Hastings Report Decries Sequencing Healthy Children as BabySeq Projects Continue to Collect Data

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NEW YORK (GenomeWeb) – As the multi-site National Institutes of Health-funded Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) effort continues to study next-generation sequencing in infants and young babies, one arm of the project focused on its ethical and social aspects has largely advised against broadly sequencing healthy babies.

Published earlier this month by bioethics think-tank The Hastings Center, the report advises that although sequencing the genomes of infants can be appropriate in some specific cases, we shouldn't implement large-scale programs to test healthy babies. Similarly, the report notes that doctors should tell their patients not to use direct-to-consumer genetic sequencing to diagnose or screen their newborns.

The report was developed through meetings of the larger NSIGHT Ethics and Policy Advisory Board, which was created as part of the University of California, San Francisco NSIGHT project and comprises representatives from each of the four research sites as well as invited outside experts. According to the report, members held monthly conference calls and conducted three two-day-long face-to-face meetings over three years.

Interestingly, the listed authors of the Hastings report wrote that while the advisory board informed the recommendations, only they take full responsibility for the conclusions, recognizing that the board "did not reach agreement about every aspect."

"Some members find this report too cautious, while some think it is not cautious enough," the six lead authors wrote.

Brigham and Women's researcher Robert Green, who directs that site's "BabySeq" NSIGHT project, said that disagreements in this arena make a lot of sense.

In Green's view, questions about the value or appropriateness of sequencing the genomes of healthy people, whether children or adults, rest on three variables — harm, benefit, and cost — which exist in sometimes complicated, multi-directional tension with each other.

For example, he said, "if you imagine there is very little harm, the equation might change to focus more on benefit and cost. But if you know that the benefit is small and cost is large, then the level of harm, becomes [a crucial question.]"

According to Green, the Hastings report tries to take a broad view and is well done and well resourced. But he questioned whether recommendations of this type may be premature, considering that the research arms of NSIGHT are still early in the process of collecting, analyzing, and reporting their data.

"We have been in the weeds trying to answer these questions, [so it's tough to grapple with] the idea of issuing recommendations when we don't yet have some of the data in hand that could actually guide those recommendations," he said.

John Lantos — a Children's Mercy physician, director of pediatric bioethics at the University of Missouri-Kansas City School of Medicine, and chair of the NSIGHT ethics advisory board — said that where the Hastings report recommends against implementation of sequencing, it does so not because the authors believe there is proof that it does more harm than good, but merely because there isn't enough evidence to know yet in either direction.

"Both views, the optimists and pessimists, remain within the realm of possibility," he said.

Green and his colleagues' "BabySeq" project is one of four NSIGHT arms, only some of which are focused on harm and benefit in sequencing healthy babies.

Other projects in the consortium include research led by Stephen Kingsmore and colleagues at Children's Mercy Hospital on the impact of rapid sequencing in critically ill, hospitalized infants; the UCSF effort, focused on the potential added value of expanding newborn screening by sequencing blood spots; and the University of North Carolina at Chapel Hill program, evaluating the prospect of exome sequencing-based universal screening.

While recognizing practical and ethical pitfalls in sequencing acutely sick babies, the Hastings authors endorse this as one of the only areas where they believe that the balance between harm and benefit tilts to the side of benefit.

"Targeted or whole-exome or whole-genome sequencing may be used to assist in diagnosis of symptomatic newborns (such as infants in neonatal or pediatric intensive care units or under the care of specialists), with parental permission and with access to genetic counseling and follow-up services, [and] results unrelated to diagnosis of the infant may be returned to families if those results could benefit family members."

This conclusion seems to be reflective of a growing clinical confidence, as Kingsmore and colleagues have moved to expand their efforts in the clinic.

The other three projects in the group address testing healthy babies – either in the context of mandated newborn screening, or in a broader context of pediatric care.

At UCSF, in addition to spearheading the ethical research that supports the Hastings report, researchers have been investigating whether there is benefit in adding targeted sequencing to current state-mandated screening protocols, in order to better detect currently screened metabolic disorders and to add the ability to pick up other issues — specifically primary immunodeficiencies.

On the question of mandated newborn screening, the Hastings authors advise that sequencing shouldn't be used as a primary tool but endorse targeted sequencing in a more limited vein: "as a secondary test following a positive screen for conditions that meet existing newborn screening criteria … [or] as a primary test to screen … where sequencing is either the more appropriate or only method for screening for that particular condition."

At UNC, investigators are studying some of the same questions as Green's BabySeq: specifically what the impact is on families who receive sequencing results beyond what is currently covered by newborn screening programs — things like carrier status, and risk information for diseases that might only emerge later in life.

Green and colleagues, have designed a randomization protocol, comparing family experiences and outcomes with infants who have their exomes sequenced and get these results versus those who receive standard newborn screening.

According to the Hastings authors, though things may change in the future and results from these two projects are not yet in, the potential benefits as they stand don't seem to be established enough to merit the associated costs and risks.

Green said he doesn't disagree that these are critical questions to be asking, but he said he wonders if approaching them from a baseline assumption of harm might make it nearly impossible for the value of genomic analysis in healthy babies, or adults, to ever prove itself.

