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Short Term Costs of Integrating Whole Genome Sequencing into Primary Care and Cardiology Settings: A Pilot Randomized Trial

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[†]For a list of additional members of the MedSeq Project, see Appendix

Conflict of interest

The authors declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. McGuire is a consultant for Human Longevity outside the submitted work. Dr. Green receives compensation for speaking or consultation from AIA, GenePeeks, Helix, Illumina, Ohana, Prudential and Veritas, and is co-founder and advisor to Genome Medical, Inc. Dr. Dukhovny reports consulting for Vermont Oxford Network, Gerson Lehrman Group, and ClearView Healthcare Partners and being faculty for Vermont Oxford Network outside the submitted work.

Abstract

Purpose—Great uncertainty exists about the costs associated with whole genome sequencing (WGS).

Methods—One hundred cardiology patients with cardiomyopathy diagnoses, and 100 ostensibly healthy primary care patients were randomized to receive a family history report alone or with a WGS report. Cardiology patients also reviewed prior genetic test results. WGS costs were estimated by tracking resource use and staff time. Downstream costs were estimated by identifying services in administrative data, medical records, and patient surveys for 6 months.

Results—The incremental cost per patient of WGS testing was \$5,098 in cardiology settings and \$5,073 in primary care settings compared to family history alone. Mean six month downstream costs did not differ statistically between the control and WGS arms in either setting (cardiology: difference = −\$1,560, 95% CI −\$7,558 to \$3,866, $p=0.36$; primary care: difference = \$681, 95% CI −\$884 to \$2,171, $p=0.70$). Scenario analyses showed the cost reduction of omitting or limiting the types of secondary findings was less than \$69 and \$182 per patient in cardiology and primary care, respectively.

Conclusion—Short-term costs of WGS were driven by the costs of sequencing and interpretation rather than downstream healthcare. Disclosing additional types of secondary findings has a limited cost impact following disclosure.

Keywords

whole genome sequencing; cardiology; primary care; economics; costs

INTRODUCTION

Whole genome sequencing (WGS) can facilitate molecular diagnoses and identify genetic variants to characterize disease risks, tailor medications, screen for recessive traits and more. Dramatic improvements in its cost, speed, and capabilities are fueling expectations that WGS will become an important part of everyday patient care,^{1,2} and some commentators hope that it will streamline diagnoses and enhance disease prevention.³ Early evidence is promising,^{4,5} but there are concerns that WGS may also initiate a cascade of confirmatory testing and ongoing screening that greatly increases healthcare expenditures.^{6,7} Empirical data to inform the discussion are sparse.

Studies to date have examined the costs of genomic sequencing to provide molecular diagnoses for specific syndromes.^{8–13} or have projected the potential cost impact of disclosing a limited set of secondary findings.¹⁴ However, these early attempts do not fully account for more extensive secondary findings such as pharmacogenomic applications and risk predictions for common disease. Furthermore, current modeling efforts assume rational responses despite evidence that patients often respond to secondary findings in unexpected ways^{15,16} and evidence that physicians are often unclear about their obligations to act on information that is unrelated to the primary indication for testing.¹⁷ Few clinical studies have examined the costs of integrating WGS into the everyday care of patients, including broader applications that capitalize on the full potential of WGS.

To fill these knowledge gaps, we conducted a cost analysis of the MedSeq Project, a pair of randomized controlled trials of WGS in cardiology and primary care settings. Limited prior analyses within the primary care setting revealed some evidence for increased healthcare utilization and costs within the Partners HealthCare system following WGS.¹⁸ The analyses presented here extend these findings through a more comprehensive accounting of in- and out-of-system healthcare services and out-of-pocket costs in both cardiology and primary care settings, including a micro-costing analysis of WGS itself and scenario and sensitivity analyses that examine the impact of different reporting strategies and cost assumptions. The objective of these analyses is to provide novel insight about the short-term cost impact of integrating WGS into medical care.

METHODS

Clinical Trial Overview

The rationale, design and primary molecular and clinical findings of the MedSeq Project were previously reported,^{17–23} and methodological details are summarized in detail in Appendix 1. Briefly, primary care physicians identified ostensibly healthy patients between 40 and 65 years of age and cardiologists identified adult patients of any age with diagnoses of hypertrophic or dilated cardiomyopathy (HCM/DCM) for recruitment by MedSeq Project staff. To compare panel-based genetic testing to WGS in patients with HCM/DCM, cardiology patients were either confirmed to have had panel testing, or provided panel testing prior to MedSeq Project disclosure sessions. At their first study visit, patients consented for participation, provided family history information, had blood drawn, and provided baseline information. Using concealed envelopes, study staff then randomly assigned patients to a “control arm” that received a structured family history review (FH) or a “WGS arm” that received FH plus a WGS analysis and report. Cardiologists also reviewed their patients’ prior genetic test results in both randomization arms.

