CRACKING THE GENETIC CODE TO CONQUER DISEASE

Above: Robert C. Green, MD, MPH, winner of the inaugural BRIght Futures Prize in 2012.

BY SARAH M. JACKSON

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Only 60 years ago, organ transplantation seemed fanciful and otherworldly. Could it work? Was it moral and ethical? In 1954, surgeons at the Peter Bent Brigham Hospital, a Brigham and Women's Hospital (BWH) predecessor institution, performed the first successful kidney transplant, sparking a field that today saves more than 28,000 people in the United States alone.

As with transplantation, BWH is paving the way for a mind-boggling first in the field of medical genetics. Robert C. Green, MD, MPH, medical geneticist at BWH and Harvard Medical School and associate director for research at the Partners Center for Personalized Genetic Medicine, stands on the precipice of this largely uncharted area.

One of few geneticists in the world conducting large-scale translational research trials, Green investigates the ways in which genetics (single gene tests) and genomics (large scale DNA testing) influence medical outcomes. To do this, Green works closely with laboratory geneticists to crack the molecular code for meaningful risk in more than 4,000 disease-associated genes, and to construct protocols to use that information in clinical care.

"Although the Human Genome Project first mapped all human genes in 2003, our DNA still holds many mysteries about our health," Green says. As such, his work seeks to realize the promise of personalized medicine, a budding field that tailors preventative efforts or treatments to match an individual's molecular profile.

But the ability to explore all human genes at the same time raises numerous questions. As Green and other scientists assemble the pieces of the genetic puzzle, it is clear treatments will soon become more precise and more personalized, reproductive decisions will be affected, and much of the predictive information will be difficult to interpret. Thus, society must plan for the medical, behavioral, and economic ramifications of using such complex data. To address some of these questions, Green is examining how an individual's knowledge of his or her own genetic predisposition to certain diseases affects that person, as well as the practice of medicine.

"Historically, geneticists have assumed that it could be dangerous for patients to have access to their own genetic information," Green says. "But we need to find out whether that's actually true."

BRIGHT FUTURES AND BABYSEQ

In 2012, Green won the hospital's inaugural $100,000 BRIght Futures Prize, which was established by BWH's Biomedical Research Institute to bolster highly promising research projects. This funding enabled Green to launch an elaborate survey of more than 1,000 parents in the BWH newborn unit, to determine their hypothetical interest in receiving detailed genomic information about their children's predisposition to certain genetic ailments. Of those who responded, more than 84 percent said they would be interested in such a service if it were available.

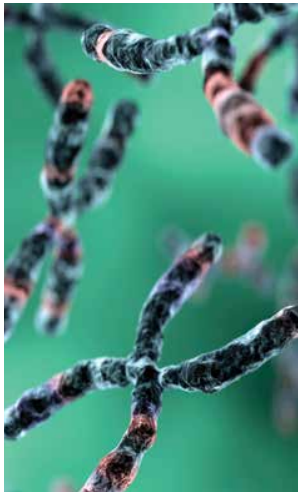
The study then followed up with these same parents after three months. More than 90 percent did not change their minds about wanting access to their newborns' genetic predispositions. Even when a subset of these parents was shown hypothetical scenarios describing intentionally ambiguous or frightening genetic results, more than 90 percent reaffirmed their interest in receiving their babies' genomic data.

"Accessing our genome—our 'Book of Life'—has been an irresistible proposition for years," Green says. "We have been sequencing some adults and children with illnesses for a long time. Now, the idea that parents of healthy newborns can learn something valuable about a baby's predisposition to certain diseases is intriguing. But we need to ask if doctors can do this in a responsible, safe way—and if so, how."

The thorough preliminary data Green obtained through the BRIght Futures Prize positioned him and joint principal investigator Alan Beggs, PhD, genetics researcher and director of the Manton Center for Orphan Disease Research at Boston Children's Hospital (BCH), to apply for a major National Institutes of Health (NIH) grant, which sought funding to launch the BabySeq project, a five-year clinical trial that

The **BabySeq Project** and its sister study the **MedSeq Project**, which focuses on adult genomes, are taking a panoramic approach to examining the usefulness and consequences of mapping a person's genetic data:

- DRAW BLOOD SAMPLE FROM THE ADULT OR NEWBORN
- SEQUENCE THE SAMPLE
- AMASS RAW DATA
- INTERPRET THE DATA TO GENERATE A MEANINGFUL REPORT THAT A DOCTOR CAN UNDERSTAND AND DELIVER EFFECTIVELY TO PATIENTS
- ASSESS PATIENTS' REACTIONS TO RECEIVING THEIR GENOMIC INFORMATION
- TRACK THE MEDICAL OUTCOMES THAT ENSUE AS A RESULT OF PATIENTS RECEIVING THIS INFORMATION.



