



Genomic Newborn Screening Studies Around the World Begin to Take Baby Steps

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NEW YORK – Newborn screening (NBS) has been a part of public health programs in many countries for decades, focusing on a limited number of rare diseases with onset in early childhood and established treatments.

Tandem mass spectrometry is currently the technology of choice for most NBS programs. But with genome sequencing becoming cheaper and quicker, and its success in diagnosing rare genetic disorders in sick infants, researchers have started to explore whether it could also find a place in newborn screening as a complement to existing programs.

The idea is not without controversy. Experts and the public have raised concerns about data privacy and security, especially if a child's genome is to be stored indefinitely. Parents have been worried, for example, by [recent reports](#) that DNA analyses on samples from existing newborn screening programs were used by US police in criminal investigations.

It is also an open question whether universal genomic newborn screening would be cost effective, and how much of a benefit it would provide to children with rare diseases by diagnosing them earlier and offering them access to effective and potentially life-saving treatments in a timely manner.

Given the low incidence of many of the 7,000 known rare diseases — though in total, they add up to 25 million to 30 million patients in the US — pharma firms developing drugs for rare conditions are eager to identify potential participants for their clinical trials, and at a younger age.

As the number of genetic diseases considered "treatable" is rapidly expanding, gene and variant lists for genetic newborn screening will also need to be frequently adjusted. It is unclear, though, how infants with a pathogenic mutation who do not show disease symptoms yet should be treated or managed.

Finally, parents may have different ideas than researchers regarding what types of conditions they



want to learn about in their children. Enrollment in genomic newborn screening research studies may also differ between population groups, potentially leading to disparities.

To address many of these questions, research studies around the world are starting to get off the ground, ranging in size from 1,000 to more than 100,000 infants. At the inaugural International Conference on Newborn Sequencing (ICoNS) in Boston last week, eight of these endeavors — based in the US, Europe, and Australia — provided outlines of their plans and goals.

BabySeq

When the original BabySeq project — a randomized controlled trial of newborn genome sequencing conducted at Brigham and Women's Hospital and Boston Children's Hospital — [got underway in 2013](#), with funding from the National Institutes of Health's Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program, it was fiercely criticized for being "unethical and inappropriate," recalled Robert Green, professor of medicine at Harvard Medical School and one of the study's principal investigators. Uptake was modest at the time — Green said that people generally don't like to participate in randomized studies, where they might not receive the intervention — and the project ended up enrolling 325 newborns and sequencing the exomes of 159. Of those, 9 percent [were found](#) to have a risk variant for a childhood-onset disease and another 2 percent for a later-onset condition. Many of the 18 children with monogenic disease risks had a change in their medical care, Green noted, as described in a *MedRxiv* [preprint](#) from his team earlier this year. A new iteration of the project, [BabySeq2](#), aims to enroll at least 1,000 infants from diverse populations in Boston, New York City, Philadelphia, Detroit, and Birmingham, Alabama, and use whole-genome sequencing to determine their disease risks.

GUARDIAN

Researchers in New York, meanwhile, are planning a couple of studies on a larger scale. The [GUARDIAN project](#) (Genomic Uniform-screening Against Rare Diseases in All Newborns), led by Wendy Chung at Columbia University Irving Medical Center in partnership with NewYork-Presbyterian, the New York Department of Health, Sema4's GeneDx, and Illumina, hopes to enroll 100,000 newborns over the next four years. The study, funded by Sema4, Illumina, and philanthropic sources, plans to use whole-genome sequencing to assess risk for an initial 250 conditions, the majority of them treatable, a number that will increase over time. Chung said that uptake has been 70 percent so far and 250 babies have been enrolled.

ScreenPlus

The ScreenPlus study, on the other hand, led by Melissa Wasserstein at Albert Einstein College of Medicine and the Children's Hospital at Montefiore, in collaboration with the New York State Department of Health, is screening infants using biochemical testing, though it might collaborate with some of the other, genome-centric programs in the future. The study, announced in 2019 and funded by NIH, along with a long list of pharmaceutical and patient advocacy sponsors, plans to enroll 175,000 babies at nine hospitals in New York that include Mount Sinai, North Shore University Hospital, NYU Langone, and Stony Brook University Hospital.

In addition to routine newborn screening, the New York State lab is testing babies in the study for another 14 disorders, all of which have FDA-approved treatments or therapies in clinical trials. Those screening positive go on to second- or third-tier confirmatory testing, including disease gene sequencing. The study also wants to follow patients over time to see if early detection has a benefit and to develop guidelines for follow-up. About 65 percent of parents approached so far have decided to join ScreenPlus, Wasserstein said, despite the challenges of enrollment during the COVID pandemic, and the biggest reason for declining to participate has been privacy concerns.

