neurology, University of Bochum, Bochum, Germany*
[y]*Department of Paediatric Neurology, University hospital Mannheim, Mannheim, Germany*
[z]*Department of Paediatric Neurology, University hospital Bonn, Bonn, Germany*

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Abstract. Now that targeted therapies for spinal muscular atrophy are available, attempts are being made worldwide to include screening for spinal muscular atrophy in general newborn screening. In Germany, after pilot projects from 2018–2021, it was included in the general newborn screening from October 2021. To ensure a smooth transition, criteria for follow-up were developed together with key stakeholders. At the beginning of the transition to nationwide screening, false positive findings were reported in 3 patients. After optimization of the screening method in the laboratories concerned, all findings have been subsequently confirmed. On average, the first presentation to a neuromuscular center occurred on day 12 of life, and in patients with 2 or 3 *SMN2* copies, therapy started on day 26 of life. Compared with the pilot project, there was no significant delay in timing.

Keywords: Spinal muscular atrophy, newborn screening, SMA treatment, 5q-SMA

INTRODUCTION

The aim of newborn screening (NBS) is to diagnose diseases that lead to severe deficits if left untreated, preferably at a pre-symptomatic stage. Half a century ago, Wilson and Jungner defined criteria for which disease could be included in NBS programs [1]. While metabolic and endocrine disorders initially used to be the focus of newborn screening, the spectrum has now expanded including other diseases such as SCID, cystic fibrosis, sickle cell disease and spinal muscular atrophy, reflecting increased therapeutic options. In the past, newborn screening was based exclusively on the determination of metabolites. Screening for spinal muscular atrophy was the first time a primarily genetic testing approach was applied.

5q13.2-associated spinal muscular atrophy (SMA-5q) is the most common neurodegenerative disorder in childhood and the leading genetic cause of death in early childhood. The disease is caused by a homozygous deletion of exon 7 of the *SMN1* gene (MIM*600354) in more than 95% of cases [2]. This gene encodes the survival motor neuron (SMN) protein, which plays a central role in the development of the peripheral nervous system during late pregnancy and the first months of life. The lack of sufficient SMN protein leads to premature apoptosis of motor neurons. Less than 5% of patients show compound heterozygosity, with a combination of a deletion in exon 7 and an additional pathogenic sequence variant on the other allele. Humans carry a second, almost identical pseudogene called *SMN2*, which differs from *SMN1* only by the exchange of five bases. One of these exchanges leads to altered splicing with a less likely inclusion of exon 7 resulting in a substantially decreased amount of fully functional SMN protein.

The *SMN2* gene is currently the most important predictor and modifier of the course of the disease [3, 4].

In the meantime, 3 different targeted therapeutic approaches that can specifically increase SMN protein production are available. These are based on either gene replacement therapy (GRT) [5, 6] or

splice-modification at the pre-mRNA level [7]. Use of GRT with onasemnogene-abeparvovec is in Germany restricted to patients with 2 or 3 copies of *SMN2*, nusinersen can be applied in any genetically proven 5q13.2 associated SMA and risdiplam can be used in children elder then 2 months. The onset of treatment is critical for clinical efficacy.

Both survival and motor skills differ markedly between children who are treated presymptomatically with nusinersen and children who receive therapy only after the onset of symptoms [7, 8]. Similar results were found in children treated with GRT [9].

For this reason, efforts are underway worldwide to include SMA in general newborn screening (NBS). In several countries corresponding pilot projects have started. In the USA and in some countries of the European Union (Germany, Norway, Belgium) newborn screening for SMA has already been included in the general screening guidelines.

Several methods for the detection of children with SMA-5q in newborn screening are now available. All are essentially based on the detection of a homozygous deletion of exon 7 in the *SMN1* gene by a quantitative PCR reaction [10].

Beginning in 2018, pilot projects in parts of Germany clearly demonstrated the benefit of newborn screening for spinal muscular atrophy in more than 500,000 newborns screened [11, 12]. While in the pilot projects a single screening laboratory performed the newborn screening using its own well-established method and the notification and follow up care of the families was provided by three well connected centers, transition to a nationwide newborn screening program is supposed to bring some new challenges.

