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Growing Up Genomic: What Happens When You Know All A Baby's Genes?

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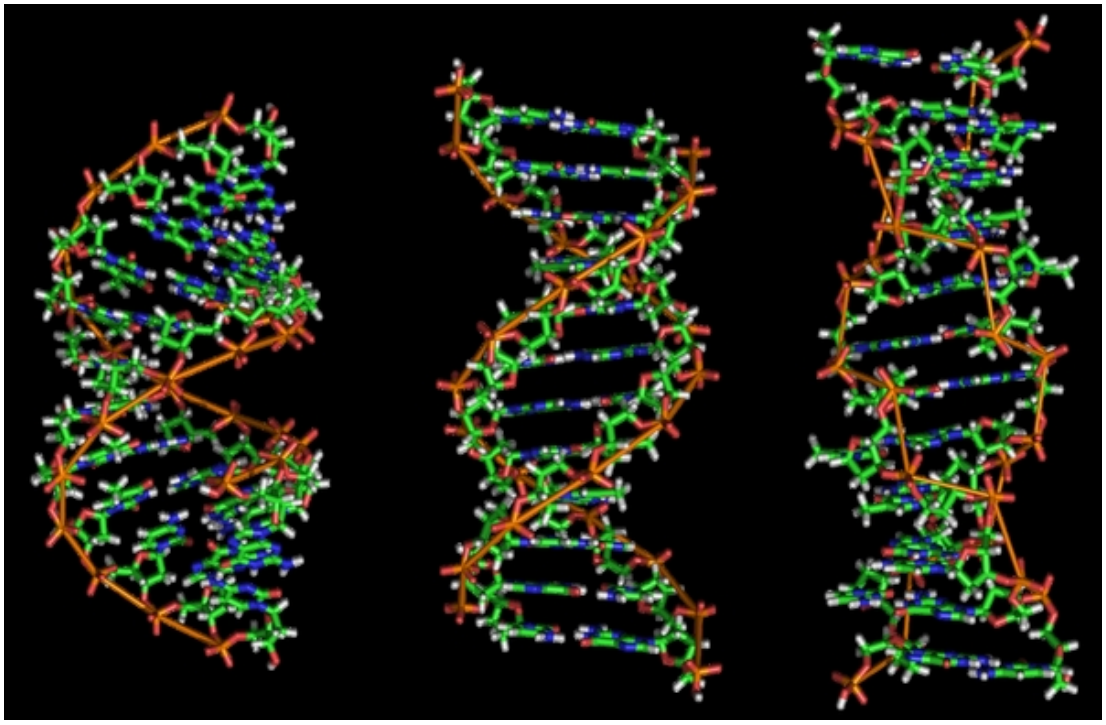

How would it change your life if you knew all your genes from the get-go? I mean, not just a little foray onto 23andMe when you're 23 and curious, but a full sequencing of all your significant DNA *at birth*? Would you grow up with

some deeply different ideas about yourself and your future than you would have otherwise? If, say, you knew you were at high risk for cancer or Alzheimer's?

This is not just a thought experiment. Boston-based researchers have just announced that they will be seeking subjects for a $6-million study called BabySeq that involves sequencing more than 200 babies' full sets of genes at birth, then following them to see how that genetic knowledge affects their lives and medical care. To which I say: Darn. This genomic future keeps arriving even faster than I expect.

The press release is below — Boston parents-to-be, take note: Recruitment is expected to begin early next year. I spoke with Dr. Robert C. Green, one of the lead researchers; our conversation, lightly edited:

So what is the question that this research project seeks to answer?

RCG: This is a research project at Brigham and Women's Hospital and Boston Children's Hospital, led by myself and Alan Beggs, that asks the question: What happens when you sequence newborn babies? What happens when you sequence healthy newborn babies and what happens when you sequence ill newborn babies?

The philopsophy with which we've started this project is that sequencing is here, it's getting cheaper and cheaper, and more accessible. And everyone thinks that this is going to be a great boon to your health; it's going to tell you about diseases and conditions that are going on, and it's going to warn you about diseases and conditions to come. And we'd like to find out how this really plays out in these two very different situations.

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and you can open it to any page you want, what do you get to read there, and how does it influence you?

