INVITED COMMENTARY

Early Check: A North Carolina Research Partnership

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Newborn screening programs rely on understanding the benefits and harms of screening, but the rarity of conditions hampers generation of high-quality data. The Early Check study, a partnership between North Carolina nonprofit, academic, and state organizations, is filling this gap by screening for conditions not included in standard newborn screening.

Newborn screening is a highly successful state-based public health program which the Centers for Disease Control and Prevention (CDC) recognized in 2011 as one of the top 10 public health achievements to date in the 21st century [1]. Although newborn screening programs have been in place for over 50 years in most states, the introduction of tandem mass spectrometry allowed for the expansion of the newborn screening panels, with 35 conditions currently recommended for inclusion in newborn screening [2, 3]. Although newborn screening panels are state-specific, with each state making an individual determination on what conditions should be on the state panel, a federal committee (the Advisory Committee on Heritable Disorders in Newborns and Children), evaluates evidence and makes recommendations for conditions to be included on a Recommended Uniform Screening Panel (RUSP). With emerging research on diseases and the development of new treatments, more conditions are being proposed for inclusion in standard newborn screening, and these conditions will need to be evaluated to determine if they meet the criteria for inclusion.

Inclusion of a condition in newborn screening requires that detection and treatment of a condition soon after birth improves outcomes for affected newborns, justifying the requirement for nearly universal screening shortly after birth. However, policymakers are often faced with limited data on the incidence, clinical spectrum, laboratory assay performance, and the benefits and harms of screening. This lack of data can result in the need for a decision about including a condition in newborn screening without the policymakers having confidence that they have all the necessary information to make a fully informed determination.

High-quality data on conditions for newborn screening is difficult to obtain primarily because the conditions are so rare. All conditions currently recommended for the RUSP are rare, but incidence can range from 1 in 5,000 births (eg, congenital hypothyroidism) to 1 in 250,000 births (eg, maple syrup urine disease) [4]. Adding to the complexity, many of the new conditions being considered for addition to newborn screening have marked heterogeneity in clinical presentation, severity, and age of onset; screening may identify individuals with clinically insignificant disease or individuals with the onset of clinical symptoms in adulthood. Decision-making is further complicated by disease advocates who are increasingly promoting inclusion of conditions, even in the absence of compelling evidence that newborn screening will improve outcomes for affected newborns [5].

There is a need to proactively generate data on conditions that are on the horizon and may be considered for newborn screening in the future. The Early Check research study in North Carolina is filling this evidence gap by offering optional screening for an additional panel of conditions not currently included in standard newborn screening. Newborns who receive standard newborn screening in North Carolina are eligible to participate, and mothers can provide permission for this additional research screening after 13 weeks gestation up until four weeks after birth. Mothers sign up for the study online at the secure project website www.earlycheck.org, and the laboratory testing is performed on the dried blood spot specimen that is left over after standard newborn screening is completed. Any newborns that have a positive test receive confirmatory testing and short-term follow-up, and the family is connected to supportive, clinical, and informational resources. The family is also invited to participate in longitudinal research studies that will provide routine developmental assessments of their child and generate additional data on the natural history of the condition. The initial panel of Early Check conditions includes fragile X syndrome, a genetic cause of intellectual disability, and spinal muscular atrophy, a severe neuromuscular condition. Recruitment started in October 2018 with current funding to continue the program through 2021.

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A North Carolina Collaboration

Early Check is a large-scale study, operating statewide in North Carolina and offering screening to parents of all 120,000 babies born in North Carolina each year. This large scope is only possible because of the combined resources of all partnering institutions. No individual partner has the expertise, capacity, or resources necessary for successful execution of the study, which requires significant effort for recruitment, consent, laboratory screening, medical follow-up, developmental assessments, and long-term follow-up. RTI International (RTI), a nonprofit research institute located in Research Triangle Park, is leading the overall study and performing outreach, recruitment, laboratory screening, developmental follow-up, and genetic counseling. The North Carolina State Laboratory of Public Health (NCSLPH), which performs standard newborn screening in North Carolina, facilitates recruitment and laboratory screening. Clinical follow-up, including additional genetic counseling, takes place at the University of North Carolina at Chapel Hill (UNC). Wake Forest University contributes expertise in medical ethics and informed consent, and Duke University contributes laboratory expertise and experience conducting clinical trials for new treatments.

