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The impact of whole genome sequencing on the primary care and outcomes of healthy adult patients: A pilot randomized trial

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Abstract

Background—Whole-genome sequencing (WGS) in asymptomatic adults might prevent disease but increase healthcare utilization without clinical value.

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Objective—Describe the effect on clinical care and outcomes of adding WGS to standardized family history assessment in primary care.

Design—Pilot randomized trial.

Setting—Academic primary care practices.

Participants—Nine primary care physicians (PCPs) and 100 generally healthy patients aged 40–65.

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

Measurements—Clinical outcomes and healthcare utilization through six months were obtained from audio-recorded PCP-patient discussions and medical records. Patients' health behavior changes were surveyed six 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% were female. Eleven FH+WGS patients (22%, 12%–36%) had new MDR results. Only two (4%, 0.01%–14%) had evidence of the phenotypes predicted by an MDR result (fundus albipunctatus due to *RDH5* and variegate porphyria due to *PPOX*). PCPs recommended new clinical actions for 16% (8%–30%) of FH patients and 34% (22%–49%) of FH+WGS patients. Thirty (17%–45%) and 41% (27%–56%) of FH and FH+WGS patients, respectively, reported making a health behavior change after six months. Geneticists rated PCP management of eight MDR results (73%, 39%–99%) as appropriate and two (18%, 3%–52%) as inappropriate.

Limitations—Limited sample size and ancestral and socioeconomic diversity.

Conclusions—Adding WGS to primary care reveals new molecular findings of uncertain clinical utility. Non-geneticist providers may be able to manage WGS results appropriately, but WGS may prompt additional clinical actions of unclear value.

Registration—ClinicalTrials.gov identifier NCT01736566

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Introduction

The benefits of clinical exome and genome sequencing are becoming clearer in the evaluation of highly heritable conditions and undiagnosed diseases(1, 2), in prenatal screening(3, 4), and in cancer treatment(5, 6). Numerous healthcare systems are moving towards the more widespread adoption of clinical sequencing for many of their patients. Compared to simpler gene- or gene panel-based testing, whole-genome sequencing (WGS) brings additional complexity in the different types of results it can deliver, ranging from monogenic disease risk (MDR) results indicating risk for Mendelian diseases to common risk alleles with small effect sizes for complex polygenic conditions. While sequencing is still predominantly the province of genetics specialists, its expansion in this era of limited

healthcare resources, including access to genetics professionals, evokes concern—namely, whether non-geneticist physicians and primary care physicians (PCPs) in particular can manage genomic information appropriately(7–9) and the degree to which the clinical integration of genomics enables early disease detection and prevention or leads to anxiety and unnecessary and costly follow-up evaluation and management(10, 11).

While the risk-benefit ratio of sequencing is likely favorable in specific clinical contexts, its potential risks and costs might outweigh its benefits for generally healthy individuals. To examine this balance, we developed a process to perform clinical WGS and variant interpretation, issue a WGS report that non-geneticist physicians could use, and measure downstream clinical outcomes. To provide early empirical evidence about the risks and benefits of integrating sequencing into primary care, we conducted a pilot randomized controlled trial (RCT) of family health history (FH) alone versus FH and WGS.

Methods

Study Design and Participants

The MedSeq Project is a pair of pilot RCTs of WGS in two clinical contexts: subspecialty care for patients with cardiomyopathy and primary care for generally healthy adults. This manuscript describes the results of the primary care trial. Details of design, methods, and recruitment have been previously described(12, 13). In brief, we used individual email outreach and presentations at staff meetings to recruit a convenience sample of nine PCPs from one academic network of outpatient practices in Boston, Massachusetts, each of whom helped study staff recruit approximately ten of his or her patients until the prespecified sample of 100 patients was reached (Appendix). Eligible patients were 40-65 years old, had no history of cardiovascular disease or diabetes mellitus, and were deemed generally healthy in the judgment of the PCP. The Partners Human Research Committee approved this study.

Interventions

At a baseline study visit, all patients reported FH using a modified version of the U.S. Surgeon General's My Family Health Portrait web tool(14). Using concealed envelopes, study staff randomly assigned patients in a 1:1 ratio to undergo a sham blood draw (FH arm) or a blood draw for WGS (FH+WGS arm; Appendix Figure 1). For each FH patient, the PCP received the pedigree resulting from the FH web tool. For each FH+WGS patient, the PCP received both the pedigree and an interpreted WGS report, described below.

