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Contact: Haley Bridger  
Brigham and Women's Hospital  
617-525-6383, hbridger@bwh.harvard.edu

### **Sequencing Healthy Patients Reveals That Many Carry Rare Genetic Disease Risks**

*First-ever randomized trial examines the impact of whole genome sequencing in healthy primary care patients*

Boston, MA – Whole genome sequencing involves the analysis of all three billion pairs of letters in an individual's DNA and has been hailed as a technology that will usher in a new era of predicting and preventing disease. However, the use of genome sequencing in healthy individuals is controversial because no one fully understands how many patients carry variants that put them at risk for rare genetic conditions and how they, and their doctors, will respond to learning about these risks.

In a new paper published June 26 in the *Annals of Internal Medicine* by investigators at Brigham and Women's Hospital and Harvard Medical School, along with collaborators at Baylor College of Medicine, report the results of the 4 year, NIH-funded MedSeq Project, the first-ever randomized trial conducted to examine the impact of whole genome sequencing in healthy primary care patients.

In the MedSeq Project, 100 healthy individuals and their primary care physicians were enrolled and randomized so that half of the patients received whole genome sequencing and half did not. Nearly 5000 genes associated with rare genetic conditions were expertly analyzed in each sequenced patient, and co-investigators from many different disciplines including clinical genetics, molecular genetics, primary care, ethics, and law were involved in analyzing the results.

Researchers found that among the 50 healthy primary care patients who were randomized to receive genome sequencing, 11 (22 percent) carried genetic variants predicted to cause previously undiagnosed rare disease. Two of these patients were then noted to have signs or symptoms of the underlying conditions, including one patient who had variants causing an eye disease called fundus albipunctatus, which impairs night vision. This patient knew he had difficulty seeing in low light conditions but had not considered the possibility that his visual problems had a genetic cause. Another patient was found to have a genetic variant associated with variegate porphyria, which finally explained the patient's and family members' mysterious rashes and sun sensitivity. The other nine participants had no evidence of the genetic diseases for which they were predicted to be at risk. For example, two patients had variants that have been associated with heart rhythm abnormalities, but their cardiology work-ups were normal. It is possible, but not at all certain, that they could develop heart problems in the future.

"Sequencing healthy individuals will inevitably reveal new findings for that individual, only some of which will have actual health implications," said lead author Jason Vassy, MD, MPH, a clinician-investigator at Brigham and Women's Hospital, primary care physician at the VA Boston

Healthcare System and assistant professor at Harvard Medical School. “This study provides some reassuring evidence that primary care providers can be trained to manage their patients’ sequencing results appropriately, and that patients who receive their results are not likely to experience anxiety connected to those results. Continued research on the outcomes of sequencing will be needed before the routine use of genome sequencing in the primary care of generally healthy adults can be medically justified.”

Primary care physicians received six hours of training at the beginning of the study regarding how to interpret a specially designed, one-page genome testing report summarizing the laboratory analysis. Consultation with genetic specialists was available, but not required. Primary care physicians then used their own judgment about what to do with the information and researchers monitored the interactions for safety and tracked medical, behavioral and economic outcomes.

Researchers note that they analyzed variants from nearly 5000 genes associated with rare genetic diseases. These included single genes causing a significantly higher risk for rare disorders than the low risk variants for common disorders reported by direct-to-consumer genetic testing companies. No prior study has ever examined healthy individuals for pathogenic (high risk) variants in so many rare disease genes.

“We were surprised to see how many ostensibly healthy individuals are carrying a risk variant for a rare genetic disease,” said Heidi Rehm, PhD, director of the Laboratory for Molecular Medicine and a co-investigator on the study who directed the genome analysis. “We found that about one-fifth of this sample population carried pathogenic variants, and this suggests that the potential burden of rare disease risk throughout our general population could be far higher than previously suspected. However, the penetrance, or likelihood that persons carrying one of these variants will eventually develop the disease, is not fully known.”

Additionally, investigators compared the two arms of the study, and found that patients who received genome sequencing results did not show higher levels of anxiety. They did, however, undergo a greater number of medical tests and incurred an average of \$350 more in health care expenses in the six months following disclosure of their results. The economic differences were not statistically significant with the small sample size in this study.