"If you find risk information, even if you discover an undiagnosed disease, you still haven’t proved that you can intervene and make that child's life better," Green explained. "Hardcore clinical utility advocates don’t want to see that you find more risk stuff or even stuff that’s really going on. They want proof positive that you have done more benefit than harm and have done so at a cost point that society is willing to pay."

Green said that we should be asking for that kind of evidence, but that in the context of genomics, it becomes a very tall order "when there are so many different ways to extract informational value and different approaches to what that value could be for an infant or a family."

Despite these challenges, he said that BabySeq has already yielded data that speaks to what he calls the first-line argument for benefit: that sequencing can identify the presence of increased risk for disease, or the presence of disease, in a baby that would otherwise not get this information.

Results are also now pushing into the second-line question of benefit: whether that information that wouldn't be available otherwise actually leads to a positive change in the health of the baby or potentially of other family members.

One example the team has already discussed is a case in which researchers found a BRCA2 mutation in an infant. "Traditionally you would not return this even to the parents. "Its an adult onset condition, and you preserve the infant's right not to know," Green said. "But in this case we are … able to return things like this, and when we did, the mother found that she was also a carrier."

"How do you measure the benefit to the child? — the potential of lifesaving information for the mother: of having her around versus not having her around," he added.

A second anecdote, Green said, is a family in the study whose sequencing revealed them to be carrier of a recessive disease mutation.

"By standard thinking you wouldn't return a recessive carrier trait because it isn't valuable until the baby is grown up and having children of their own," Green said. But in this case, the finding in the baby prompted the parents to have themselves tested, finding, surprisingly, that they each carried a mutation in this gene, and their child had escaped inheriting two copies by chance. Future children would have had a one in four chance of getting both copies and suffering a destructive disease.

In this case, the family was able to use reproductive technology — IVF with preimplantation genetic screening of their embryos — to have a second healthy child.

The Hastings report fails to delve deeply into what we know so far about the potential benefits to babies or to families of broad sequencing, but Green said that he hopes that as more data comes out of the NSIGHT projects, there will be an opportunity to pivot from saying that not enough is known about the benefit to outweigh potential harms, to saying something more like "maybe we haven't answered this question comprehensively yet but here is what we know so far."

Green added that he expects BabySeq to be able to answer some of the important questions that groups like the NSIGHT ethics board are looking for in terms of the question of harm as well.

He and his team haven't finished these analyses in their infant project yet, but its not outlandish to expect that the results might be in line with what they reported from their adult-focused MedSeq effort, and from older and ongoing studies by Green on direct-to-consumer genetic testing, which has been generally minor harm if any, and much less than predicted by naysayers.

Because so much of the debate over sequencing healthy people starts at an assumption of harm, Green argued that even when his group finishes BabySeq, there will still likely be thresholds that the data will not meet.

A hard truth for the field, he argued, is that without a clear consensus on what the cutoff point is for proving greater benefit than harm, it becomes hard to know how to convince people.

"There is a philosophy of science quote: 'The plural of anecdote is not data,'" Green said. "But in some ways, the aggregation of carefully collected stories are a kind of data — and maybe the only kind of data we can fairly apply to the multiple opportunities for benefit and harm that you get out of a human genome."

Some in the field have argued that to be able to quantify the benefits and harms of sequencing healthy people, we are going to have sequence many more healthy people in order to build a real understanding of the value.

In that light, reports like the Hastings paper can feel like they are putting the kibosh on what should be enthusiasm for moving forward with the research necessary to answer these questions.

In Lantos' eyes, although starting from an assumption of harm may present challenges, starting from an assumption of benefit isn't great either, and there can be a thin membrane between research and public health.

He raised the example of screening newborns for Krabbe disease, a neurodegenerative genetic disorder caused by deficiency of galactocerebrosidase, which New York state began as public program in 2006.

"We now know 10 years into it how little we knew when we started," Lantos said, and debate continues about whether the ability to identify and try to treat these cases early offers more benefit than harm even as other states begin programs modeled on New York's.

Is it research, or public health, he asked, to implement something like this before you know whether it does more good than bad?

A final area the Hastings authors weigh in on is the question of direct-to-consumer tests — which now comprise both existing services that are marketed primarily for adults but could be applied to children, and newer tests being launched specifically for the pediatric population.

The Hastings report concludes that while "research in adults indicates that direct-to-consumer genetic testing may be neither as beneficial nor as harmful as originally thought," the specific case of children involves more complicated questions of consent and harm, which are enough to recommend that health professionals tell their patients not to use these products.

According to Green, "it’s a very tough call whether that should be more regulated than other self-help things we give parents permission to do with their children."

"If people want to pay out of pocket for an exome or genome to find out whatever is there, I think it's hard to tell people they can't do that," he said.

The Hastings authors agree, saying that they are not arguing for a law against parents accessing direct-to-consumer sequencing of their newborns. "Such a law would likely be inconsistent with the broad discretion that parents have to make decisions for their children."

That said, the report offers "precautionary admonitions," especially for clinicians interacting with parents, despite a recognition that these admonitions could "prove insufficient in the face of rapid industry growth and advertisement-driven consumer demand."