WGS reports included findings related to the patients’ condition (cardiology patients only), monogenic disease risks associated with well-established genetic conditions, carrier status for autosomal recessive conditions, pharmacogenomic findings, and risk predictions based on markers for cardiometabolic traits.^{19,20,22} Prior to disclosure, physicians could contact a Genome Resource Center staffed by genetic counselors and medical geneticists to ask questions about reports or study procedures. Investigators were not blinded to randomization, although patient participants were blinded until disclosure sessions and physician participants were blinded until they received family history and WGS reports, if applicable. The Partners Human Research Committee and Baylor College of Medicine Institutional Review Board both approved the study protocol ([ClinicalTrials.gov #NCT01736566](https://clinicaltrials.gov/ct2/show/study/NCT01736566)). The protocol, statistical code, and data set are available upon request from the corresponding author. Genetic data is available via dbGaP (accession #phs000958.v1.p1).

Cost-Analysis

Overall Approach—We undertook a planned cost analysis alongside the pilot randomized controlled trial using guidelines published by the International Society for

Pharmacoeconomics and Outcomes Research (ISPOR) and the Second Panel on Cost-Effectiveness in Health and Medicine.^{24,25} Costs are presented in 2015 US dollars.

Costs of WGS—To understand the costs of WGS to the healthcare system, we used a microcosting approach with program operation logs,²⁶ where staff measured personnel effort and resource use using a combination of forms that tracked each DNA sample and by reviewing audiorecorded consent and disclosure sessions to determine their lengths. Consent sessions for MedSeq Project participation were assumed to be comparable in length to consent sessions for WGS. Personnel effort was translated to costs using 2015 wage data as described in more detail in Appendix 4. We assigned costs for disclosure sessions based on Centers for Medicare and Medicaid Services (CMS) fee schedules for outpatient evaluation and management visits. The cost of sequencing was estimated from data provided by the National Human Genome Research Institute,²⁷ while costs for confirming monogenic and carrier findings via Sanger sequencing were based on 2015 Laboratory for Molecular Medicine rates for familial variant testing.

Downstream Healthcare Utilization and Costs—To understand the short-term impact of WGS disclosure on follow-up health sector spending, we assessed costs over the six months preceding results disclosure and the six months following disclosure for both randomization arms. We compared post-disclosure costs by randomization status, as well as separately comparing whether the difference in pre-disclosure and post-disclosure costs differed by randomization status. We supplemented healthcare services identified in administrative data accessed via the Partners HealthCare Research Patient Data Registry (RPDR) with services identified through a review of medical records. We also incorporated services reported in patient surveys completed at disclosure sessions and 6 weeks and 6 months post-disclosure that were not identified in RPDR or medical records data. Costs for services were estimated by multiplying utilization by cost weights derived from CMS fee schedules as described in Appendix 4. Patient out-of-pocket expenses during the post-disclosure period were assessed using survey items adapted from the McMaster Cost of Care Questionnaire,²⁸ where patient participants reported average monthly costs for procedural and visit co-pays, medical equipment, medications, and additional expenses related to their healthcare. Differences from prior-reported costs¹⁸ are primarily due to the addition of services identified through patient self-report.

Sensitivity and Scenario Analyses—Sensitivity and scenario analyses incorporating both WGS costs and downstream costs examined how findings varied with different analytic assumptions. First, we examined how costs changed when different types of downstream healthcare services were included. One approach examined “immediately attributable” services, including only services that physicians reported recommending in response to FH review and/or FH review and WGS reports, and that were confirmed through medical record review or patient self-report. Another approach included estimates of the costs for a comprehensive work-up of monogenic disease risks per guidelines such as GeneReviews, clinical synopses such as Online Mendelian Inheritance in Man, and published medical literature.^{29,30} We also examined the implications of different reporting criteria, such as omitting carrier status or polygenic risk predictions, and reporting no secondary findings or

reporting only secondary monogenic disease risk and carrier findings classified as likely pathogenic or pathogenic, per ACMG recommendations.³¹ In addition, we varied cost assumptions of WGS to reflect the range of prices available at CLIA-certified labs, and we varied healthcare price weights to be 50% to 200% of CMS fee schedule amounts. Finally, we analyzed costs from a third-party payer perspective by omitting patient out-of-pocket expenses.

Statistical Approach

A priori enrollment goals were not established given that this was a pilot study. We used multivariable linear regression to compare arithmetic mean costs by randomization arms, as recommended,²⁴ including all observed data and imputing data for missing observations. Models included terms for WGS vs control randomization status, cardiology vs primary care, an interaction term, and baseline health status. Covariates were included if they improved model precision (i.e., $p < 0.05$). We also used this approach to compare the difference in health care spending in the six month period post-disclosure against the six month period pre-disclosure, but omitted patient out-of-pocket expenses because relevant survey data were not available. Sub-analyses included additional terms as relevant to examine changes over time, to examine the impact of learning about an unexpected monogenic disease risk or to examine the impact of cardiometabolic risk predictions. Although terms for interactions between cohorts and randomization status were not significant, we report cohorts separately because downstream costs among cardiology patients were much larger than downstream costs among primary care patients. To compare changes in health care utilization, we used nonparametric tests (Wilcoxon rank-sum and Wilcoxon signed-rank tests) because data were highly skewed.