In other words, if you have access to the reference book of life, and you can open it to any page you want, what do you get to read there, and how does it influence what your doctor does with you, what your doctor says to you, what your parent-and-child bonding is like? These are tremendously controversial issues, they're issue we simply don't know the answers to because the technology is so new, but it's hurtling down the track at such speed that we must ask these questions as soon as we can, and as scientifically as we can, so that we understand the answers as the technology is being rolled out, not after it's rolled out.

How many babies will be sequenced in this 'BabySeq' project?

There will be 480 babies enrolled, of whom half — or 240 — would be sequenced. It's designed as a randomized, controlled trial.

Have babies been sequenced like this before?

I'm certain that many newborn babies have been sequenced, because clinical sequencing is going on now in response to uncertain diagnoses throughout the country. One lab has done over 1,000 sequences in sick individuals, mostly children.

So what's really new here is sequencing the healthy babies?

Yes, but also the notion of rigorously putting these individuals into a randomized clinical trial so that we can truly sort out what are the downstream impacts of the sequencing.

The benefits seem obvious — you could get early warning of potential risks — but what are the concerns?

The genomic sequence that you receive is a mixed bag. There are some mutations that are very well understood and many mutations that are not well understood. So part of the problem is, how do you create a pipeline for interpretation? Among the many things you can find in that pipeline, which do you give back to families and which do you hold onto and not report back because you're not sure enough what they mean?

So part of the process of this grant is: what is an appropriate set of pieces of information to give back? So for example, we all agree you'd give back a known mutation that predisposes a child to a preventable childhood cancer, say, of the colon or the thyroid. That would be pretty straightforward.

To what extent are you saddling that child and that family with information they won't be able to use for a long time?

Other things would be highly controversial to return to a pediatrician and to family members, such as an adult-onset condition. Is it appropriate to tell a pediatrician and hence the family that there is an adult-onset condition that this child is at risk for? It might not occur for 18 years or 50 years. To what extent are you saddling that child and that family with information they won't

be able to use for a long time, and that might change the very fundamental perception of the child in the parents' eyes?

Of course, another side to that is that if, in this moment in time, you have genetic information about a child for an adult-onset disease, you have learned something about one of that child's parents. One of the parents likely has that mutation, to have passed it on to the child, and may himself or herself be at risk for an adult-onset disease. One of the issues in genetics is whether the child in front of you is your sole patient or whether the entire family is your patient.

What are the best examples of the kinds of things parents are likely to learn from a baby's DNA?

The BabySeq project will have two types of babies.

NICU babies: These are very sick children, often with heart or brain problems that may be due to genetic variations or may not. In these cases, the sequencing could provide clues as to the cause of their medical problems or the direction of treatment

Normal newborn babies: These are healthy newborns and in most cases, parents will only find out that their infant is a carrier of two to four recessive traits (one copy of these mutations would not make the baby have a disease), and some pharmacogenomic features — insights about dosage and side effects for certain drugs that the infant might or might not encounter in their lives.

In a small proportion of babies — maybe 2 percent — mutations could be discovered that would signal a significant risk of future disease, typically cancer predisposition or disposition to cardiac disease.

What else might be controversial?

Another area is: What, among the many things that you *can* report, do you

choose to report? So for example if there's a very well-known mutation that puts a child at risk for a childhood-onset disorder, that's one thing. But if you have a mutation that no one has ever seen before that is in the same gene, and you truly do not know if it puts that child at risk or might put that child at risk, it's an enormous challenge to decide not only whether to communicate that but *how* to communicate it so that it's neither over-interpreted or under-interpreted.

How far are we from the time when it will be routine to sequence virtually all newborns?

I think we're five to ten years away from the time when it will be very easy and very inexpensive for any parent who wants genomic sequencing of their newborn to obtain it either through their health care provider or through a private entity. And it may be even sooner than that.

The question is, given that this is going to be available, what kinds of procedures and perspectives should there be? What can our research tell us about the ways in which it should be implemented safely, appropriately and for the true betterment of the child and the family involved?

We already have 23andMe and other commercial providers who can do this, right?