"Don't be afraid to fail. Every time you ask a question where there could be an unexpected outcome, you're taking a risk. If you fail, there will be time to learn from that and create a better path to success. Don't give up on your ideas." ROBERT C. GREEN, MD, MPH

will sequence the genomes of healthy babies via the BWH newborn unit and sick babies via the BCH neonatal intensive care unit. While other institutions have mapped genomes of sick infants, none have mapped healthy newborns concurrently—another aspect of the BabySeq Project that sets it apart from any other trial.

The Green-Beggs team was awarded one of four such grants over scores of application from across the United States. "The work we accomplished with the BRIght Futures Prize funding prepared us very well for the NIH grant process," Green says. "We were able to demonstrate the feasibility of our proposed recruitment methods. The $100,000 has come back to us in the form of a $6 million NIH grant. That's the very real impact an initial gift can have."

With preliminary research complete and NIH funding in place, the clinical study protocol for the BabySeq Project is now undergoing revisions to ensure it is as safe and clear as possible. The BWH and BCH Institutional Review Boards (IRBs) will then examine the revised protocol. "Pending IRB approval, our next step is to enroll 480 newborn patients—half of whom will receive sequencing—and then follow them for behavioral, medical, and economic outcomes that result from having their genetic information," Green says.

As part of this challenge, the BabySeq Project team will need to create a simple, easily understood report that can be used by a doctor and the parents of his or her patient. As Green recently explained in an interview with Boston radio station WBUR, "We're maybe five to 10 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. 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 family involved?"

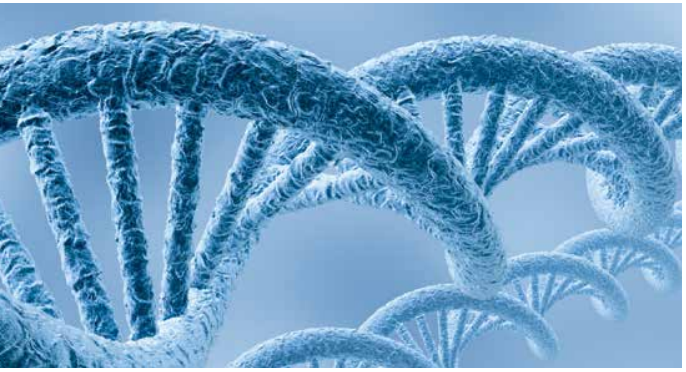
HARNESSING GENOMES ACROSS THE LIFESPAN

The $6 million NIH-funded BabySeq Project is launching on the heels of another major research effort, the MedSeq Project, also led by Green. The $10 million MedSeq Project is the first NIH-funded clinical trial to examine the impact of an adult's genomic data on medical practice.

"While the BabySeq Project focuses on newborns, the MedSeq Project focuses on the same types of data-gathering and exploration in adults," Green says. "In this sense, we are conducting translational genomics research through the entire lifespan—and also through the lenses of health and sickness. The totality of this work helps us to inform new laws, policies, and procedures that will guide genetics' integration into standard healthcare practice."

As Green's joint study leader for the BabySeq Project, Beggs agrees. "We have formed a wonderfully collaborative group," says Beggs. "Synergies among the MedSeq Project, BabySeq Project, and Manton Center for Orphan Disease Research at Boston Children's Hospital will help us discover how best to integrate genomic sequencing and medical interpretation of genetic results into reports that benefit patients and their families."

Green offers sage advice to this year's BRIght Futures Prize finalists (see article, p. 12): "Don't be afraid to fail. We honestly didn't know if newborns' parents would want to have their babies sequenced, or if they would change their minds after a few months. We had to be bold enough to take the risk and ask the question. Every time you ask a question where there could be an unexpected outcome, you're taking a risk. If you fail, there will be time to learn from that and create a better path to success. Don't give up on your ideas." ●



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