Four randomized individuals who did not attend disclosure sessions were omitted from analyses (Appendix 5). Analyses were conducted using R version 3.4.3. As recommended for smaller samples, confidence intervals were calculated using nonparametric bootstrapping (1,000 samples).²⁴ We assumed that missing survey data were missing at random, and imputed non-response with fully conditional specification, running 20 iterations to create each of 20 imputed datasets for each bootstrapped sample. Imputed data accounted for less than 1% of WGS costs through disclosure and 1.2% of downstream medical costs.

RESULTS

Sample Characteristics and Whole Genome Sequencing Findings

Two hundred participants attended results disclosure sessions. Demographic characteristics did not vary by randomization status except on educational attainment among primary care patients (Table 1). Table 2 summarizes monogenic and carrier findings among patients who received WGS. All cardiomyopathy variants that had been identified during panel testing of cardiology patients were confirmed by WGS, although an 18-base pair duplication in *MYBPC3* may have been missed if investigators did not know to look for it because it had been identified during prior targeted HCM genetic testing. In addition, among the 22 cardiology patients randomized to WGS who had no variants identified in panel testing, a pathogenic variant associated with HCM was identified in one. Among the 27 cardiology

patients who had positive or inconclusive panel testing results, three with inconclusive prior results were identified with a previously-unreported variant of uncertain significance associated with their DCM or HCM diagnosis. Secondary findings about monogenic disease risks and carrier status for autosomal recessive conditions were identified in 8 (16%) and 41 (84%) cardiology patients in the WGS arm, respectively.

Among the 50 primary care patients who received WGS, we identified variants associated with monogenic disease in 13 (26%), although two patients who received information about hereditary hemochromatosis had already been diagnosed with the condition. All primary care patients in the WGS arm (100%) received information about carrier status for autosomal conditions. Specific variants are detailed in Appendix 6 (monogenic disease risk findings) and Appendix 7 (carrier findings).

As noted previously, all cardiology and primary care patients in the WGS arms also received polygenic risk predictions for eight cardiometabolic traits and pharmacogenomic information for five drugs, summarized in Appendix 8.

Cost of Sequencing

Table 3 summarizes the time demands and associated costs of family history review and WGS reporting. The average incremental cost per patient for WGS, including variant interpretation and disclosure, was \$5,098 in cardiology settings and \$5,073 in primary care settings, with the large majority attributed to sequencing itself (\$4,000). Across cohorts, the study incurred an additional \$613 (12% of total WGS costs) per patient randomized to WGS, on average, to confirm monogenic and carrier status variants via Sanger sequencing; and subanalyses of patients randomized to WGS showed an average incremental cost of \$111 for each variant reported ($p<0.001$). Laboratory personnel time for variant interpretation and reporting increased by 13% for every variant reported ($p<0.001$), while overall time demands decreased by an average of 158 minutes per patient per study year ($p=0.033$).

Notably, cardiologists consulted the Genome Resource Center only once during the study, to discuss carrier status findings (compared to 11 consultations in primary care with a variety of questions). In addition, WGS increased the length of cardiology disclosure sessions by an average of 10.7 minutes (WGS arm: 15.3 min; control arm: 4.6 min; $p<0.001$) and primary care disclosure sessions by an average of 18.7 min (WGS arm: 30.1 min; control arm: 11.4 min; $p<0.001$). The added length of WGS disclosure sessions increased costs \$23 per patient, on average.

Downstream Healthcare Utilization and Costs

Healthcare utilization and costs from disclosure through six months post-disclosure from a healthcare sector perspective are summarized in Table 4, and commonly-observed procedures during the post-disclosure period are summarized in Appendix 9. In cardiology care, mean six month total downstream costs were \$1,560 lower in the WGS arm compared to the control arm (95% CI: $-\$7,558$ to $\$3,866$, $p=0.357$), although mean downstream costs in the WGS arm were \$700 higher when hospitalizations were omitted (95% CI: $-\$1,634$ to $\$3,440$, $p=0.393$). In primary care, mean six month total downstream costs were \$681

greater in the WGS arm compared to the control arm (95%CI: -\$884 to \$2,171, $p=0.699$) when hospitalizations were included and \$374 greater (95%CI: -\$991 to \$1,570) when hospitalizations were omitted.

