



International Newborn Genome Sequencing Projects Discuss Differences, Future Goals

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LONDON – Newborn genome sequencing projects focusing on seemingly healthy babies shortly after birth are forging ahead around the world, but their approaches differ according to each country's population structure, disease prevalence, healthcare system, treatment availability, and more.

At the second International Conference on Newborn Sequencing (ICoNS), held at the Royal Institution in London last week, researchers representing 12 newborn sequencing research programs in the US, the UK, Europe, Australia, and the Middle East discussed their progress to date and future plans, along with broader discussions on healthcare economics, downstream treatment, and patient perspectives.

While some projects are in the preparation stage, others have enrolled their first infants, and at least one project has returned results to thousands of participants, among them more than a hundred positive results.

The goal of these programs is basically the same: By identifying a genetic risk for a rare disease early, the thinking goes, children can be tested further and closely monitored for phenotypes and receive treatment at the earliest possible moment when irreversible damage can still be prevented. In addition, they can be considered for clinical trials of new drugs in development. David Bick, principal clinician of the newborn genomes program at Genomics England, pointed out that treatable rare genetic diseases are both numerous and, in aggregate, common. Among 766 treatable genetic diseases, he noted, 727 are found in children, and one in 175 individuals are born with such a disorder.

Apart from differences in the timing of enrollment — prior to birth, or in the days and weeks after — and the mode of obtaining informed consent, along with what type of sample is used for sequencing and how quickly results are generated and returned to families, one notable difference among the projects is their initial "gene list," or which genes they decided to analyze for variants associated with



treatable or otherwise actionable diseases. Several presenters noted that there is only modest overlap between their own gene list and that of other projects, despite the fact that their overall goals are similar.

Newborn genome projects are also beginning to engage with existing newborn screening programs, which differ significantly among countries, ranging from the UK, which screens for only nine conditions, to the US, where the Recommended Uniform Screening Panel (RUSP), a national guideline that is followed by many states, includes about three dozen core and another couple of dozen secondary conditions.

Both keynote speakers at this year's ICoNS meeting — Sir Michael Richards of the UK National Screening Committee and Carla Cuthbert of the US Centers for Disease Control and Prevention's Newborn Screening and Molecular Biology Branch — provided perspectives of traditional newborn screening programs. In Richards' words, these aim to "do more good than harm at a reasonable cost," and in the past, they have been slow to add new conditions, mostly in order to avoid false positive results and overtreatment. Several meeting participants mentioned that the addition of hundreds of conditions through genomic testing might make parents opt out of newborn screening altogether, which has enjoyed high participation rates in many countries.

As such, it remains to be seen if, how, and when newborn genome sequencing will be integrated into traditional newborn screening, or whether it might remain a separate, optional test instead. Already, companies have started offering newborn genomic sequencing tests to parents of neonatals, such as Revvity's ViaCord. At the meeting, Madhuri Hegde, CSO and senior VP of Revvity, presented results from a [recently published](#) study of ViaCord's service. Robert Green, professor of medicine at Harvard Medical School and a co-PI of the BabySeq2 study, also mentioned during his presentation that he founded a company, Nurture Genomics, that plans to launch similar services.

Conference attendees maintained, though, that assuring equitable access to screening and treatment remains the most important ethical issue newborn sequencing programs are facing. In a poll conducted during the meeting, almost a quarter of 123 participants chose this issue as their top priority, while another quarter picked developing appropriate return of results protocols.

Likewise, asked to pick the most pressing equity issue for newborn genomic sequencing programs to address, almost half of respondents chose assuring access to follow-up care and treatment, while more than a quarter voted for universal access to sequencing. Regarding the most important outcome for harmonization across newborn sequencing projects, two-thirds of survey participants voted for clinical utility and associated measures.

A dozen projects provided updates during the two-day meeting, including many that presented at [last year's inaugural conference](#) in Boston. New this year was NewbornsInSA, a study in South Australia that plans to use a multiomics approach, including whole-genome sequencing on 1,000 newborns, but has not started enrollment yet; and the Perigenomed project in France that plans to enroll 2,500 newborns in a pilot study and will be part of the European-wide Screen4Care consortium. According to Laurence Faivre, a professor at Dijon University Hospital, Perigenomed's current gene list has only 60 genes in common with a number of existing newborn sequencing projects.

Another new project, presented by Khalid Fakhro, chief of research at Sidra Medicine in Qatar, plans to enroll 2,000 babies for a pilot study and scale up to 5,000 infants by 2025. In addition to screening for treatable inherited conditions, the project will also include polygenic risk

scores with certain conditions, such as type 1 diabetes.

Among the studies presented, the [GUARDIAN study](#), presented by Wendy Chung, chief of the department of pediatrics at Boston Children's Hospital, appears to be the farthest along. Conducted by Columbia University, NewYork-Presbyterian, and the New York State Department of Health in collaboration with GeneDx and Illumina, the project has so far approached 7,050 families, of which 5,133, or 73 percent, have enrolled and 4,256 have received results. Almost all families were consented in person and only 4 percent remotely. The cohort remains diverse with more than 30 percent of participants reporting as Hispanic, about 25 percent White, more than 10 percent Asian, almost 10 percent Black, and almost 10 percent mixed ancestry. Mean turnaround time for results has been 36 days and has been getting shorter lately.