Early Check

Meanwhile, the ongoing Early Check study in North Carolina, led by RTI International, a nonprofit research institute based in Research Triangle Park, in collaboration with the NC State Laboratory of Public Health, the University of North Carolina at Chapel Hill, Wake Forest School of Medicine, and Duke University, is gearing up to expand into genome sequencing. Early Check is supported by the NIH's National Center for Advancing Translational Sciences program, as well as groups including industry and patient advocacy organizations, with new funding for the new sequencing component to be announced in coming weeks.

Over the past four years, the study, presented at ICoNS by Don Bailey and Holly Peay of RTI, has enrolled almost 23,000 babies throughout the state of North Carolina, showing "remarkable diversity" in their ethnic makeup, Bailey said. It started with screening for spinal muscular atrophy and fragile X syndrome — though it no longer includes these conditions — and added Duchenne muscular dystrophy in 2019.

The new sequencing project, initially planned for three years, aims to analyze the genomes of 10,000 newborns for an initial 200 childhood-onset, monogenic conditions, study the uptake among parents, implement short-term follow-up procedures, and follow children who test positive and their caregivers for 12 months. Parents will have a choice of two panels, one with conditions that are highly actionable during the first two years of life and another with conditions that are actionable after the age of 2 or have treatments in clinical development. Starting in the summer or fall of 2023, parents can also receive a genetic risk score for type 1 diabetes for their child.

BeginNGS

BeginNGS, a [consortium](#) spearheaded by Stephen Kingsmore at Rady Children's Institute for Genomic Medicine (RCIGM) in collaboration with Alexion Pharmaceuticals, Traverre Therapeutics, Inozyme Pharma, Fabric Genomics, Genomenon, Illumina, and TileDB, differs from the other, more local projects in that it wants to provide a platform for implementing whole-genome sequencing for newborn screening, disease management and interventions, and rare disease drug development for use by partners around the world. Following a small pilot study at Rady's focusing on about 400 diseases, BeginNGS plans to enroll about 2,000 infants at seven or more sites in the US and Greece and expand to 500 disorders. Its Genome-to-Treatment (GTRx) tool is providing treatment guidelines for babies screening positive.

[Earlier this month](#), RCIGM signed a partnership with healthcare data firm PlumCare RWE and researchers in Greece to start a pilot project in that country. Funded by philanthropic sources, study

researchers plan to enroll 1,000 infants at three academic centers throughout Greece starting in early 2023, according to Petros Tsipouras, PlumCare's cofounder and CEO. Kingsmore said he hopes to implement similar projects in 20 countries, providing collaborators with protocols, knowledge, and resources from biotechnology and pharmaceutical sponsors.

Genomics England

Genomics England is in the midst of planning a genomic newborn screening study that will launch next year. Its goal is to enroll more than 100,000 newborns per year in order to find about 500 children with childhood-onset, actionable conditions annually. Later this year, the project, presented at ICoNS by Richard Scott, chief medical officer, and Alice Tuff-Lacey, program lead for the newborn genomes project at Genomics England, plans to publish a list of genes, conditions, and variants it will screen for initially. Their team is also currently running a study to help determine what type of sample is best suited for newborn genome sequencing. The new project will look into the clinical utility of genomic newborn screening along with its cost effectiveness and implications of storing genomic data over long periods of time.

Screen4Care

Across the English Channel in Europe, the Screen4Care project is preparing a multinational study. [Launched a year ago](#) with a €25.4 million (\$24.7 million) budget, the private-public partnership is funded by the European Union, the pharmaceutical industry, and academic institutions. Coordinated by Alessandra Ferlini, head of medical genetics at the University of Ferrara in Italy, and Nicolas Garnier, head of patient advocacy for oncology and rare diseases at Pfizer, Screen4Care has 36 partners in 15 countries. In a pilot study, which is close to finalizing its design, Screen4Care plans to generate targeted or whole-genome sequencing data for at least 18,000 infants and look for treatable as well as otherwise actionable diseases. In addition, it wants to use new algorithms to detect early disease symptoms in babies' electronic health records.

Baby Beyond

Down under in Australia, researchers at the Murdoch Children's Research Institute in Melbourne and their colleagues are preparing to launch a new project called Baby Beyond, funded with A\$12 million from the Australian government, that plans to enroll 1,000 newborns for whole-genome sequencing.

Parents will be consented during pregnancy, and babies' genomes will be analyzed for about 500 treatable, childhood-onset disorders. Results will go into the children's EHR, and their data will be stored for future analysis in the context of their healthcare. Lilian Downie, a clinical geneticist at Melbourne Genomics Health Alliance, explained that the project grew out of an [earlier effort](#) called Baby Beyond Hearing, which was testing infants diagnosed with hearing loss but also gave parents the option to find out about other genetic conditions, including diseases with a known treatment and those with no clear intervention. The new project is currently defining its gene list, she said, and investigators are having "heated conversations about what's treatable." There are still concerns about how feasible scale-up will be, she added.

Editor's Note: The inaugural International Conference on Newborn Sequencing (ICoNS) conference was organized by Genomes2People and Ariadne Labs in partnership with GenomeWeb.

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