We already have direct-to-consumer companies that provide technologies that look at specific variant markers along the genome but these are not the same thing as whole-exome or whole-genome sequencing, because that looks at every single letter, if you will, in the genetic code and has the opportunity to pick up *new* mutations that would not be picked up by these array-based technologies. But I think it certainly is only a matter of time and cost before there are direct-to-consumer opportunities for people to get their [full] sequencing done.

So are you recruiting families in the Boston area already?

I suspect we're going to start recruiting in early 2014. We'll soon begin in the Boston area, and there are three other sites, in San Francisco, Kansas City and Chapel Hill, NC.

So in a best-case scenario, a preventable cancer gets picked up. What's a worst-case scenario?

The kind of scenarios that keep people awake at night are situations where a family hears information and either correctly understands it or misunderstands it and this somehow colors their entire psychology going forward: it fills them with fear, apprehension; it interferes with parent-child bonding; it may cause medical procedures that were not necessary; those procedures might have not only financial costs but side effects. So there's a whole cascade of downstream bad outcomes that people are legitimately concerned about.

On the other side of the spectrum are people who are true information seekers, people who are excited about learning absolutely as much as they can about the future of themselves and their children. They're people who are willing to receive ambiguous and uncertain information, they're willing to live with it. And we're seeing more and more of those people, people who are asking for any and all information about their future health from the medical establishment. So I think there is a real tension here — and neither side is absolutely right or wrong — there's simply a tension between worlds in which information is seen as an unabashedly good thing and worlds in which information may be seen as frightening or productive of actually bad outcomes.

Readers, where do you come down? Geneticists emphasize that most DNA findings are not destiny, they're just probabilities, but somehow I keep thinking of Sleeping Beauty and the fairies each bestowing virtues on the newborn Aurora....

Read the Globe's coverage of the project here, and here's the press release:

Randomized trial is the first to explore the benefits and risks of genome sequencing in newborns

Families who volunteer could have their baby's genomic data available as a resource to aid in the baby's medical care.
Boston, MA – Parents of some Boston-area newborns will have a rare opportunity to have their baby's DNA completely analyzed as part of the first-ever randomized trial to explore the benefits and risks of genome sequencing (reading the entirety of a person's DNA) in this age group. The five-year study will assess the baby's risks of future diseases and how that information affects the baby's medical care, and the relationship between the parents, baby and baby's pediatrician. The study is funded by a $6 million grant from the National Institutes of Health to Brigham and Women's Hospital and Boston Children's Hospital. The study will be led equally by principal investigators Robert C. Green, MD, MPH at Brigham and Women's Hospital and Alan H. Beggs, Ph.D. at Boston Children's Hospital, both faculty at Harvard Medical School.

"This first-of-its-kind study will accelerate the use of genomics in clinical pediatric medicine by creating and safely testing novel methods for integrating sequencing into the care of newborns," said Green, a medical geneticist in the Division of Genetics at Brigham and Women's Hospital and director of the Genomes2People Research Program. "We will implement and study a futuristic goal: that genomic information examined shortly after birth can serve as a resource throughout infancy and childhood to inform clinical care and identify appropriate and timely interventions."

Beginning in early 2014, the study will enroll 480 newborns and their parents in order to compare outcomes that occur when genomic newborn sequencing is added to the conventional newborn screening that babies currently receive. The volunteers, healthy newborns from Brigham and Women's Hospital and infants from Boston Children's Hospital's Neonatal Intensive Care Unit, will be divided into two groups. One group will receive conventional state-mandated newborn screening, the other will receive conventional screening and genome sequencing. Researchers will collect

and analyze the genomic sequences, which may include information on potential causes of any birth defects, predispositions to future medical conditions and predictions about responses to certain drugs, and will return that information to parents and pediatricians to evaluate the medical, psychosocial and economic outcomes.

"These analyses will help illuminate the full spectrum of benefits and risks associated with genome sequencing of newborns," said Beggs, director of the Manton Center for Orphan Disease Research and a professor of pediatrics and scientist in the Division of Genetics at Boston Children's Hospital.

This research project follows the start of a similar NIH-funded study at Brigham and Women's Hospital, the MedSeq Project, which is the first NIH-funded randomized clinical trial to study the integration of whole genome sequencing into the practice of adult medicine.

This program aired on September 4, 2013. The audio for this program is not available.

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Carey Goldberg is the editor of WBUR's CommonHealth blog.
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