The Preventive Project

FIRST PERSON

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*Modern medicine is missing something, but **Dr. Robert C. Green** is filling the gap with preventive measures.*

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Dr. Robert C. Green

It has become axiomatic that the healthcare system is quite good once you are sick with cancer or heart disease but terrible at prevention. I want to change that. In my academic, philanthropic, and entrepreneurial work, my mission is to bring preventive genomics into modern medicine for all patients worldwide to avert needless suffering and death, particularly in children. Today, we have a tool in hand that can predict who will fall ill, who may have a devastated or autistic child, and who will respond poorly or well to specific medications.

I'm referring to the technological miracle of DNA analysis and the medical potential of preventive genomics.

Between 1990 and 2003, the largest collaborative biology project in history sequenced 93 percent of the human genome for $2.7 billion. Since then, the cost of sequencing a complete genome has come down more than a million-fold to around $400, and the interpretation of which genetic changes are deleterious has steadily improved. But we still aren't using preventive genomics to save lives. If you are a generally healthy person reading this column, chances are your doctor has never recommended a genetic screening test to you.

Twenty Years of Research Answering Basic Questions in Preventive Genomics

I entered the field of genomics in 2004. When I asked why we were not using it to predict and prevent disease, I was given two reasons: learning about genomic risk would cause catastrophic distress for patients and proving medical benefits at reasonable costs was impossible.

I've spent the last 20 years conducting real-world experiments to generate empirical evidence about these two questions and have shared my results in over 400 scientific publications.

Here's what I found:

Learning About Genomic Risk

Between 2004 and 2011, we enrolled over 1,000 diverse volunteers in a series of randomized controlled trials (the REVEAL Study) funded by the National Institutes of Health (NIH). We demonstrated that when people volunteer to receive predictive genetic information, they do a good job understanding the results and emotionally processing risk information. Later, we replicated these findings by measuring personal utility and distress when we returned results to research participants whose DNA had been sequenced in biobanks and large-scale epidemiology studies. The results were always the same: most people wanted to receive any genetic results that could make a difference in their health, and almost all of them were grateful, not traumatized, to receive even unanticipated information.

Medical Benefits of Preventive Genomics

Proving that preventive genomics saves lives is harder than it sounds,

Green (back row center) with staff and supporters

especially in the United States, where employer-based insurance often refuses to pay for predictive genomic testing and ongoing surveillance. However, studies such as Geisinger's *MyCode*, Renown Health's *Healthy Nevada*, Sanford's *Imagenetics*, and Genomics England have demonstrated the life-saving benefits of genetic screening for cancer and heart disease. In 2011, I challenged a group of genetics experts to define the most treatable genetic conditions, leading to the development of the ACMG list from the American College of Medical Genetics and Genomics, which has expanded from 56 to 81 genes. Over a decade later, this remains the only gene list for genomic screening ever generated by a medical society.

Screening More and More Genes

Starting in 2011, my team and I reasoned that medical benefits might be even greater if genomic screening were broadened to include more genes. In the MedSeq Project, our team was the first in the world to sequence and report on over 5,000 disease-associated genes. We found that 20 percent of healthy adults were carrying monogenic disease risks. In later studies, we confirmed that nearly everyone's genome carries genetic information that will be actionable at some point in their lives, leading to changes in medical care.

In screening healthy adults, we were excluding humans who had developed genetic diseases during childhood. But what if every child could have their genome analyzed shortly after birth? What would we find, and how many of these findings would point us toward actionable risks?

Francesco Carrozzini and Green

Screening for Genomic Conditions in Newborns and Infants

The concept of sequencing newborns was discussed decades ago, even before the Human Genome Project. In 2012, NIH director Francis

Zara campaign

Collins predicted that complete sequencing of newborns was "not far away." Yet, newborn and childhood sequencing is still not available. In 2013, my team began the first real-world clinical trial of comprehensive sequencing in newborns, known as the BabySeq Project. We found that 11 percent of healthy infants were carrying monogenic disease risks. Parents of sequenced infants were no more distressed than those whose infants were not sequenced. We found abundant medical benefits in that every finding met the criteria for medical actionability!

Prioritizing Diversity

Someday, early infant DNA analysis and genomic medicine will be integral to preventive care for everyone. Until then, there is concern that only the privileged will benefit from genomic technologies. Our research has been successfully involving diverse populations. Today, the BabySeq Project involves multiple stakeholders as members of the research team, enrolling approximately 50 percent Black and over 38 percent Hispanic families.

The Twin Accelerants of Philanthropy and Entrepreneurship

I am a physician who sees patients but also a physician-scientist focused on generating knowledge to accelerate genomic medicine. Academic careers are defined by scientific impact, but ultimate changes based on federal grants often come too slowly. Philanthropy and entrepreneurship can be powerful accelerants for change. The Franca Fund, named after the editor of *Vogue Italia*, Franca Sozzani, and established by her son, filmmaker Francesco Carrozzini, and life-sciences investor D.A. Wallach, has been instrumental in supporting our work. Thanks to this unlikely connection between fashion and genetics, the company Zara created a line of designer shirts celebrating Franca's

life, with all 29,000 pieces selling out and the revenue benefiting our research. Other fashion companies, such as Tommy Hilfiger, have also pitched in.

Philanthropy held our team together while we developed the BabySeq Project and recruited diverse families. Each dollar of philanthropy has been leveraged into over a thousand dollars of subsequent funding. But putting the benefits of our discoveries into millions of lives happens best through entrepreneurship.

We recently launched the start-up Nurture Genomics with three incredible co-founders to innovate and streamline newborn and childhood genetic screening. Nurture's first offering screens hundreds of genes for treatable conditions, including childhood cancers or heart problems that can be cured if detected early. Nurture Genomics is bringing AI technology to variant curation and clinical decision support, in the service of driving down costs so that this screening can soon be made affordable to all.

Preventive Genomics and the Future of Medicine

Our research has established the initial safety and clinical utility of newborn and childhood sequencing, sparking a revolutionary vision to transform "sick care" into true health care. We plan to expand the BabySeq Project to over 100 recruitment sites, enrolling up to one million families. We are on the cusp of a new era in health care, where early detection prevents future illnesses, reduces long-term healthcare costs, and improves lives on an unprecedented scale. LM

To learn more, visit genomes2people.org and nurturegenomics.com.