“Because participants in the MedSeq Project were randomized, we could carefully examine levels of anxiety or distress in those who received genetic risk information and compare it to those who did not. While many patients chose not to participate in the study out of concerns about what they might learn, or with fears of future insurance discrimination, those who did participate evinced no increase in distress, even when they learned they were carrying risk variants for untreatable conditions,” said Amy McGuire, PhD, director of the Center for Medical Ethics and Health Policy at Baylor College of Medicine. McGuire supervised the ethical and legal components of the MedSeq Project.

There has also been great concern in the medical community about whether primary care physicians can appropriately manage these complicated findings. But when a panel of expert geneticists reviewed how well the primary care physicians managed the patients with possible genetic risk variants, the experts determined that only two of the 11 cases were managed inappropriately and that no harm had come to these patients.

MedSeq Project investigators note that the study’s findings should be interpreted with caution because of the small sample size and because the study was conducted at an academic medical center where neither the patients nor the primary care physicians are representative of the general population. They also stressed that carrying a genetic risk marker does not mean that patients have or will definitely get the disease in question. Critical questions remain about whether

discovering such risk markers in healthy individuals will actually provide health benefits, or will generate unnecessary testing and subsequent procedures that could do more harm than good.

“Integrating genome sequencing and other omics technologies into the day-to-day practice of medicine is an extraordinarily exciting prospect with the potential to anticipate and prevent diseases throughout an individual’s lifetime,” said senior author Robert C. Green, MD, MPH, medical geneticist at Brigham and Women’s Hospital, an associate member of the Broad Institute, and professor of medicine at Harvard Medical School who leads the MedSeq Project. “But we will need additional rigorously designed and well-controlled outcomes studies like the MedSeq Project with larger sample sizes and with outcomes collected over longer periods of time to demonstrate the full potential of genomic medicine.”

The MedSeq Project is one of the sites in the Clinical Sequencing Exploratory Research Consortium and was funded by the National Human Genome Research Institute, part of the National Institutes of Health.

*The Genomes2People Research Program at Brigham and Women’s Hospital, the Broad Institute and Harvard Medical School conducts empirical research in translational genomics and health outcomes. NIH-funded research within G2P seeks to understand the medical, behavioral and economic impact of using genetic risk information to inform future standards. The REVEAL Study has conducted several randomized clinical trials examining the impact of disclosing genetic risk for a frightening disease. The Impact of Personal Genomics (PGen) Study examined the impact of direct-to-consumer genetic testing on over 1000 consumers of two different companies. The MedSeq Project has conducted the first randomized clinical trial to measure the impact of whole genome sequencing on the practice of medicine. The BabySeq Project is recruiting families of both healthy and sick newborns into a randomized clinical trial where half will have their baby’s genome sequenced. Robert C. Green, MD, MPH directs the Program.*

*Brigham and Women’s Hospital (BWH) is a 793-bed nonprofit teaching affiliate of Harvard Medical School and a founding member of Partners HealthCare. BWH has more than 4.2 million annual patient visits and nearly 46,000 inpatient stays, is the largest birthing center in Massachusetts and employs nearly 16,000 people. The Brigham’s medical preeminence dates back to 1832, and today that rich history in clinical care is coupled with its national leadership in patient care, quality improvement and patient safety initiatives, and its dedication to research, innovation, community engagement and educating and training the next generation of health care professionals. Through investigation and discovery conducted at its Brigham Research Institute (BRI). BWH is an international leader in basic, clinical and translational research on human diseases, more than 3,000 researchers, including physician-investigators and renowned biomedical scientists and faculty supported by nearly \$666 million in funding. For the last 25 years, BWH ranked second in research funding from the National Institutes of Health (NIH) among independent hospitals. BWH is also home to major landmark epidemiologic population studies, including the Nurses’ and Physicians’ Health Studies and the Women’s Health Initiative as well as the TIMI Study Group, one of the premier cardiovascular clinical trials groups. For more information, resources and to follow us on social media, please visit BWH’s online newsroom.*