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BabySeq: Early results of newborn genomic sequencing are mixed

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While a previous study indicated parents were very interested in newborn sequencing, just 7 percent of those approached have enrolled in BabySeq so far.

It seems like a great idea. We all have our genomes sequenced at birth, and any findings that suggest a future medical problem are addressed with early interventions, optimizing our health and extending our lives. But are parents of newborns ready to embrace the vision? Yes and no, according to interim results of a first-of-its-kind **randomized trial of newborn sequencing**. Findings from what's known as the **BabySeq Project** were presented last week at the American Society of Human Genetics (ASHG) 2016 Annual Meeting.

The NIH-funded project is led by **Robert C. Green, MD, MPH**, of Brigham and Women's Hospital and **Alan Beggs, PhD**, at Boston Children's Hospital. Thus far, the researchers have approached 345 families of infants in neonatal ICUs at the two hospitals, and 2,062 families of healthy newborns in Brigham and Women's well-baby nursery.

Although a **previous study** indicated parents were very interested in newborn genomic testing, actual enrollment was just 7 percent in each group.

"While many parents are excited about the prospect of learning about their child's genetic information, the study involves several rounds of questionnaires, a return visit to receive results and a one-year follow-up period, so not every family can make the commitment," says Beggs. "After that, uncertainties around the potential future uses of genetic information are leading many parents to adopt a 'wait-and-see' attitude."

Many parents declined to enroll their babies even before meeting with a genetic counselor, most commonly for logistical reasons. Those who did meet with the counselor received detailed information on risks and

benefits, which may well have scared some of them off. Parents cited three main reasons for declining: not wanting to learn of unfavorable or uncertain findings (38 percent), concerns about insurance discrimination (26 percent) and concerns about privacy (22 percent).

Saying yes to WES

Of the 24 NICU infants and 138 apparently healthy infants who were ultimately enrolled, half were randomized to have all their protein-coding genes sequenced — a.k.a. whole exome sequencing (WES). The other babies had only the existing, state-mandated newborn screening tests (in Massachusetts, testing covers more than 60 conditions).

Genetic counselors shared WES results only for 954 carefully curated genes: those strongly associated with childhood-onset conditions and those with lesser evidence for a link but with clinically actionable implications. To date, families of 51 infants — six NICU infants and 45 healthy infants — have gotten their results. They waited an average of 50 days, less if their baby had clinical indications for testing.

Overall, testing turned up pathogenic or likely pathogenic variants in four of the well babies. All were dominant, requiring only one copy to cause disease. Three of the variants have been linked to heart conditions, though the infants have not yet shown symptoms; two are being followed at Boston Children's. The fourth variant was linked to an enzyme defect not picked up by newborn screening. It hasn't yet caused symptoms, but the infant will likely be treated with nutritional supplements as a precaution.

Another 47 infants were found to be carriers of recessive variants, and apparently unaffected. Two infants had **pharmacogenomic** variants that could alter their metabolism of certain drugs.

Another infant had a variant in *BRCA2*, a gene linked to breast cancer. Since breast cancer is an adult disease, the team decided to get special permission from the study's ethics board to disclose the result, since the mother could also be at risk. She "was obviously concerned but grateful," Green **told *Science***.

Weighing the risks and benefits of newborn sequencing

A companion ethics study, led by researchers at Baylor College of Medicine, surveyed parents of enrolled newborns and their primary pediatricians. Asked about state-mandated newborn screening, 81 percent of parents and 97 percent of doctors agreed that it has health benefits. Conversely, 18 percent of parents and 33 percent of doctors saw risks. As for genomic sequencing, fewer parents and doctors (67 and 57 percent, respectively) saw health benefits, and more saw risks (35 and 73 percent). These included psychological distress, genetic discrimination and negative impact on the family.

Parents saw benefits not only in opportunities for early intervention, but also in knowing what to expect and for family planning. "We are finding that having detailed information about their newborn sometimes has implications for the parents themselves, or for close relatives," says Beggs. "In genetics, the 'patient' is really the whole family."

Will widespread newborn sequencing cause a surge in medical visits and testing for genetic findings that aren't clinically relevant? This question will take time to answer, as families are followed and we learn more about the effects of genetic variants. In the surveys, both parents and physicians thought genomic sequencing would have more of a role to play 10 years from now.

And so the study continues. The researchers hope to enroll several hundred additional infants and families in the coming months and assess the usefulness of WES information over time.

"This is the first rigorously designed study to examine the often-cited vision that humans will benefit from having genomic information from the very first days of life," says Green of Brigham and Women's. "We are already learning a tremendous amount about creating the process for returning genomic information in newborns, parental hopes and concerns, and the kinds of results that are emerging."

If you are a physician with a complex-care patient to refer, call Boston Children's priority line (1-844-BCH-PEDS).

Read more about the study in the ***Washington Post***, **BuzzFeed** and ***The Scientist***.

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