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The Big Questions:
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The Genomic Oracle

If your DNA is sequenced at birth, how would it affect your life? A new project aims to find out.

By Carl Zimmer

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In June 2007, James Watson, a co-discoverer of the structure of DNA, went to Houston to pick up his genome. At a ceremonial press conference at Baylor College of Medicine, scientists handed the 79-year-old Nobel Prize-winner a DVD on which they had recorded a highly accurate reading of all the DNA nestled in the nucleus of each of his cells. There was, however, one glaring gap.

Watson spoke at the conference about the value of genomes to medical research. "I think we'll have a healthier and more compassionate world 50 years from now because of the technological advances we are celebrating today," he **declared.** In addition to giving Watson his genome on a DVD, the Baylor team also **put the sequence** into the public database GENBANK, where scientists can download it and compare it to other publically available human genomes. But scientists will not be able to see one of Watson's 20,000 genes. The gene encodes a protein called apolipoprotein E. A variant of the gene, called ApoE4, dramatically increases the risk of developing late-onset Alzheimer's disease. Watson's grandmother had died of Alzheimer's disease, and Watson decided he would rather not know if he carried the variant.

If Watson does, in fact, carry ApoE4, he would not have had much time to dread Alzheimer's before the disease arrived. **The mean age of onset** of Alzheimer's in people with one copy of ApoE4 is 76. In those with two copies, the age drops to just 68. Six years since receiving his genome, Watson is 85 and shows no sign of the disease.

Today, you don't have to be James Watson to find out if you carry ApoE4. In 2011, the personal gene-testing company 23andMe **began offering** a test for the variant to anyone who sent them a DNA sample. After first reading a page of information and warnings, customers can see for themselves if they carry the variant—which may lead to decades of anticipating the possible decline of their senses.

Now imagine taking this sort of revelation to its logical extreme. You're the parent of a newborn daughter. The doctors take a blood sample from her and run it through a genome-sequencing device. Within a couple days you get a full report on your daughter's genome. It shows whether she has ApoE4 and how many copies she carries. Does she deserve to know what may lie ahead? Or should she enjoy a blissfully ignorant youth? Because you have her whole genome, and not just a test for a single gene, you can potentially look for a vast number of other gene variants that raise the risk of other diseases of adulthood, such as the BRCA1 gene for **breast cancer**. Should she get the whole report or not? Will you be prepared for what her genome sequence may reveal about you or your spouse, since she got all her DNA from you? And would the specter of a deadly gene loom over your years raising your child?

"The notion of sequencing everyone at birth has been around for a long time in a pie-in-the-sky way," says Robert Green of Brigham and Women's Hospital. But now, Green says, it's rapidly approaching reality. Last week, Razib Khan **wrote** about getting his daughter's DNA sequenced by 23andMe for a few hundred dollars. He didn't get the full genome sequenced, but rather a few million genetic markers sprinkled across her chromosomes. Still, that was enough for Khan to determine her risk for at least one genetic condition.

The cost to sequence an entire genome is still substantially higher, at several thousand dollars. A few clinics in the United States are starting to sequence the full genomes of patients whose diseases can't be identified by the standard battery of genetic tests, or whose diseases resist conventional treatments.

As the cost of sequencing genomes falls, our understanding of how variations in the genome affect our health is growing. And some medical researchers think that newborn genome sequencing could be a huge boon to people's health. Looking over a baby's genome, a pediatrician might spot a mutation linked to an aggressive childhood cancer, for instance. It could also allow doctors to avoid giving children medicine that would have devastating side effects. Children with certain variants of a gene called TMPT, for example, can't break down some of the drugs used for **leukemia**, which end up poisoning their bone marrow.

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But we cannot say in advance how much benefit genomes at birth would provide, nor can we predict how much anxiety they would create in children or their parents. Next year, however, Green and his colleagues are embarking on a study to start getting some answers to those questions. **BabySeq**, as the project is known, **received** a $6 million award last month from the National Institutes of Health, and will be led by Green at Brigham and Women's Hospital and Alan Beggs at Boston Children's Hospital.

Green sums up the goal of BabySeq with a simple question: "If you have your genome readily available from birth, how is that likely to influence your life?"

Green and his colleagues are now putting together their protocol for the project. It will then be reviewed by an Institutional Review Board, which will evaluate the ethics of their plan. Green and his colleagues foresee enrolling 240 healthy babies from Brigham and Women's and 240 sick babies from the Neonatal Intensive Care Unit at Children's Hospital. The BabySeq team will sequence half the babies in each group and provide the genomes to their doctors, along with information about what scientists have determined about the genetic variants carried by each baby. Green, Beggs, and their colleagues will then track the babies for at least a year, seeing whether any differences emerge between them and the unsequenced babies.

It's easy to look at BabySeq and see it as proof that the future has arrived—whether you see that future as the golden age of personalized medicine or a dystopia fashioned after the movie ***GATTACA***. But either conclusion would be wrong. The mutations that pose the biggest risks to children are very rare. In a group of 240 sequenced babies, such mutations may never turn up, and so the BabySeq team may never see how doctors use genomic information to guide their treatments. "The chances of finding something that really alters your sense of a child's health is probably pretty small," says Green.

BabySeq is, at best, a pilot study. When it's over, scientists might then be able to launch a full-blown study with 10,000 babies and start seeing real results. For now, Green is just happy to move the debate about the ethics of genomic medicine from the abstract to the physical. "We'll be grappling with them in real life, with real babies and real families and real clinicians and real laboratory results," says Green.

It might sound odd to hear Green savoring the prospect of real lab results. But that's the first step in a huge challenge—communicating the results of genome sequencing—one that BabySeq may help overcome. The data from a genome can be overwhelming, ambiguous, confusing, and upsetting all at once. The BabySeq team will be working on ways to distill the results into reports that are useful for doctors who aren't trained as genome experts.

"We don't even have a process in place for how your doctors starts to use information from your genome," says Green. And the question about what to tell parents will be even more challenging. "What happens when a family says, 'I'd like to have the hard drive'?" asks Green. "I think that's something we'll have to figure out."