Physician Education and Support

Before enrolling patients, PCP participants underwent a brief educational curriculum consisting of 4 hours of case-based online modules and 2 one-hour in-person group classes, including an orientation to the genome report, described previously(9). During the study, PCPs had the opportunity to contact a Genome Resource Center (GRC) staffed by medical geneticists and genetic counselors affiliated with the study to ask questions about patients' results. If consulted, GRC staff assisted the PCPs with result interpretation but did not make clinical recommendations. The study protocol did not otherwise include genetic counselors or geneticists.

Whole Genome Sequencing, Interpretation, and Reporting

WGS was performed in the Clinical Laboratory Improvement Amendments (CLIA)-certified Illumina Clinical Services Laboratory (San Diego, CA), as described in the Appendix and previously(15). Raw data files were analyzed in the Partners Laboratory for Molecular Medicine, where molecular geneticists classified variants selected for possible clinical relevance from a curated list of 4,631 disease-associated genes into five categories: benign, likely benign, uncertain significance (VUS), likely pathogenic (LP), and pathogenic (P), described further in the Appendix. A subset of VUS were subclassified as "VUS: favor benign" or "VUS: favor pathogenic" (VUS:FP). The genome report and cardiac risk supplement delivered to PCPs have been described previously(15–17) and are illustrated in the Appendix. They included sections for monogenic disease risk (MDR), recessive carrier risk, pharmacogenomic associations, and polygenic risk estimates for eight cardiometabolic traits(17). Variants were included in the MDR section of the report if they denoted Mendelian genetic disease risk for the patient, such as a single P, LP, or VUS:FP variant in a gene associated with autosomal dominant or X-linked (in males) disease or biallelic P, LP, or VUS:FP variants in a gene associated with autosomal recessive disease. The report included a summary of the variant interpretation, disease information, and familial risk but did not include recommendations for clinical management. Pedigrees and genome reports were delivered directly to the PCP before an audio-recorded disclosure visit, during which each patient met with his or her PCP to learn his/her randomization status and discuss the study reports before they were uploaded to the electronic health record (EHR).

Outcomes

This trial is registered at ClinicalTrials.gov (Identifier NCT01736566). We collected a range of pre- and post-specified outcomes to study the process and impact of integrating WGS into primary care. In this manuscript, we present clinical and healthcare outcomes. Namely, we include the following registered primary outcomes: healthcare utilization, anxiety, depression, perceived health, and health behaviors. We also include the following outcomes, which were not pre-specified: molecular and clinical diagnoses, appropriateness of clinical management, and healthcare costs. Other registered primary and secondary psychosocial outcomes will be published separately.

Patient-Reported Outcomes—Patient surveys both at baseline and six months after the disclosure visit included the 14-item Hospital Anxiety and Depression Scale (HADS)(18) and self-reported health status on a 5-item Likert scale ranging from *poor* to *excellent*(19). The six-month survey also included the following health behavior question(20): "Have you made any of the following health or wellness changes that were specifically motivated by the information you discussed with your doctor?" Response options included *diet*, *exercise*, *use of vitamins/herbal supplements*, *use of medications*, and *other*.

Appropriateness of Clinical Management—To assess how PCPs managed MDR results, we used the validated RAND/UCLA Appropriateness Method(21), described further in the Appendix. An external panel of 11 academic geneticists not otherwise involved in the study rated the appropriateness of the PCPs' immediate management of each MDR variant on a validated 9-point scale, ranging from 1 (*Extremely inappropriate*) to 9 (*Extremely*

appropriate). After reviewing all cases, these experts proposed general guidelines for PCPs managing a variant in an asymptomatic adult. To examine whether WGS impacted guideline-concordant primary care, we used EHR review at six months to determine each patient's concordance with U.S. Preventive Services Task Force (USPSTF) guidelines, further described in the Appendix.

Healthcare Utilization and Costs—Healthcare utilization and associated costs were assessed immediately after the disclosure visit (immediate attributable utilization/costs) and six months after disclosure (six-month utilization/costs). Immediate attributable utilization was determined from a checklist survey that asked PCPs after each disclosure visit which clinical actions they ordered, if any, as a result of the FH and/or WGS results. For each action reported, the checklist asked the PCP to identify which specific FH and/or WGS result(s) prompted the action. Data from both the Partners Research Patient Data Registry (RPDR)(22) and EHR review were used to determine six-month utilization and to confirm whether immediately attributable actions from the checklist were completed by the patient. Counts of clinical actions during the six months after the disclosure visit were determined from EHR review and billing codes from the RPDR. We determined six-month costs using 2015 Centers for Medicare and Medicaid Services (CMS) price weights (Appendix). The Appendix provides additional details of the measurement of utilization and costs.

