Editorial

April 8, 2024

Universal Newborn Screening for Spinal Muscular Atrophy

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JAMA Pediatr. 2024;178(6):520-521. doi:10.1001/jamapediatrics.2024.0489

Evidence of benefit is often viewed differently by regulators, clinicians, and patient communities. This is especially true in rare disease. Newborn screening (NBS) for spinal muscular atrophy (SMA) has been gradually implemented worldwide, yet is not universally available.[1] There is no doubt that initiating disease-modifying therapy (DMT) earlier in newborns who will otherwise develop symptoms of SMA in infancy or childhood results in improved outcomes.[2] The magnitude of this benefit is dependent on *SMN2* copy number, clinical condition at treatment onset, and time to treatment initiation. In this context, improving the processes to remove barriers for rapid diagnosis confirmation and treatment onset is key. However, not all newborns identified with SMA will develop symptoms in childhood; this is especially true for those with 4 or more copies of *SMN2*. While genetic confirmation of SMA is relatively easy and approximately 96% of patients can be diagnosed with simple qualitative assays,[1] *SMN2* copy number determination requires quantitative methods that are not easily implemented in most laboratories. A discrepancy of up to 69% between laboratories[3,4] or even within the same laboratory in the assessment of copy numbers has been shown, especially with higher *SMN2* copy numbers, which calls for in-depth research into the impact of the *SMN2* genotype on response to treatment.[5] In the 4% of individuals with SMA who have mutations not detectable by polymerase chain reaction–based NBS, diagnostic delays will possibly get longer with reduced experience of clinicians to recognize early signs of SMA. Whole-genome sequencing–based NBS could potentially enable detection of these individuals in the future.

Weighing the potential for harm and creating a realistic health economic model are dependent on good data. The best evidence would be generated from the perfect counterfactual model, where time travel would enable the same infants to undergo or not undergo NBS and have the outcome measured, but this is unattainable. Without time travel, the method used to ensure the 2 experimental groups are interchangeable is randomization. Short of this, presymptomatic SMA pivotal trials have used a historic comparator group of symptomatic infants. While this approach provides a clinically intuitive comparison point, especially when objective outcomes are used, there is a risk of bias limiting the internal validity of these studies. Historic cohorts differ substantially from the experimental group—as clinical standards have significantly evolved over time, time to diagnosis has potentially shortened, and historic cohorts would not include newborns who did not develop symptoms in childhood. In addition, approximately 40% of infants identified by NBS with 2 copies of *SMN2* present with symptoms at the time of treatment[2,6] and would not have been included in presymptomatic trials.

In rare disease, there is lost opportunity to inform clinical decisions when data are not systematically captured from clinical encounters. While registry data can be fraught with methodological challenges that often reduce their consideration in regulatory decisions, the Registry Evaluation and Quality Standards Tool (REQUEST) is available to guide evidence developers to optimize their data quality and ensure their data can be used for this purpose.[7] SMARTCARE provides a platform to collect longitudinal routine clinical data on patients with SMA in Germany, Austria, and Switzerland and presents an excellent model. It is financed by industry, with explicit contracts giving the investigators full oversight and ownership of the data generated and published while enabling industry to fulfill their duty in continuing long-term data collection after approval.