Analyses that compared healthcare utilization and costs in the post-disclosure period to the pre-disclosure period showed some increases. Among cardiology participants (Appendix 10), we observed more imaging tests (all $p=0.047$) in both arms in the six months following disclosure compared to the six months preceding disclosure, although changes over time on costs were observed only for visits (all $p=0.002$) and for imaging tests in the WGS arm ($p=0.048$). Changes over time in total costs were non-significant, with an increase of \$2,939 (95%CI: -\$2,857 to \$8,772) in the control arm and an increase of \$1,728 (95%CI: -\$3,067 to \$6,387) in the WGS arm (Appendix 11). Changes over time did not differ by randomization status ($p=0.376$).

Among primary care participants and comparing the post-period to the pre-disclosure period, we observed more healthcare visits in the WGS arm ($p=0.020$) and greater visit-related costs in both randomization arms (all $p<0.001$). Changes in total costs were non-significant, with an increase of \$682 (95%CI: -\$472 to \$1,680) in the control arm and an increase of \$1,919 (95%CI: -\$1,151 to \$2,828) in the WGS arm. Changes over time did not differ by randomization status ($p=0.572$).

Sub-analyses of participants receiving WGS showed no statistically significant association between mean downstream costs among individuals with a previously unknown monogenic disease risk and individuals without one in either primary care (\$4,800 vs. \$2,900, respectively, $p=0.76$) or cardiology (\$6,861 vs \$9,611, respectively, $p=0.47$). Analyses on specific categories of costs were also inconclusive (all $p=0.161$).

Sensitivity and Scenario Analyses

Sensitivity analyses (Table 5) compared randomization arms on total costs, including WGS and downstream costs. Varying the WGS costs had the largest impact, where differences between randomization arms were observed at \$10,000 but not at \$500. Among cardiology patients, differences between randomization arms were observed when the WGS costs were \$10,000, when healthcare services were assigned cost weights at 50% of CMS fee schedule amounts, and when only immediately attributable services were analyzed. Notably, immediately attributable services (Appendix 12) were observed for only one cardiology patient in the control arm and one cardiology patient in the WGS arm. Among primary care patients, differences between randomization arms were also observed in all analyses except when WGS costs were \$2,500 or less and when healthcare services were assigned cost weights at 150% or more of CMS fee schedule amounts (Appendix 13). Among cardiology patients, omitting secondary findings altogether reduced costs by \$69 per patient, whereas among primary care patients, limiting reporting to only pathogenic variants for monogenic disease and carrier status reduced costs by \$182 per patient.

DISCUSSION

As the first randomized trial of WGS in primary and specialty care, the MedSeq Project presents a unique opportunity to collect novel data about the costs of WGS. Our data showed that the short-term costs were primarily driven by the costs of sequencing, interpretation, and disclosure, and we did not find evidence that WGS increased downstream healthcare costs. Although the MedSeq Project was not powered to draw definitive conclusions about the cost impact of WGS in cardiology and primary care settings, these findings may provide an important early foundation for future trials.

The patient-level data from the MedSeq Project adds to the paucity of economic literature surrounding WGS, particularly patient level data.³² Our findings are in line with previous work that provided microcosting data about whole exome sequencing,⁹ and extend them by providing insight about whole genome sequencing and how costs may vary with different reporting strategies and cost assumptions. Advances in next generation sequencing approaches are continuing to make WGS less expensive,²⁷ but approximately 25% of the total costs for providing WGS in our study were for steps such as variant confirmation and bioinformatic analyses. Nevertheless, it is possible that the costs associated with these associated steps will also drop, given recommendations to forego confirmation of nucleotide substitutions via Sanger sequencing.³³ In addition, the emergence of large genomic data sets such as ExAC,³⁴ improvements in data sharing between laboratories, and innovations in approaches to variant interpretation such as cross-species analyses³⁵ are likely to decrease bioinformatic costs even further by reducing the number of variants that require manual review and classification. Open questions also remain about whether the incremental benefits of WGS are worth its incremental costs compared to approaches such as exome sequencing, which is typically at least 25% cheaper expensive, or gene panels which can be thousands of dollars less expensive.

Notably, our study showed that WGS had a limited impact on the actions of cardiologists. Cardiologists in our study consulted the Genome Resource Center only once for assistance, spent only 10 additional minutes during disclosure sessions addressing WGS reports, and ordered immediate follow-up testing in response to WGS findings in only one instance. Cardiologists in our study tended to be familiar with genetic testing and regularly reviewed their patients' family histories, and all of the cardiology patients had received panel genetic testing for their diagnoses prior to disclosure sessions. It is possible that cardiologists had already addressed any important family history patterns, and that they believed they already had most of the information they needed to judge the importance of WGS findings, despite the novelty of most secondary findings.