Purpose of the study

The following article will describe

- the process of implementation of SMA screening into nationwide NBS in Germany
- the organizational requirements that were used in Germany in an attempt to ensure the smoothest possible transition from the pilot project to nationwide screening
- The challenges encountered in the first 6 months of nationwide NBS since the start in October 2021
- the timeframe of necessary steps towards final diagnosis and treatment in the pilot projects compared to the nationwide NBS program

METHODS

Information on the patients including the time course of the individual steps up to the final diagnosis were assessed via an online survey (lime-survey) which was filled out by each neuromuscular center taking care of the children with suspected SMA. Findings were compared to the data of the pilot projects which have been published previously [12].

The project was approved by the university of Munich (LMU) local ethics committee (project no. 22-0549 KB and project no 18–269). Compliance with guidelines on human experimentation was assured.

RESULTS

Definition of prerequisites for neuromuscular centers which advise parents with newborns detected in the NBS

In order to optimize the process from initial positive NBS of SMA to final diagnosis and, if necessary, start of treatment, in a first step criteria were developed together with representatives of professional societies and patient advocacy groups to determine standardized qualify criterions for follow-up care.

In an online conference, organized by the patient organization "Deutsche Gesellschaft für Muskelkranke/DGM" and the professional society "Deutsche Gesellschaft für Neuropädiatrie/GNP" the neuromuscular treatment centers available in German-speaking countries defined the staffing requirements and content of possible aftercare centers. The created proposal was then circulated and agreed upon among the participants. This resulted in criteria which are shown in Table 1.

Selection process

In a second step, all clinics and treatment centers in the field of neuropediatrics in Germany were contacted and asked about their experience in the field of spinal muscular atrophy. This included the number of patients suffering from SMA (especially patients in the first year of life) who were treated in these centers, what kind of diagnostic methods (genetic testing, clinical neurophysiology and physiotherapeutic testing) were available and if SMA specific treatment experience was available.

Based on the results of this questionnaire, centers were selected according to the criteria listed

Table 1
Selection criteria for newborn screening follow-up centers

1) Possibility to offer a consultation appointment within 4 working days at the neuromuscular center
2) Close cooperation with a genetic laboratory in order to get genetic confirmation including determination of *SMN2* copy number within 1 week after collection of the control blood sample
3) Ability to perform electroneurography (and electromyography)
4) Pediatric neurologist with experience in the field of SMA (treatment of a minimum of 20 patients within the last 2 years)
5) Personal experience with all currently available SMA specific treatments (nusinersen, risdiplam, onasemnogene-abeparvovec) in order to be able to advice the parents
6) Availability of physiotherapists with training in neuromuscular tests (HINE, CHOP-INTEND, HMFSE, time function tests, 6-min-walk test) to evaluate the outcome of the children
7) Availability of psychological and social support

in Table 1, which had agreed to be available as initial contacts for the screening laboratories. The final selection of centers was made by a panel of national and international experts with experience in the field of neuromuscular diseases and/or NBS programs. The panel of the experts was confirmed by the German Society for Pediatrics and Adolescent Medicine (DGKJ), German society for pediatric neurology (GNP), German society for newborn screening and the patient organization" Deutsche Gesellschaft für Muskelkranke (DGM)".

Care was taken to consider both the quality of care and aspects such as sufficient spatial coverage to avoid families traveling too far to the nearest center.

A total of 20 neuromuscular centers were selected for patient follow-up, covering most of Germany so densely (with the exception of northeastern Germany with a low population density) that families had to travel a maximum of 200 km to the nearest neuromuscular center. It was agreed that the selection of centers would be re-evaluated at annual intervals in the future to take account of changes in the structure of care in Germany. To this purpose, it was agreed that the centers would document the timing of various steps in newborn screening. Communication of the established network to patients and stakeholders.

In order to provide information to screening laboratories, obstetric clinics and parents about the next steps after a positive screening as well as about the available treatment centers, a website was developed together with the German Muscular Dystrophy Society (DGM), on which detailed contact information about the aftercare centers is presented on a map (https://dgm-behandlungszentren.org). This is to facilitate that those affected can easily find the nearest treatment center.