Researchers at RTI International, UNC, Duke, and Wake Forest applied for and obtained substantial federal and nonprofit support for the study, while also building the capacity and expertise to organize and execute a large research study that could obtain consent from over 120,000 mothers per year, perform the laboratory screening, and provide clinical follow-up for those babies who screen positive for a condition. However, a screening study led by RTI and the academic partners alone without support from a state partner would, by necessity, likely recruit from only academic medical center settings. This would result in overall fewer newborns enrolled in the study, a less diverse study population, and a requirement for a separate collection of a dried blood spot from the newborn. In contrast, the North Carolina newborn screening program collects newborn screening dried blood spot samples from over 95% of all newborns born in North Carolina but does not have the capacity to perform such a large research study.

RTI and academic partners sought to partner with the North Carolina newborn screening system to make it feasible to offer screening for thousands of babies, and all partners recognized the potential benefit of data generated by the study, given that it could be designed to obtain the appropriate opt-in parental informed consent. Early Check is an example of how a large research study with significant public health impact can be performed by a research team working in conjunction with a state public health system. The research team works in parallel with—yet separate from—standard newborn screening public health activities. This approach enables the study to leverage resources not otherwise available to an individual organization, producing an overall study with the potential for large-scale public health impact.

Generation of Data Relevant to Policymaking in North Carolina and Nationally

The Early Check research study will generate a large volume of valuable data relevant to newborn screening and other public health activities. It will gather information on the performance of the screening assay, incidence of the condition, the clinical spectrum of disease in identified newborns, the impact of screening on the family, and the benefits and harms of screening—all data that will aid future newborn screening decision-making for any condition included on the Early Check panel. Having Early Check as a North Carolina resource to generate data on these conditions will improve policymakers’ ability to make evidence-based, well-informed choices for newborn screening programs.

Beyond data that is directly relevant to newborn screening, the study will demonstrate the feasibility of recruiting thousands of study participants through low-touch recruitment methods like social media campaigns and could provide a model for other ways that entire populations could engage with the public health system or other research studies. If proved to be successful, the Early Check methods of outreach and virtual engagement with research participants could be used in other population-based studies or by public health systems to reach people across the state. In addition, Early Check will test the use of novel technology for newborn screening follow-up, including tele-genetic counseling, that could subsequently be implemented by a state newborn screening program to decrease costs and increase the capacity for short-term follow-up for newborn screening.

A Choice for North Carolina Parents to Receive Additional Screening for their Newborn

Early Check is an opportunity for interested North Carolina parents to obtain additional screening and information about their individual newborn free of charge. In addition, parents’ participation allows them to contribute to newborn screening research that may benefit children born in the future. Some parents may not want additional screening, for example if it would cause them increased anxiety or if they do not want to participate in research, but the choice remains for those parents who do want the additional information. If a newborn is identified with one of the conditions being screened for, parents will receive genetic counseling, confirmatory testing, and follow-up assessments. In addition, parents can access earlier medical care, learn about the consequences of the condition, and seek social support from other parents of affected children. As a result, parents may be able to prepare for future challenges, enabling them to better care for their child as the child and family are impacted by a serious condition.
Early Check as a Flexible Infrastructure in North Carolina

Early Check is intended to be a long-term flexible infrastructure that can continue to generate valuable data for newborn screening policymakers, clinicians, researchers developing new treatments, and patients. Conditions can be added or removed from the Early Check panel as needed. As knowledge is generated, conditions may “graduate” from Early Check when they are recommended for standard newborn screening, and new conditions that may be considered for future inclusion in newborn screening could be added to the Early Check panel. Although adding a new condition to Early Check will require establishing new follow-up protocols, laboratory assays, and other condition-specific activities, all other aspects of the study will already be in place. The infrastructure will allow for a nimble newborn screening research program that is less costly, more efficient, and faster to respond to emerging needs in newborn screening research and policy. With the rapid development of new treatments for disease, many more conditions may be good candidates for newborn screening in the future, and it will be important to test the benefits and harms of screening for these conditions. The Early Check infrastructure will have the flexibility to quickly implement studies and be a resource that can respond to new needs for evidence in the larger newborn screening ecosystem.

Conclusion

Early Check is a large-scale North Carolina study only made possible because academic, nonprofit, and state organizations have come together to build a statewide research infrastructure, leveraging the resources and talents of each partner. The resulting research program has a scope otherwise unobtainable through smaller research studies based at an individual organization and will generate data directly impacting newborn screening policymaking decisions at both the state and federal levels. North Carolina, as an entire state, can make a substantial contribution to the overall newborn screening ecosystem as newborn screening programs continue to grapple with the addition of new conditions to newborn screening panels. In addition to supporting the overall system, Early Check will provide North Carolina parents a choice to receive additional testing for their child free of charge, giving parents of an affected child the opportunity to access earlier clinical and supportive care. Finally, Early Check will provide a flexible research infrastructure through which all study stakeholders, including both study participants and study partner organizations, can have a future translational impact on newborn health.

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