While the short-term impact on patient wellbeing was not assessed, WGS did identify health-relevant variants in a large majority of participants, including diagnosis-related variants in half of sequenced cardiology patients and additional monogenic disease risks in eight cardiology patients and 13 primary care patients. The clinical significance of most of these variants was unclear. Guidelines to help physicians respond to monogenic findings identified in healthy patients or as secondary findings exist for only a few genes and conditions currently, although frameworks defining actionability have been proposed.³⁶

Among our participants, ClinGen Actionability Working Group Evidence-based Summaries currently existed for two of the eight secondary monogenic disease risks identified in cardiology patients (both in *F5*), and five of the thirteen monogenic disease risks identified in primary care patients (*HFE* (x2), *KCNQ1*, *TNNT2*, and *F5*).³⁷

Importantly, incorporating WGS into primary care and cardiology settings did not appear to increase downstream health sector costs over the short-term, even among patients who learned about a monogenic risk for disease through secondary findings. We observed more healthcare visits in both randomization arms and both cohorts in the six months following disclosure relative to the six months preceding disclosure, and in cardiology settings, we also observed more imaging and cardiology tests in both arms in the post-disclosure period. These differences are possibly a result of the study design, which mandated an in-person appointment for disclosure that physician participants often also used as well-care visits and health maintenance exams. Regardless, changes in healthcare utilization and associated costs did not differ by randomization status. The study may have been too small to detect differences, especially considering the primary analytic approach to include all healthcare services and out-of-pocket expenses. In addition, it is also possible that physicians within the MedSeq Project considered few of the WGS findings to be actionable, as evidenced by the small number of immediately attributable services we identified. If a Genome Resource Center had not been available, it is possible that we would have observed additional patient referrals to specialists, particularly among primary care patients who received WGS, and there would have been additional costs associated with these referrals. Nevertheless, the null findings around downstream health costs are notable given that the MedSeq Project's reporting criteria that was far broader than recommendations from the American College of Medical Genetics and Genomics (ACMG). The MedSeq Project examined a far more extensive list than most research or clinical studies, examining over 4,600 genes and including findings about carrier status, pharmacogenomic information, and polygenic risk predictions. Our sensitivity analyses suggest that using more liberal reporting criteria doubled the number of potentially health-relevant findings that were reported while increasing overall costs minimally (e.g., less than \$200 per patient, on average, to report secondary findings classified as likely pathogenic or uncertain significance: favor pathogenic). Numerous commentators have encouraged strict criteria for the reporting of secondary findings and discourage the use of WGS among healthy populations altogether, citing the possibility that disclosure could initiate follow-up testing and screening that increase costs while accruing limited benefits and possibly causing harms.^{13,38,39} Our data may begin to assuage those concerns.

Although this was a randomized controlled trial with a planned cost analysis, there are notable limitations. Physicians and patients were enrolled from a single well-supported health care system in metro Boston, Massachusetts, and physicians and patients in other settings may be less willing to undertake WGS for clinical and financial reasons. It is possible that we would have observed more use of support resources, like the Genome Resource Center, and more follow-up screening and testing if we had enrolled physicians who were less familiar with genomics or had less access to knowledgeable colleagues. As noted above, the sample size was too small to draw conclusions on a population level, and the six month time horizon may have been too short to observe the full impact on costs and

health benefits. Patient time costs were not assessed, nor were the effects of disclosure on participants' family members, precluding a complete analysis from a societal perspective. Physicians benefitted from extensive study-specific education, and were supported by a Genome Resource Center. Control arm participants received a family history review that was more rigorous than standard of care, which may have increased their downstream costs. Finally, our patient participants were more educated and less ethnically diverse than the general population. Lack of diversity has been an ongoing problem in genomic research,⁴⁰ although recent efforts such as the All of Us Research Program have prioritized enrolling more representative populations. Nevertheless, our study provides novel and much-needed data to help decision makers begin to understand the short-term cost implications of integrating WGS into clinical care, and provides insight about what data are needed to provide more clarity about the economic implications of this technology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Participant characteristics