Several webinars aimed at pediatricians and at gynecologists and obstetricians, were held to inform physicians about the need to confirm the diagnosis as soon as possible. Several articles on newborn screening for SMA have been published in German journals [13]. Publications in the lay press, both in widely circulated print media and in short features on television, have been used to inform parents about the possibilities and opportunities of newborn screening for SMA.

Workflow from suspicion to treatment

Patients

During the pilot projects (January 2018 – September 2021) 67 children with a suspected homozygous deletion of exon 7 in the *SMN1*-gene were found. In the period from October 1, 2021 to March 31, 2022, a total of 50 children with suspected homozygous deletion in the *SMN1* gene were detected nationwide. The mean gestational age was 38.9 week of gestation (range 30–42). The mean birth weight was 3320 grams (range 1480–3840).

Communication of the NBS results

The screening laboratory informed the sender of the probe of the suspicion of SMA after a mean of 7.7 days after birth (median 7, range 4–15). In 1 case delayed mailing of the screening card was responsible for a delay until day 15.

According to the legal guidelines applicable in Germany, the screening laboratory is responsible for the communication of the test result to the sender of the laboratory sample who has to assure that the parents are informed about the positive screening. During the pilot project [11, 12], based on a special consent, which the parents had to sign before the screening, a direct information transfer from the screening laboratory to one of the three neuromuscular centers (Munich, Essen, Münster) participating in

the pilot project was possible. Parents were informed directly by the neuromuscular center.

After the introduction of nationwide SMA-NBS the framework conditions differed between the German federal states. In 44.5% cases the parents were informed by the nearest neuromuscular center, in 32% by the hospital where the child was born, in 10% by the screening laboratory and in 4% by the practicing pediatrician.

Communication of screening results to parents was delayed in five cases due to known NBS problems such as wrong phone number on the screening card, hearing loss of parents with the need to contact the family in writing. In one case the help of police was necessary to find out where the current place of residence of the family was. One family did not believe in the suspicious findings and initially refused to come for confirmation.

First appointment at a neuromuscular center

Parents were able to come to a neuromuscular center for the first time on a median of 10 days (range 5–46) after birth with the longest time interval observed in 2 premature patients in whom care was coordinated between the maternity hospital and the neuromuscular center. In both cases, parents opted for gene replacement therapy and the children were transferred to the appropriate clinics as soon as they met the indication criteria for gene therapy. Both children did not show signs of SMA before treatment was started.

In four cases, uncertainty about which neurological center should provide further care for the children resulted in delayed presentation. All of these cases occurred in the first 2 months after the nationwide implementation of the SMA screening program.

One infant with one *SMN2*-copy who had to be ventilated immediately after birth was treated until death at day 17 in the NICU of the birth clinic. The neuromuscular centers group discussed whether to treat or not to treat this child. No disease modifying treatment was initiated.

Quality of newborn screening (false positive findings)

Confirmation

During the pilot project, newborn screening for SMA was performed exclusively in a single laboratory. The analysis was performed according to a method that had been developed in this laboratory [10]. After the introduction of the general newborn screening, the laboratory samples for the screening were distributed to 11 different screening laboratories depending on the maternity hospitals. The method used in each case was at the discretion of the laboratory.

Blood for confirmatory diagnostics was drawn in 82% of the cases in the nearest neuromuscular center and at a hospital in 8%. No information was available in 10%.

Confirmation and determination of the *SMN2* copy number was available at median 13th day of life.

False negative and false positive findings in the NBS

During the pilot projects and so far during the nationwide screening no false negative patients were detected in which homozygous deletions in exon 7 of the *SMN1*-gene was missed [12].

One patient (not included in the list of screening patients) presented to a neuromuscular center on day 68 of life with clinical symptoms of spinal muscular atrophy. The subsequent molecular genetic diagnosis revealed the combination of a deletion and a point mutation. For this reason, this child could not be detected by NBS.