Data Synthesis and Analysis

Sample size was based on the number of WGS that could be performed and not on statistical considerations. One enrolled patient was randomized to the FH+WGS arm but withdrew from the study before learning his allocation; we present the results from the 50 FH and 50 FH+WGS patients who received their allocated interventions. Sensitivity analyses for six-month counts and costs were performed by limiting the data only to those actions with billing codes obtained from the RPDR(22). Exact 95% confidence intervals (CI) were calculated with R 3.2.2 statistical language (Vienna, Austria).

Role of the Funding Source

The National Institutes of Health had no role in the design of the study; the collection, analysis, and interpretation of the data; or the decision to approve publication of the finished manuscript.

Results

Participant Characteristics

Table 1 and Appendix Table 1 show the characteristics of the 100 patient-participants receiving FH or FH+WGS results and the nine PCP-participants, respectively.

WGS Results

All samples achieved a minimum coverage of 8 reads per base for at least 95% of the genome, with a mean average coverage across the genome of 42.3 reads per base. A range of 5,179,293 to 5,788,580 variants per patient in the FH+WGS arm was identified. Eleven FH

+WGS patients (22%, CI 12%–36%) had new MDR results previously unknown to them (Table 2). Two other patients were homozygous for the pathogenic p.Cys282Tyr variant in *HFE* but had received a diagnosis of hereditary hemochromatosis previously and were already receiving medical care. Of the 11 patients with a new MDR molecular diagnosis, supporting phenotypic evidence for a new clinical diagnosis was identified in two (4%, 95% CI 0.01%–15%) within the subsequent six months. One patient was homozygous for a pathogenic p.Trp95X variant in *RDH5*, associated with fundus albipunctatus. Presented with this result, he acknowledged an ophthalmic history of difficulty with dark adaptation and "white spots" seen on prior fundoscopy. A second patient with a pathogenic p.Leu67X variant in *PPOX*, associated with variegate porphyria, described occasional "odd rashes," and a follow-up genetics consultation confirmed a subclinical porphyria phenotype based on dermatologic symptoms and a family history of photosensitivity in the proband's mother and son, not reported on her pedigree. For the remaining nine patients with a new MDR result, six-month EHR review found no evidence of the predicted phenotypes from routine clinical evaluation. For example, a patient with a LP p.Ser276ProfsX13 variant in *KCNQ1* demonstrated no evidence of long QT syndrome on subsequent evaluation with resting electrocardiogram (ECG) or exercise stress testing. Two of the 12 MDR variants were in medically actionable genes (*KCNQ1* and *TNNT2*) as defined by the American College of Medicine Genetics and Genomics (ACMG)(23) but were classified as LP and VUS:FP, respectively.

All sequenced patients had at least one carrier variant associated with a recessive condition (median 2, range 1–7, Appendix Table 2). Appendix Figure 2 and Appendix Table 3 show the distribution of reported pharmacogenomic and polygenic results, respectively. Overall, 48 patients (96%, 95% CI 85%–99%) received a pharmacogenomic result indicating atypical or non-standard response to at least one medication. Six patients were taking any of these medications at baseline (simvastatin, n=5; metformin, n=1), and no prescription change or adverse effect was documented during the six-month observation period. The patient taking metformin (1500 mg daily for metabolic syndrome) received a pharmacogenomic result predicting decreased glycemic response to the drug, but she and her PCP decided not to increase her dose of metformin, choosing instead to use hemoglobin A1c to guide management.

PCP Management of MDR Variants

Table 2 summarizes the PCP's management of each newly identified MDR result in 11 patients. In six of these patients, no additional management was recommended beyond history, physical examination, and counseling, while six variants in five patients prompted additional evaluation: two ECG (variants in *KCNQ1* and *ANK2*), four referrals to specialists (variants in *KCNQ1*, *PPOX*, *TNNT2*, and *ANK2*), and one serum ferritin level (two variants in *HFE*). The external panel of geneticists judged that eight cases (73%, 95% CI 39%–99%) were managed appropriately and two (18%, 95% CI 3%–52%) inappropriately: one because of under-evaluation of a pathogenic variant and one because of miscommunication about inheritance. The panel rated the management of one variant, p.Gly137Ala VUS:FP in *ARSE*, associated with chondrodysplasia punctata, as neither appropriate nor inappropriate. Panelists thought the PCP under-evaluated the patient for subtle clinical manifestations of

chondrodysplasia punctata but did not rate the management as inappropriate, given the VUS categorization. After discussion, panelists generated the five general recommendations shown in the Text Box. The proportions of patients with USPSTF guideline-concordant care did not differ between the two arms at six months (Appendix Table 4).