Characteristic n (%) unless noted	Cardiology		Primary Care	
	Control (n=51)	WGS (n=49)	Control (n=50)	WGS (n=50)
Mean age (sd)	55.6 (12.2)	56.1 (16.2)	54.6 (7.6)	55.1 (7.1)
Age range	26.0 – 72.1	18.7 – 84.6	41.6 – 67.9	41.2 – 65.9
Gender				
Female	19 (37.3%)	24 (49.0%)	30 (60.0%)	28 (56.0%)
Male	32 (62.7%)	25 (51.0%)	20 (40.0%)	22 (44.0%)
Race				
Non-Hispanic white	45 (88.2%)	43 (87.8%)	43 (86.0%)	44 (88.0%)
Other	6 (11.8%)	6 (12.2%)	7 (14.0%)	6 (12.0%)
Annual Household Income				
<\$100,000	19 (37.3%)	24 (49.0%)	16 (32.0%)	9 (18.0%)
\$100,000	30 (58.8%)	23 (46.9%)	31 (62.0%)	40 (80.0%)
No response	2 (3.9%)	2 (4.1%)	3 (6.0%)	1 (2.0%)
Education				
Did not graduate from college	9 (17.6%)	13 (26.5%)	11 (22.0%)	3 (6.0%)
College graduate or higher	42 (82.4%)	36 (73.5%)	39 (78.0%) *	47 (94.0%) *
Diagnosis (Cardiology Cohort)				
Hypertrophic cardiomyopathy	37 (72.5%)	42 (85.7%)		
Dilated cardiomyopathy	14 (27.5%)	7 (14.3%)		
Has health insurance	51 (100%)	49 (100%)	49 (98.0%)	49 (98.0%)
Self-reported health				
Excellent	4 (8%)	2 (4%)	16 (32%)	23 (46%)
Very good	19 (37%)	16 (33%)	24 (48%)	21 (42%)
Good	20 (39%)	20 (41%)	8 (16%)	4 (8%)
Fair	6 (12%)	9 (18%)	2 (4%)	2 (4%)
Poor	2 (4%)	2 (4%)	0 (0%)	0 (0%)

*
p=0.021 in within-cohort analyses

Table 2

Summary of findings from whole genome sequencing.*

Variant Classification	Variants Related to Condition				Monogenic Disease Risk Secondary Findings				Carrier Findings			
	Patients with this result (%)	Mean per patient (sd)	Range per patient	Patients with this result (%)	Mean per patient (sd)	Range per patient	Patients with this result (%)	Mean per patient (sd)	Range per patient	Patients with this result (%)	Mean per patient (sd)	Range per patient
<i>Cardiology cohort (n=49)</i>												
Any results	24 (49%)	0.6 (0.6)	0–2	8 (16%)	0.2 (0.4)	0–1	41 (84%)	1.9 (1.4)	0–6			
Pathogenic	12 (24%)	0.2 (0.4)	0–1	2 (4%)	0.0 (0.2)	0–1	33 (67%)	1.2 (1.1)	0–4			
Likely pathogenic	4 (8%)	0.1 (0.3)	0–1	3 (6%)	0.1 (0.2)	0–1	18 (37%)	0.4 (0.6)	0–2			
VUS: Favor pathogenic	4 (8%)	0.1 (0.3)	0–1	1 (2%)	0.0 (0.1)	0–1	6 (12%)	0.2 (0.6)	0–3			
VUS*	5 (10%)	0.1 (0.5)	0–2	-	-	-	-	-	-			
Risk allele†	0 (0%)	0.0 (0.0)	0	2 (4%)	0.0 (0.2)	0–1	1 (2%)	0.0 (0.1)	0–1			
<i>Primary care cohort (n=50)</i>												
<i>Monogenic Disease Risk Findings</i>												
All results	13 (26%)	0.3 (0.4)	0–1	50 (100%)	2.7 (1.5)	1–7						
Pathogenic	6 (12%)	0.1 (0.3)	0–1	45 (90%)	1.9 (1.3)	0–5						
Likely pathogenic	3 (6%)	0.1 (0.2)	0–1	21 (42%)	0.6 (0.8)	0–3						
VUS: Favor pathogenic	3 (6%)	0.1 (0.2)	0–1	10 (20%)	0.2 (0.5)	0–2						
Risk allele†	1 (3%)	0.0 (0.1)	0–1	0 (0%)	0 (0.0)	0						

* Variants of uncertain significance (VUS) where evidence did not favor pathogenicity were only disclosed if they potentially explained a cardiology patient's diagnosis of hypertrophic or dilated cardiomyopathy. All patients also received polygenic risk predictions about 8 cardiometabolic traits and pharmacogenomic results about 5 drugs. See Appendix 6 and Appendix 7, respectively

† Two cardiology patients and one primary care patient were identified with risk alleles for Factor V Leiden thrombophilia, which were reported as monogenic disease risk findings. In addition, one cardiology patient was identified with an allele associated with HEXA pseudodeficiency which was reported as a carrier finding.

Table 3

Per-patient time requirements and costs to review family history reports and whole genome sequencing reports.*

