Genetically Sequencing Healthy Babies Yielded Surprising Results

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Robert C. Green, MD, MPH January 22, 2019 8 MINUTE READ

A newborn and mother in the hospital - first touch. (© martin81/Shutterstock)

Today in Melrose, Massachusetts, Cora Stetson is the picture of good health, a bubbly precocious 2-year-old. But Cora has two separate mutations in the gene that produces a critical enzyme called biotinidase and her body produces only 40 percent of the normal levels of that enzyme.

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That's enough to pass conventional newborn (heelstick) screening, but may not be enough for normal brain development,

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putting baby Cora at risk for seizures and cognitive impairment. But thanks to an experimental study in which Cora's DNA was sequenced after birth, this condition was discovered and she is being treated with a safe and inexpensive vitamin supplement.

Stories like these are beginning to emerge from the BabySeq Project, the first clinical trial in the world to systematically sequence healthy newborn infants. This trial was led by my research group with funding from the National Institutes of Health. While still controversial, it is pointing the way to a future in which adults, or even newborns, can receive comprehensive genetic analysis in order to determine their risk of future disease and enable opportunities to prevent them.

Some believe that medicine is still not ready for genomic population screening, but others feel it is long overdue. After all, the sequencing of the Human Genome Project was completed in 2003, and with this milestone, it became feasible to sequence and interpret the genome of any human being. The costs have come down dramatically since then; an entire human genome can now be sequenced for about $800, although the costs of bioinformatic and medical interpretation can add another $200 to $2000 more, depending upon the number of genes interrogated and the sophistication of the interpretive effort.

Two-year-old Cora Stetson, whose DNA sequencing after birth identified a potentially dangerous genetic mutation in time for her to receive preventive treatment. (Photo courtesy of Robert Green)

The ability to sequence the human genome yielded extraordinary benefits in scientific discovery, disease diagnosis, and targeted cancer treatment. But the ability of genomes to detect health risks in advance, to actually *predict* the medical future of an individual, has been mired in controversy and slow to manifest. In particular, the oft-cited vision that healthy infants could be genetically tested at birth in order to predict and prevent the diseases they would encounter, has proven to be far tougher to implement than anyone anticipated.

But in the last few years, the dream of predicting and preventing diseases through genomics, starting in childhood, is finally within reach. Why did it take so long? And what remains to be done?

Great Expectations

Part of the problem was the unrealistic expectations that had been building for years in advance of the genomic science itself. For example, the 1997 film *Gattaca* portrayed a near future in which the lifetime risk of disease was readily predicted the moment an infant is born. In the fanfare that accompanied the completion of the Human Genome Project, the notion of

predicting and preventing future disease in an individual became a powerful meme that was used to inspire investment and public support for genomic research long before the tools were in place to make it happen.

Another part of the problem was the success of state-mandated newborn screening programs that began in the 1960's with biochemical tests of the "heel-stick" for babies with metabolic disorders. These programs have worked beautifully, costing only a few dollars per baby and saving thousands of infants from death and severe cognitive impairment. It seemed only logical that a new technology like genome sequencing would add power and promise to such programs. But instead of embracing the notion of newborn sequencing, newborn screening laboratories have thus far rejected the entire idea as too expensive, too ambiguous, and too threatening to the comfortable constituency that they had built within the public health framework.

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Creating the Evidence Base for Preventive Genomics

Despite a number of obstacles, there are researchers who are exploring how to achieve the original vision of genomic testing as a tool for disease prediction and prevention. For example, in our NIH-funded MedSeq Project, we were the first to ask the question: "What can you find when you look as deeply as possible into the medical genomes of healthy individuals?"

Most people do not understand that genetic information comes in four separate categories: 1) dominant mutations putting the individual at risk for rare conditions like familial forms of heart disease or cancer, (2) recessive mutations putting the individual's children at risk for rare conditions like cystic fibrosis or PKU, (3) variants across the genome that can be tallied to

construct polygenic risk scores for common conditions like heart disease or type 2 diabetes, and (4) variants that can influence drug metabolism or predict drug side effects such as the muscle pain that occasionally occurs with statin use.

The technological and analytical challenges of our study were formidable, because we decided to systematically interrogate over 5000 disease-associated genes and report results in all four categories of genetic information directly to the primary care physicians for each of our volunteers. We enrolled 200 adults and found that everyone who was sequenced had medically relevant polygenic and pharmacogenomic results, over 90 percent carried recessive mutations that could have been important to reproduction, and an extraordinary 14.5 percent carried dominant mutations for rare genetic conditions.

A few years later we launched the BabySeq Project. In this study, we restricted the number of genes to include only those with child/adolescent onset that could benefit medically from early warning, and even so, we found 9.4 percent carried dominant mutations for rare conditions.

At first, our interpretation around the high proportion of apparently healthy individuals with dominant mutations for rare genetic conditions was simple – that these conditions had lower “penetrance” than anticipated; in other words, only a small proportion of those who carried the dominant mutation would get the disease. If this interpretation were to hold, then genetic risk information might be far less useful than we had hoped.

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But then we circled back with each adult or infant in order to examine and test them for any possible features of the rare disease in question. When we did this, we were surprised to see that in over a quarter of those carrying such mutations, there were

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already subtle signs of the disease in question that had not even been suspected! Now our interpretation was different. We now believe that genetic risk may be responsible for subclinical disease in a much higher proportion of people than has ever been suspected!

Meanwhile, colleagues of ours have been demonstrating that detailed analysis of polygenic risk scores can identify individuals at high risk for common conditions like heart disease. So adding up the medically relevant results in any given genome, we start to see that you can learn your risks for a rare monogenic condition, a common polygenic condition, a bad effect from a drug you might take in the future, or for having a child with a devastating recessive condition. Suddenly the information available in the genome of even an apparently healthy individual is looking more robust, and the prospect of preventive genomics is looking feasible.

Preventive Genomics Arrives in Clinical Medicine

There is still considerable evidence to gather before we can recommend genomic screening for the entire population. For example, it is important to make sure that families who learn about such risks do not suffer harms or waste resources from excessive medical attention. And many doctors don't yet have guidance on how to use such information with their patients. But our research is convincing many people that preventive genomics is coming and that it will save lives.

In fact, we recently launched a Preventive Genomics Clinic at Brigham and Women's Hospital where information-seeking adults can obtain predictive genomic testing with the highest quality interpretation and medical context, and be coached over time in light of their disease risks toward a healthier outcome. Insurance doesn't yet cover such testing, so patients must pay out of pocket for now, but they can choose from a menu of genetic screening

tests, all of which are more comprehensive than consumer-facing products. Genetic counseling is available but optional. So far, this service is for adults only, but sequencing for children will surely follow soon.

As the costs of sequencing and other Omics technologies continue to decline, we will see both responsible and irresponsible marketing of genetic testing, and we will need to guard against unscientific claims. But at the same time, we must be far more imaginative and fast moving in mainstream medicine than we have been to date in order to claim the emerging benefits of preventive genomics where it is now clear that suffering can be averted, and lives can be saved. The future has arrived if we are bold enough to grasp it.

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