A survey between the neuromuscular centers or the neuropediatric institutions in Germany did not reveal any further evidence of children with spinal muscular atrophy who were not included in the screening. Thus, the sensitivity of SMA-NBS was 98%.

While during the pilot project all suspected findings could be confirmed (67/67), after the start of general screening. diagnosis was confirmed in 46/50 cases (92%) and not confirmed in 8%. All these false positive results occurred in the first 2 months after beginning of nationwide screening. The screening laboratories were informed about the problem. They then reviewed and modified the screening process.

In one false positive case confirmation showed two normal copies of exon 7 of the *SMN1*-gene, in 2 cases a heterozygous deletion of exon 7 was detected and in one case laboratory diagnosis had to be repeated due to inconsistent results in different parts of the dry blood card.

During the pilot projects, none of the children tested showed only one *SMN2* copy, 46% showed two copies, 24% three copies, 26% four copies, and 4% showed five or more copies. After expansion of screening to all of Germany, 2% showed one *SMN2*

copy, 43% two copies, 28% three copies, 22% four copies, and 4% five or six copies.

AAV-titer

AAV titer determinations were ordered in 36/50 children. On average, blood samples were taken on the 12th day of life. In these cases, a titer <1:50 was found in 97% and a titer of 1:200 in one child.

Incidence of genetically proven spinal muscular atrophy

Based on an estimated number of 795000 newborns per year in Germany and a participation rate in the NBS of 99% the calculated annual incidence was 1:8554 following the nationwide screening. During the pilots between January 2018 and September 2021, the incidence based on the number of screenings performed was 1:7637.

Treatment decisions

After confirmation of the diagnosis of SMA, 52% of parents opted for therapy with omnasenogen abeparvovec, 14% for treatment with nusinersen, 16% for therapy with risdiplam, and 18% for a wait-and-see strategy.

In the group with two *SMN2* copies 85% opted for gene replacement therapy, 15% for nusinersen therapy. In the group with three *SMN2* copies 11/15 (73%) of children received onasemnogene abeparvovec, 2/15 (13%) nusinersen and 2/15 (13%) risdiplam. In children with four or more *SMN2* copies, in whom only nusinersen or risdiplam are available according to the European approval, 50% of parents favored treatment with risdiplam, and 50% favored a wait-and-see strategy under clinical observation.

In patients in whom therapy was started, it began on a mean age of 31.9 days (median 26 days, range 13–66). Corrected for gestational age therapy started in the group with 2 and 3 copies of *SMN2* at a mean gestational age of 42.5 weeks (range 38.5–48.7).

The mean time between receipt of confirmation and start of therapy in the group with 2 or 3 *SMN2* copies was 14.3 days.

One child received "bridging therapy" with nusinersen prior to gene replacement therapy due to cholestasis. The child received three injections of nusinersen prior to gene replacement therapy at the age of 11 weeks.

DISCUSSION

In this paper, we present the experience gained in Germany during the transition from the pilot project of newborn screening for SMA to nationwide screening. When moving from a pilot project involving a strictly limited number of stakeholders, who are usually committed to the success of the project, to a nationwide screening with multiple stakeholders, some difficulties are to be expected. Regarding laboratory diagnostics, in Germany NBS is performed by 11 laboratories, which are free to choose the PCR methods used. Confirmatory diagnostics can also be performed by the laboratories cooperating with the respective local centers according to their own standards. Recent data has shown that estimating the *SMN2* copy number in particular can be critical [14]. Organizational structures in the cooperation between neuromuscular centers, obstetric clinics and screening laboratories cannot be assumed to exist, since the previous NBS almost exclusively concerned metabolic and endocrine diseases.

It turns out that early involvement of all stakeholders in the field is necessary. Together with patient advocacy groups and professional organizations common criteria were defined. It was agreed that centers that should care for newborns with suspected spinal muscular atrophy in NBS should have several years of experience in the field of spinal muscular atrophy and should be able to offer all currently available therapies. Only in this way an open-ended consultation seems feasible.