	Mean Time (SD)		Mean Costs, USD (SD)		Difference in Mean Costs, USD (95% CI)		p
	Control (n=51)	WGS (n=49)	Control (n=51)	WGS (n=49)			
Cardiology Cohort							
Informed consent for WGS	0 (0)	16 (6)	0 (0)	15 (5)	15 (13 to 17)		<0.001
Sequencing [†]	-	-	0 (0)	4000 (0)	4000 (4000 to 4000)		<0.001
Sanger confirmation [†]	-	-	0 (0)	603 (118)	603 (571 to 637)		<0.001
Variant interpretation and report drafting	0 (0)	305 (219)	0 (0)	292 (209)	292 (231 to 356)		<0.001
Laboratory report signout	0 (0)	82 (54)	0 (0)	101 (66)	101 (83 to 120)		<0.001
Data storage [†]	-	-	0 (0)	75 (0)	75 (75 to 75)		<0.001
Consultation with Genome Resource Center	0 (0)	0 (2)	0 (0)	0 (2)	0 (0 to 1)		0.863
Disclosure of results	14 (9)	24 (11)	170 (27)	183 (25)	12 (2 to 22)		0.026
Total, cardiology	14 (9)	428 (228)	170 (27)	5268 (288)	5098 (5022 to 5182)		<0.001
Primary Care Cohort							
Informed consent for WGS	0 (0)	16 (5)	0 (0)	14 (5)	14 (13 to 16)		<0.001
Sequencing [†]	-	-	0 (0)	4000 (0)	4000 (4000 to 4000)		<0.001
Sanger confirmation [†]	-	-	0 (0)	624 (120)	624 (591 to 660)		<0.001
Variant interpretation and report drafting	0 (0)	214 (155)	0 (0)	204 (148)	204 (162 to 248)		<0.001
Laboratory report signout	0 (0)	95 (63)	0 (0)	116 (77)	116 (95 to 139)		<0.001
Data storage [†]	0 (0)	0 (0)	0 (0)	75 (0)	75 (75 to 75)		<0.001
Consultation with Genome Resource Center	0 (1)	9 (23)	0 (1)	6 (17)	6 (2 to 11)		0.003
Disclosure of results	17 (10)	35 (18)	149 (26)	183 (28)	34 (23 to 44)		<0.001
Total, primary care	17 (10)	368 (184)	149 (27)	5222 (273)	5073 (4995 to 5155)		<0.001

* Cardiology patients also received a review of findings from prior genetic testing for their cardiomyopathy diagnoses. Analyses exclude research-specific costs, such as consenting participants for study participation. Except where noted, costs were estimated using a microcosting approach by tracking time demands and applying relevant wage rates. Steps that were not applicable to participants randomized to the control arm were not assigned times and assigned zero for associated costs.

[†] Costs for these steps were estimated from market rates, and we did not track associated laboratory time demands.

Healthcare utilization and costs during 6 months after review of review family history reports and whole genome sequencing reports, if applicable.*

Table 4

	Mean Counts (SD)		Mean Cost, USD	Difference in Mean Costs, USD (95% CI)		P
<i>Cardiology Cohort</i>	<i>Control (n=51)</i>	<i>WGS (n=49)</i>	<i>Control (n=51)</i>	<i>WGS (n=49)</i>		
Visits	7.2 (7.5)	7.8 (6.5)	1347	1344	-3 (-517 to 488)	0.504
Labs, outpatient care	6.9 (6.8)	9.5 (15.5)	109	137	28 (-39 to 132)	0.388
Imaging tests, outpatient care	2.1 (1.9)	2.1 (2.2)	638	696	58 (-300 to 445)	0.385
Cardiology tests, outpatient care	3.2 (1.7)	3.1 (1.9)	188	192	4 (-42 to 52)	0.473
Other outpatient procedures	†	†	1489	2265	776 (-1401 to 3091)	0.337
Hospitalizations	0.3 (0.8)	0.2 (0.4)	4978	2717	-2261 (-7283 to 2459)	0.280
Medications	4.5 (2.6)	5.2 (3.1)	437	468	31 (-211 to 292)	0.389
Medical equipment	†	†	39	20	-19 (-65 to 17)	0.318
Visit co-pays	†	†	319	208	-111 (-409 to 126)	0.516
Patient procedural co-pays	†	†	75	46	-29 (-84 to 23)	0.627
Additional out-of-pocket	†	†	51	15	-36 (-94 to 7)	0.406
Total, Cardiology			9670	8109	-1560 (-7558 to 3866)	0.357
Excluding hospitalizations			4692	5392	700 (-1634 to 3440)	0.393
<i>Primary Care Cohort</i>	<i>Control (n=50)</i>	<i>WGS (n=50)</i>	<i>Control (n=50)</i>	<i>WGS (n=50)</i>		
Visits	6.9 (7.4)	8.4 (8.7)	1347	1581	234 (-317 to 759)	0.403
Labs, outpatient care	4.4 (4.8)	5.5 (5.9)	66	96	30 (-9 to 76)	0.410
Imaging tests, outpatient care	0.9 (1.5)	1.0 (1.4)	149	227	78 (-40 to 205)	0.586
Cardiology tests, outpatient care	0.4 (0.6)	0.5 (0.9)	49	52	3 (-28 to 39)	0.579
Other outpatient procedures	†	†	540	625	85 (-460 to 634)	0.787
Hospitalizations	0.0 (0.2)	0.0 (0.1)	142	449	307 (-473 to 1211)	0.811
Medications	2.0 (2.1)	1.8 (1.9)	159	157	-2 (-108 to 99)	0.674
Medical equipment	†	†	7	4	-3 (-24 to 12)	0.645
Visit co-pays	†	†	357	317	-41 (-518 to 287)	0.424
Patient procedural co-pays	†	†	110	150	40 (-124 to 231)	0.370
Additional out-of-pocket	†	†	62	11	-52 (-183 to 17)	0.371
Total, Primary Care			2989	3670	681 (-884 to 2171)	0.699
Excluding hospitalizations			2847	3221	374 (-991 to 1570)	0.577

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* Cardiology patients also received a review of findings from prior genetic testing for their cardiomyopathy diagnoses.