The SMARTCARE study group present an important addition to the body of evidence supporting NBS for SMA by looking at real-world effectiveness of NBS.[8] Effectiveness will include infants who are treated late and are already symptomatic, ie, infants who would have otherwise been excluded from the presymptomatic clinical trials. When counseling families of infants identified through SMA NBS programs or when building a health economic model for these programs, it is important to consider potential outcomes based on effectiveness studies rather than efficacy in presymptomatic treatment trials. Although no randomized trial of newborns with SMA will ethically ever be conducted, a parallel group comparison within comparable populations with similar health care access is the best available evidence to inform these decisions. In Germany, a pilot NBS program in 2 regions enabled a nonrandomized experimental cohort study at a time when the registry platform was already in place to capture outcomes systematically. The authors rightfully argue that infants born across Germany were interchangeable and the care standards were reasonably similar across the country. While the NBS cohort demonstrated clear benefit compared with the clinical symptom onset (CSO) cohort (40% of patients with NBS can walk independently at 18 months compared with 5% in the CSO cohort), none of the infants in the NBS cohort who already demonstrated symptoms before treatment initiation attained independent ambulation by 18 months. Shortening time to treatment in infants with 2 *SMN2* copies is needed to optimize outcomes, as many have motor neuron loss beginning in the third trimester of pregnancy. Treatment choice in both cohorts showed approximately two-thirds receiving onasemnogene abeparvovec either

by itself or after a bridge with nusinersen (28 of 44 in the NBS cohort and 138 of 190 in the CSO cohort), with a greater number of adverse events noted in the CSO cohort, some needing hospitalization. Although most countries provide no further DMTs accessed after onasemnogene abeparvovec, with expected long-term effects in nonreplicating motor neurons, longer-term follow-up of the SMARTCARE cohorts will be valuable to demonstrate variations in treatment choices after onasemnogene abeparvovec.

The SMARTCARE study also contributes data that can inform the estimation of direct medical cost-saving in the group of patients identified by NBS. Of note, data to inform estimation of nonmedical or indirect costs, which account for a major part of SMA-related costs, were not reported. The cost of DMTs for SMA is very high; however, the cost of symptom management over a lifetime is even higher.[9] Patients identified by NBS in Germany were approximately 10 times less likely to receive no ventilatory support at the end of follow-up vs 8.4% in the other group who required permanent ventilation support. Increased cost in patients after symptom onset and not through NBS will also result from hospitalizations, which are 3.8 times more frequent. Similar estimation can be conducted on the cost of nutritional support, which was 12 times less frequent in the NBS group in Germany. Equipment needs can be estimated by the percentage of patients who have achieved and maintained the ability to walk independently, which is approximately 4 times higher in the NBS group. It is very likely that other direct costs will be similarly favorable for the NBS cohorts in the future, such as scoliosis management, which will be incurred at a later age. Altogether, these data support the recent health economic models that demonstrated a negative incremental cost-effectiveness ratio of SMA NBS when compared with costs associated with delayed diagnosis after symptom onset. In other words, years of life and quality of life saved by NBS not only do not cost money but also save money for the community.[10-14]

Immediate implementation of NBS in countries where DMT is available for SMA constitutes a medical, ethical, and economic emergency. It is also a matter of equity, as diagnostic delays are impacted by both geographic and socioeconomic factors and NBS offers more equitable access to diagnosis and care. The next step is the identification of patients with point mutations, which can be achieved by whole-genome sequencing, a method of screening that is currently implemented in several pilot studies.[15] For couples who choose to carry the affected pregnancy, noninvasive in utero testing could lead to therapeutic trials for in utero treatment or to elective late prematurity to allow treatment initiation before permanent loss of motor neurons occurs.[16] The worldwide universal implementation of NBS, as well as optimization of the current NBS strategy, will be driven by evidence-based consensus. This carefully conducted SMARTCARE study unequivocally demonstrates the middle-term benefit of NBS at both the individual and community levels.

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Published Online: April 8, 2024. doi:10.1001/jamapediatrics.2024.0489

Conflict of Interest Disclosures: Dr Oskoui reported grants from Roche, Novartis, and Biogen outside the submitted work. Dr Dangouloff reported grants for Project NBS SMA from Biogen, Roche, and Novartis, and lecture fees from Novartis, Roche, and Biogen outside the submitted work. Dr Servais reported personal fees and grants from Roche, Biogen, Novartis, Scholar Rock, BioHaven, and Zentech, and personal fees from Illumina outside the submitted work. No other disclosures were reported.

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