A successful screening program requires that both parents and all professional partners are convinced of the benefits of the program. With respect to parents, there is concern that uncertainty about the use of data obtained from newborn screening may lead to unwillingness to participate in screening programs [15]. As we saw in the pilot projects, the fact of genetic screening does not affect parents' willingness to screen [11]. Nevertheless, continued information to parents about the usefulness of newborn screening in a variety of lay media with the widest possible dissemination seems necessary. Especially the information that therapies are available, that an early diagnosis leads to a better therapeutic outcome is essential for the positive evaluation by parents. However, it can be assumed that for most parents it is not the information about the specific clinical picture that is decisive, but a general assessment of the benefits. In a study in Japan, 99% of the parents interviewed considered screening to be useful, although not a single respondent knew

Table 2
Time to treatment in the German pilot projects and in the first 6 months of nationwide SMA-screening

	Pilot-project	Nationwide SMA-NBS
Number of patients with suspected SMA	67	50
Confirmed patients	67	46
Median time to information of physicians about suspicion of SMA (days)	6 (3–15)	7 (4–15)
Median time to information of parents (days of life)	7 (6–45)	8 (4–15)
Median time to genetic confirmation of diagnosis (days of life)	13 (9–14)	13 (9–19)
Median time to first appointment at neuromuscular center (days of life)	8 (6–54)	10 (5–46)
Median Time to start of treatment (2/3 copies) (days of life)	19 (7–728)	26.5 (13–66)

about the disease spinal muscular atrophy [16]. The approval rate for NBS in Germany is also in the range of 99% [17].

Especially at the beginning of nationwide NBS, lack of information about essential steps to take after receiving a suspicious finding and the nearest contact persons can lead to a delay in the process. This results in the need to provide necessary information and contacts on an easily accessible platform.

Patient information is a critical issue in any newborn screening program. Both the initial notification of patients of suspected SMA and the discussion of confirmation diagnostics requires both factual and communication skills. All experts involved in the selection of centers agreed that a dedicated team responsible for this process needs to be available. A similar model is being implemented in other countries [18].

In everyday life, parents generally look to the Internet as their first source of information. For this reason, we have also included brief information on newborn screening on the treatment center page. However, it has become apparent that, given the very diverse ethnic backgrounds of families, information must be available in as many languages as possible to meet the need for information. While comprehensive information about the clinical picture of SMA in all its variants can be found on the Internet, there is still a lack of sufficient information in layman's terms about the special situation of children treated very early, possibly even pre-symptomatically.

In contrast to the pilot project, in which no false positive findings were observed, four children had false positive findings in the first two months after the start of nationwide screening. The findings were reported back to the screening laboratories and led to modifications in the technical procedure. Given the enormous psychological impact of a false positive result on the family, care must be taken to ensure that the number of false positives approaches zero [12, 19]. Figures such as 61% of suspicious results which could not be confirmed in a pilot project are definitely too high [20]. To improve the quality of NBS, both preanalytical and analytical problems need to be addressed. Especially in the initial phase of other NBS programs, a rather high number of false positive results was observed in some projects, which improved as SMA-NBS became more established. This clearly demonstrates the need for feedback between treatment centers and screening laboratories.

In the period after the initiation of nationwide SMA NBS one patient with a compound heterozygeous mutation was detected who was missed by the NBS. Due to the fact that NBS is not allowed to screen for heterozygeous carriers this cannot be avoided. A similar case was found in the Belgium NBS project [21]. It underlines the necessity to inform the neuropediatric community about this blind spot of the NBS and about the necessity to extend genetic testing to sequence analysis in cases with a heterozygeous mutation and a clinical suspicion of SMA as proposed by the treatment guidelines by Cure SMA working group [22]. Other patients who were not detected by the newborn screening have not been noticed so far. Of course, it must be mentioned that the observation period is still short and that any forms that may occur at a later stage may not yet be clinically conspicuous.

