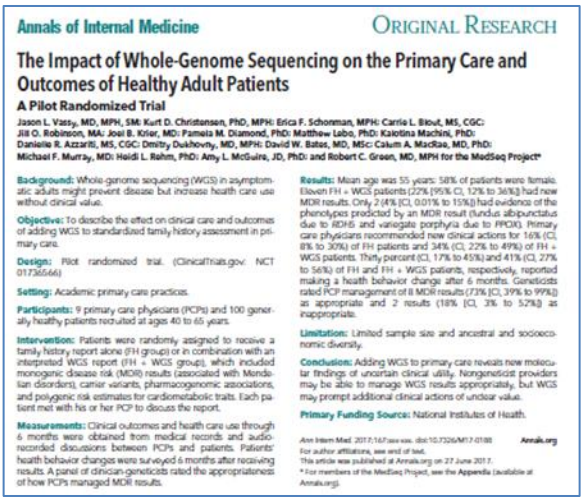
Flagship Results Paper from the MedSeq Project Published in *Annals of Internal Medicine*

The final flagship results paper from the 4-year, $10-million NIH-funded MedSeq Project, the first-ever randomized trial conducted to examine the impact of whole genome sequencing (WGS) in healthy primary care patients, was published June 26, 2017, in the *Annals of Internal Medicine*.



Annals of Internal Medicine — ORIGINAL RESEARCH

The Impact of Whole-Genome Sequencing on the Primary Care and Outcomes of Healthy Adult Patients

A Pilot Randomized Trial

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Background: Whole-genome sequencing (WGS) in asymptomatic adults might prevent disease but increase health care use without clinical value.

Objective: To describe the effect on clinical care and outcomes of adding WGS to standardized family history assessment in primary care.

Design: Pilot randomized trial. (ClinicalTrials.gov: NCT 01736566)

Setting: Academic primary care practices.

Participants: 9 primary care physicians (PCPs) and 100 generally healthy patients recruited at ages 40 to 65 years.

Intervention: Patients were randomly assigned to receive a family history report alone (FH group) or in combination with an interpreted WGS report (FH + WGS group), which included monogenic disease risk (MDR) results (associated with Mendelian disorders), carrier variants, pharmacogenomic associations, and polygenic risk estimates for cardiometabolic traits. Each patient met with his or her PCP to discuss the report.

Measurements: Clinical outcomes and health care use through 6 months were obtained from medical records and audio-recorded discussions between PCPs and patients. Patients' health behavior changes were surveyed 6 months after receiving results. A panel of clinician-geneticists rated the appropriateness of how PCPs managed MDR results.

Results: Mean age was 55 years; 58% of patients were female. Eleven FH + WGS patients (22% [95% CI, 12% to 36%]) had new MDR results. Only 2 (4% [CI, 0.01% to 15%]) had evidence of the phenotypes predicted by an MDR result (fundus albipunctatus due to *RDH5* and variegate porphyria due to *PPOX*). Primary care physicians recommended new clinical actions for 16% (CI, 8% to 30%) of FH patients and 34% (CI, 22% to 49%) of FH + WGS patients. Thirty percent (CI, 17% to 45%) and 41% (CI, 27% to 56%) of FH and FH + WGS patients, respectively, reported making a health behavior change after 6 months. Geneticists rated PCP management of 8 MDR results (73% [CI, 39% to 99%]) as appropriate and 2 results (18% [CI, 3% to 52%]) as inappropriate.

Limitation: Limited sample size and ancestral and socioeconomic diversity.

Conclusion: Adding WGS to primary care reveals new molecular findings of uncertain clinical utility. Nongeneticist providers may be able to manage WGS results appropriately, but WGS may prompt additional clinical actions of unclear value.

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For author affiliations, see end of text.

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* For members of the MedSeq Project, see the Appendix (available at Annals.org).

This paper is of note because it is the first randomized clinical trial of "end-to-end" WGS in the day-to-day practice of medicine, enrolling healthy adults and delivering sequencing reports to their primary care physicians without intermediation by a geneticist or genetic counselor. Additionally, this is the first study to comprehensively analyze and report nearly 5,000 disease-associated genes, including monogenic disease risks, carrier variants, pharmacogenomic associations and polygenic risk estimates. A remarkable 22% of the patients had new monogenic disease risk results - higher than previously suspected or documented. Moreover, overall, patients did not exhibit anxiety or distress about their findings, and the actions of the primary care doctors in response to the sequencing were rated by genetics experts and were found to be largely appropriate. Finally, this new paper reports the first estimates of potential economic burden of WGS in healthy adults on the health care systems, showing that resulting consultations, clinical tests and other downstream health care costs were modestly increased for the patients who received WGS in comparison to the control group.

Senior author and director of the Genomes2People Research Group, Robert C. Green, MD, MPH (left) and first author and assistant professor, Jason Vassy, MD, MPH, SM.

Several mainstream media and scientific outlets covered the announcement of this exciting paper; read on for links to those articles in addition to links to the newly published MedSeq paper, press release, video of first author Dr. Jason Vassy, and a complete list of MedSeq Project publications, which investigators have previously published from this implementation study.

NPR All Things Considered
Routine DNA sequencing may be helpful and not as scary as feared

MIT Technology Review
DNA testing reveals the chance of bad news in your genes

Wired
You can get your whole genome sequenced. But should you?

The Scientist
The consequences of sequencing healthy people

Science
One in five 'healthy' adults may carry disease-related genetic mutations

The Washington Post
Scientists discover DNA might not be that useful as part of your annual checkup

Reuters
Whole genome sequencing not ready for routine use: study

STAT News
In healthy patients, genome sequencing raises alarms while offering few benefits

Bio-IT World
Sequencing healthy patients reveals that many carry rare genetic disease risks

CardioBrief
Does whole genome sequencing have a role in primary care?

Science Daily
Sequencing finds rare genetic disease risk in one out of five healthy adults

GenomeWeb
Studies make case for sequencing healthy individuals, but questions remain

Front Line Genomics
Questioning the value of genome sequencing in healthy people

Xconomy
New study: DNA tests for healthy people have "uncertain value"

American Journal of Managed Care (AJMC)
Genome Sequencing Reveals Rare Disease Risk in 1 of 5 Generally Healthy Adults