† Counts data were not collected for these items.

Table 5

One-way scenario and sensitivity analyses of total costs.*

Costs Considered and Parameter Assumptions	Control Arm, USD	WGS Arm, USD	Difference between Arms, USD (95% CI)	p
Cardiology Cohort	(n = 51)	(n = 49)		
Base case	9841	13376	3535 (–2490 to 8970)	0.236
<i>Downstream costs analyzed</i>				
Immediately attributable services	176	5270	5094 (5015 to 5175)	<0.001
Full genetics workup	9841	13400	3559 (–2457 to 8980)	0.234
<i>Secondary findings reported</i>				
Omitting carrier status	9841	13194	3353 (–2634 to 8780)	0.247
Omitting polygenic risk predictions	9841	13372	3531 (–2494 to 8971)	0.236
<i>Reporting criteria for secondary findings about monogenic disease risks and carrier status</i>				
Pathogenic or likely pathogenic	9841	13250	3409 (–2595 to 8838)	0.243
Only pathogenic	9841	13244	3403 (–2601 to 8839)	0.244
No secondary findings	9941	13307	3366 (–1042 to 7774)	0.134
<i>Total cost of integrating WGS (base: \$5,268)</i>				
\$500	9841	8610	–1231 (–7234 to 4198)	0.371
\$1000	9841	9110	–731 (–6734 to 4698)	0.387
\$2500	9841	10609	769 (–5234 to 6198)	0.374
\$10000	9841	18110	8269 (2266 to 13698)	0.035
<i>Healthcare costs</i>				
50% of CMS rates	5838	10058	4219 (1059 to 7044)	0.038
75% of CMS rates	7840	11717	3877 (–712 to 7983)	0.144
150% of CMS rates	13845	16695	2850 (–6094 to 11029)	0.323
200% of CMS rates	17848	20013	2165 (–9718 to 13041)	0.358
<i>Perspective</i>				
Health sector (base case)	9841	13376	3535 (–2490 to 8970)	0.236
Third-party payer (excludes out-of-pocket costs)	9397	13107	3710 (–2272 to 9082)	0.220
Primary Care Cohort	(n = 50)	(n = 50)		
Base case	3137	8894	5756 (4196 to 7232)	0.017
<i>Downstream costs analyzed</i>				
Immediately attributable services	196	5290	5094 (4982 to 5211)	<0.001
Full genetics workup	3137	9018	5881 (4330 to 7388)	0.015
<i>Secondary findings reported[†]</i>				
Omitting carrier status	3137	8668	5531 (3974 to 7014)	0.021
Omitting polygenic risk predictions	3137	8878	5741 (4177 to 7224)	0.017
<i>Reporting criteria for monogenic disease risk and carrier status findings</i>				
Pathogenic or likely pathogenic	3137	8772	5635 (4079 to 7124)	0.019
Only pathogenic	3137	8712	5576 (4031 to 7029)	0.020
<i>Total cost of integrating WGS (base: \$5,136)</i>				
\$500	3137	4169	1032 (–538 to 2525)	0.617

Costs Considered and Parameter Assumptions	Control Arm, USD	WGS Arm, USD	Difference between Arms, USD (95% CI)	p
\$1000	3137	4669	1532 (−38 to 3025)	0.490
\$2500	3137	6169	3032 (1462 to 4525)	0.186
\$10000	3137	13669	10532 (8962 to 12025)	<0.001
<i>Healthcare costs</i>				
50% of CMS rates	2331	7792	5461 (4331 to 6480)	<0.001
75% of CMS rates	2734	8343	5609 (4279 to 6866)	0.003
150% of CMS rates	3942	9996	6054 (3946 to 8125)	0.077
200% of CMS rates	4748	11098	6350 (3689 to 9031)	0.154
<i>Perspective</i>				
Health sector (base case)	3137	8894	5756 (4196 to 7232)	0.017
Third-party payer (excludes out-of-pocket costs)	2607	8416	5809 (4571 to 7091)	0.013

* Analyses compared randomization arms after varying the components that were examined or cost assumptions. Costs included those associated with reviewing family history reports, prior genetic test results (cardiology cohort, only) and whole genome sequencing reports, if applicable; and additional health-related costs over the six-month period afterwards.

[†] Scenario analyses of primary care patients assumed monogenic disease risks were considered primary findings.