In general, the availability and timing of targeted therapy is one of the cornerstones of any successful SMA-NBS program. The lack of accepted reimbursement for therapy in presymptomatic children is one of the major obstacles in some countries [23]. Time to treatment is largely influenced by non-medical factors such as transport time for blood testing, time to obtain insurance, and time to approve required reimbursement for therapies, in addition to medical issues

such as time for genetic confirmation of suspicious findings, elevated liver enzymes, or AAV antibodies [24]. Care must be taken to minimize the time necessary to complete the various steps before treatment can begin. Depending on the structures in place in different countries, the time to notify families of the suspicious finding varied from 8 to 11 days after birth. The median start of treatment in patients with 2 or 3 SMN2 copies varied from 19 days after birth in our pilot study to 34 days [19, 24]. Knowing that at the time of the first clinical examination, up to one third of patients already show the first symptoms of SMA [19, 25], shortening this period is an important goal. For this reason, it is important to follow all children diagnosed with SMA-NBS and to reanalyze from time to time the problems during the process from screening to initiation of treatment.

The results of the present study show that, with appropriate preparation, it is possible to extend newborn screening without a significant loss of speed or quality. Only the time until confirmation diagnostics and *SMN2* copy number were available was slightly longer than in the pilot project. This clearly shows how important it is to establish a close cooperation between molecular genetics and treatment centers at an early stage. Experiences from other programs show that these times can be further shortened with longer duration of the screening program and thus better-established procedures [21].

SMN2 copy number is generally considered a major modifier of disease severity and response to therapy [26]. Quantification is thus considered crucial for the selection of therapeutic options. In Germany, gene replacement therapy is only available for SMA patients with 2 and 3 *SMN2* copies. Risdiplam is so far in Europe only approved for children older than 2 months, whereas nusinersen is approved for the entire spectrum of 5q-associated SMA. As our data show, a timely determination of *SMN2* copy number is feasible if follow-up is performed by centers where established diagnostic structures exist. In the children included in nationwide NBS in Germany, this was predominantly done by certified neuromuscular centers. This highlights the need for pre-selection of follow-up centers.

While at the beginning of the pilot project a large uncertainty regarding the outcome in early treated spinal muscular atrophy complicated the counseling of parents, data are now available from several centers that allow a better estimation of the prognosis in early therapy [25]. While the prognosis for children with 3 *SMN2* copies can be considered very good with timely treatment, a somewhat worse outcome for children with 2 *SMN2* copies, however, must also be discussed with the parents. Corresponding data can be found in pilot studies as well as in clinical trials with presymptomatic patients [8].

In our study, most parents of children with 2 or 3 copies of the *SMN2* gene were in favor of treatment with onasemnogene abeparvovec. Similar experiences have been reported by other research groups [24, 27]. However, a proportion of parents prefer RNA-based therapy mainly because of what they perceive as the unclear risk of gene replacement therapy. The lack of timely cost coverage by the health insurance is another reason that leads to a change of the therapy decision in individual cases. From our point of view, it seems important that parents are informed as objectively as possible about the benefits and risks of the individual therapeutic strategies.

Based on current data, the timing of treatment initiation is much more important than the choice of one of the targeted drugs [12, 28, 29]. For this reason, it is reasonable to perform SMA-NBS even at a time when not all treatment options are available.

In the case with 1 *SMN2* copy, the decision was made to choose a purely palliative path. Overall, the indication of disease-modifying therapy in this particular situation is seen as problematic even if lesser progress is possible in individual cases [30, 31]. For ethical considerations, a palliative pathway is preferred by some authors. In this difficult situation, it is useful to allow a broader opinion to be formed through close interaction between neuromuscular centers.

Two of these were premature infants who did not yet meet the formal criteria for gene replacement therapy. The main problem in this situation is the knowledge that, on the one hand, progressive loss of motor neurons can occur before the calculated date of birth and, on the other hand, the safety profile of all three available substances is not sufficiently known for premature infants. In the meantime, it has been suggested to start the therapy at the latest at the 37th week of gestation [32].

In children with 4 *SMN2* copies, a majority of the participating centers decided together with the parents to start therapy as early as suggested by the recommendations of the American ad-hoc committee [33, 34]. The discussion about this group is still ongoing. However, the fact that newborn screening has not led to an increase in the incidence of SMA compared with known figures in the German population [35] suggests that most children in this group

will develop the disease, i.e. the number of long-term asymptomatic patients will be vanishingly small.