Overall, 3.5 percent of participants have obtained a positive result, Chung reported, among them 131 true positive and 20 false positives. As an example, she mentioned a child who was found to have a pathogenic variant in the *KCNQ1* gene that has been associated with long QT syndrome 1, which appeared to be a *de novo* variant. After EKG confirmation of the diagnosis, the infant is now on a beta blocker and will have follow-up treatment by a pediatric cardiologist. The program also identified a child with a likely pathogenic variant in the *IL2RG* gene that is associated with X-linked SCID, a fatal disease without treatment that was missed by traditional newborn screening, which also looks for SCID. The diagnosis was confirmed, and the child is receiving a bone marrow transfer. Another baby was found to have a pathogenic variant in the *CDKL5* gene, which has been linked to Rett-like syndrome, and developed symptoms at the time of the genetic diagnosis. The child is now being treated with an antiepileptic drug. In all three cases, there was no family history of the conditions, Chung pointed out.

ScreenPlus, a study conducted at several hospitals in New York in collaboration with the New York State Department of Health, is focusing on adding to existing newborn screening through additional biochemical testing with genetic testing sometimes used for confirmatory testing. According to Melissa Wasserstein, chief of the division of pediatric genetic medicine at Children's Hospital at Montefiore, the project has now enrolled 11,459 infants, making up 58 percent of families who talked to a recruiter. More than 90 percent of families were consented in person in the hospital and very few after discharge or online, she noted. Even though the project provided study materials in 10 languages, consenting happened in English for 86 percent of families. The reason most often cited for not wanting to participate was that parents did not think their baby needed additional testing, followed by an unwillingness to participate in research. Wasserstein did not provide any data on how many families have received a positive finding in the study so far.

Genomics England's newborn genome sequencing program, called Generation Study, is now getting underway at UK National Health Service sites throughout England. Earlier this month, the study published a list of more than 500 genes that it has decided to analyze. These are associated with 223 conditions that usually appear within the first five years of life and have a treatment or intervention available through NHS England. According to Richard Scott, chief medical officer and deputy CEO of Genomics England, the first infants will be recruited later this year, and the program will be rolled out to up to 40 sites over the first half of next year with the aim to return results within two weeks. Alice Tuff Lacey, a program leader, added that families will be consented before birth and that umbilical cord blood will be the primary sample for analysis with newborn dried blood spot samples as a backup.

North Carolina's Early Check program, meanwhile, which [recently announced](#) a partnership with Illumina and GeneDx, is using genome sequencing to supplement the state's existing newborn screening program. In addition to screening for rare diseases — a panel of about 180 treatable conditions and an optional panel of about 30 diseases with treatments in development — it is also returning a genetic risk

score for type 1 diabetes. According to Holly Peay, director of the program and a senior research scientist at RTI International, mothers can enroll babies up to a month after birth, and the project is using the same dried blot spot sample that is already collected for routine newborn screening. Recruitment has just started, and the first samples will be analyzed this month, she said. Over the next year, the program plans to scale up and test 100 babies per week. It also will continue growing its gene panels and might consider adding another polygenic risk score, she added.

[BabySeq 2](#), the successor to Brigham and Women's original BabySeq study, continues to enroll at community health centers in several US cities, focusing on African American and Hispanic infants. The randomized controlled study will compare standard pediatric care with standard care enhanced by genomic screening and assess a variety of outcomes. According to Ingrid Holm, professor of pediatrics at Boston Children's Hospital and a co-PI of the study, 29 percent of families approached so far have declined to participate, citing a lack of interest in research as the most common reason.

Australia's BabyScreen+ study, presented last year under the name "Baby Beyond," is now recruiting pregnant women in Victoria for a pilot study of 1,000 newborns that will undergo whole-genome sequencing. Testing will be performed alongside standard newborn screening and will use the same dried blood sample. The study will analyze 604 genes associated with severe, early-onset, treatable conditions but only has 55 genes in common with a number of other newborn sequencing projects, according to Lilian Downie, clinical geneticist at the Victorian Clinical Genetics Service. She added that 100 babies have been recruited so far and 30 reports issued.

Screen4Care, a multinational project in Europe that involves 35 partners from 14 countries, has now selected a panel of 245 genes it plans to analyze, called TREAT-panel, according to Alessandra Ferlini, professor of medical genetics at the University of Ferrara in Italy. The project has almost finalized ethical reviews of newborn whole-genome sequencing or targeted sequencing studies and is completing the design of pipelines. Recruitment will likely start at a small number of sites including in Italy, Germany, France, and Greece, Ferlini told *GenomeWeb*.

In Greece, the FirstSteps study is ongoing and has been enrolling patients at three public hospitals since July, according to Petros Tsipouras, CEO of PlumCare RWE and scientific director of the program, which had partnered with Rady Children's Institute for Genomic Medicine (RCIGM) a year ago but is currently proceeding independently. More than 100 newborns have been enrolled so far, he said, and samples are being analyzed at the National Center for Research and Technology Development. There has been one positive finding thus far, he noted.

BeginNGS, a consortium that provides a platform for newborn genome sequencing projects developed by RCIGM, has enrolled 73 newborns of diverse ancestry at Rady's for a prospective pilot study that will screen for 411 rare, actionable disorders by whole-genome sequencing. So far, the pilot has seen a consent rate of 46 percent, according to Meredith Wright, a genomics scientist at RCIGM, who added that the goal is to scale the study in coming years by expanding it to other sites.

Editor's Note: The 2023 International Conference on Newborn Sequencing (ICoNS) conference was organized by the ICoNS consortium in partnership with Ariadne Labs and GenomeWeb.

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