There is no generally accepted opinion on which drug should be used in these patients: In contrast to the U.S., onasemnogen abeparvovac is not approved in the EU and Canada for patients with ≥4 SMN2 copies because there are insufficient trial data on efficacy and safety for this patient population [36]. Given the less severe disease course expected in patients with ≥4 SMN2 copies, we believe further analysis of the benefit-risk ratio of gene replacement therapy in this patient group is warranted at this time.

In summary, our data confirms the possibility to expand a genetic NBS from a small, well defined pilot group to nationwide implementation with no loss of speed and quality.

CONFLICTS OF INTEREST

Becker, M.: owner of a commercial entitiy (Labor Becker, Munich, Germany)

Blaschek, A.: speaker honorarium Roche

Brockow, I.: nothing to declare

Burggraf, S. : nothing to declare

Cirak, S. : scientific advisory board Novartis gene therapy

Durner, J.: nothing to declare

Eggermann, K.: nothing to declare

Flotats-Bastardas, M.: scientific advisory board for Biogen, Avexis, Roche. Travel expenses from Biogen. Speaker fees from Avexis.

Friese J: scientific advisory board Novartis gene therapy

Gläser, D. : nothing to declare

Hagen,v.d. M.: member of a scientific advisory board for Avexis, Biogen, Novartis, Pfizer, Roche and Sarepta and received travel expenses and speaker fees from Biogen, Avexis, PTC, Pfizer, Roche, Sarepta

Hahn, A. : scientific advisory board for Biogen, Novartis Gene therapies and speaker fees from Biogen, Novartis Gene Therapies, PTC and Sanofi-Aventis

Hannibal, I. : nothing to declare

Hartmann, H.: nothing to declare

Horber, V-: participated in workshops and received compensation for advisory boards from Novartis and Biogen

Illsinger, S. : scientific Advisory board Novartis

Johannssen, J.: scientific advisory board participation and/or lectures and/or manuscript writing from Avexis/Novartis, Biogen, Roche, PTC, Pfizer and Sarepta

Kirschner, J.: Received honoraria for consultancy/educational activities and clinical research from Biogen, Novartis, Roche and ScholarRock.

Köhler, C.: honoraria for lectures from PTC, Biogen, Roche, Sanofi-Genzyme

Kölbel, H.: scientific advisory board for Novartis and received travel expenses and speaker fees from Biogen and Sanofi-Aventis

Moers von, A. : nothing to declare

Müller, Ch.: nothing to declare

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AUTHOR'S CONTRIBUTION

Wolfgang Müller-Felber, Astrid Blaschek and Katharina Vill conceptualized and designed the clinical study, co-drafted the initial manuscript, collected clinical data, and reviewed and revised the manuscript.

Oliver Schwartz, Uta Nennstiel, Inken Brockow, Heike Kölbel, Christine Müller, Iris Hannibal, Ulrike Schara, Arpad von Moers, Regina Trollmann, Jessika Johannssen, Andreas Ziegler, Sebahattin Cirak, Andreas Hahn, Maja von der Hagen, Claudia Weiss, Gudrun Schreiber, Marina Flotats-Bastardas, Hans Hartmann, Sabine Illsinger, Astrid Pechmann, Veronka Horber, Jan Kirschner, Cornelia Köhler collected clinical data and reviewed the manuscript.

Siegfried Burggraf, Wulf Röschinger, Marc Becker, Jürgen Durner,Bernd Olgemöller developed the NBS method used in the pilot projects.

Dieter Gläser, Brunhilde Wirth and Katja Eggermann performed the genetic confirmation and the SMN2 copy number determination and reviewed the manuscript.

All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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The Cystinosis Foundation initiated, designed, and conducted the pilot project for genetic newborn screening for SMA and cystinosis in Germany in 2017. Within this pilot project (in the period from January 2018 to May 2019) 200,901 newborns were tested and a total of 29 newborns with a homozygous deletion in the SMN1 gene were identified [37]. The "Initiative SMA, Deutsche Gesellschaft für Muskelkranke" supported the pilot project from June 2019 to September 2021. Biogen, Novartis, Roche contributed to the pilot project.

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