Healthcare Utilization and Costs After FH and WGS Results

PCPs recommended at least one immediately attributable clinical action for 16% (95% CI 8%–30%) of FH patients and 34% (95% CI 22%–49%) of FH+WGS patients (Table 3). Even in these established PCP-patient dyads, discussion of FH alone prompted additional actions, such as a dermatology referral for a FH of melanoma and C-reactive protein testing for a FH of heart disease. In the FH+WGS arm, referrals were often prompted by MDR results; in contrast, most additional laboratory and cardiac testing in the FH+WGS arm was prompted by polygenic risk estimates for cardiometabolic traits or *HFE* carrier variant status. Total costs for the immediately attributable recommended actions averaged $41 (median $0, range $0-$1,063) and $68 (median $0, range $0-$603) in the FH and FH+WGS arms, respectively.

Table 4 shows healthcare utilization and costs in the six months following results disclosure. Six-month costs averaged $1,142 (median $548, range $0-$10,704) in the FH arm and $1,490 (median $694, range $0-$15,026) in the FH+WGS arm. Appendix Table 5 shows the results of sensitivity analyses without costs of imputed billing codes. Within the FH+WGS arm, the six-month costs of the 11 patients with a new MDR result averaged $2,526 (median $694, range $0–$15,026), while those in the 39 without a new MDR results averaged $1,198 (median $694, range $0-$10,238).

Patient-Reported Outcomes

Table 5 shows the self-reported health, anxiety, depression of patients at baseline and six months. At six months, 30% (95% CI 17%–45%) and 41% (95% CI 27%–56%) of FH and FH+WGS patients, respectively, reported making a health behavior change related to their study results, most frequently involving diet or exercise.

Discussion

Despite excitement about how sequencing might revolutionize disease detection and prevention(24), there is concurrent concern that its introduction into clinical care, particularly of generally healthy individuals, might cause patient anxiety and harm and increase healthcare costs. Rigorous empiric evidence about these potential benefits and risks has been scant(25–27), but the development of clinical sequencing programs has continued apace in many healthcare systems. In this trial of WGS integrated into primary care settings, we found that about one in five generally healthy adult patients who were sequenced had a previously unrecognized variant with potential risk for a Mendelian disease. Only about one in 25 had clinically confirmed abnormalities related to a variant. Identified variants were associated with rare diseases likely to be unfamiliar to many clinicians, although the PCPs in this study were generally able to manage them appropriately, according to expert review. WGS did not appear to cause patient anxiety or depression, but considerable proportions of

patients in both arms reported making health behavior changes related to the results they received in the study. Both FH and WGS prompted medical decision-making and new immediate clinical orders. We observed directions of effect consistent with increased six-month healthcare utilization and costs due to WGS, but larger studies are needed to confirm these differences.

While it is important to determine whether WGS increases healthcare utilization and costs, a separate but critical first question is the value derived from WGS(28). Although the value of recessive carrier states to inform reproductive decisions and pharmacogenomic associations to inform pharmacotherapy might accrue over a longer term, at least some of the clinical benefit of identifying an MDR variant in a middle-aged adult patient might reasonably be expected to occur within a short timeframe. We attempted to assess this value in four ways. First, examining the clinical courses of patients undergoing WGS, we observed no patients whose new molecular diagnoses clearly improved short-term health outcomes. Two patients had some evidence of the phenotypes associated with their reported variants, but the clinical value of making these diagnoses (fundus albipunctatus and subclinical variegate porphyria) is unclear. Avoidance of medications that precipitate porphyria attacks might benefit the patient with subclinical variegate porphyria.

Many variants classified as disease-causing or pathogenic in databases such the Human Gene Mutation Database and by certain submitters to ClinVar are determined not to be pathogenic upon expert review(29–34). Our analytic pipeline allowed for the identification of reported pathogenic variants in more than 4600 disease-associated genes but concluded with a manual review of the supporting evidence of each identified variant, allowing for variant classification using current ACMG standards and inclusion of only those variants meeting a rigorous evidence base for pathogenicity(35). The list of genes and variants considered reportable will likely change as new gene-disease associations are identified, better estimates of penetrance from unbiased samples are generated, and implications for prognosis and therapy are defined(36, 37). Indeed, the *PDE11A* variant (p.Thr58ProfsX41) reported to one participant was reclassified from VUS:FP to VUS after the study period and thus no longer meets MedSeq Project reporting criteria. These advances will maximize the clinical value of genomic medicine by increasing the likelihood that a molecular diagnosis results in a clinical diagnosis while minimizing the use of unnecessary follow-up evaluation for variants known to be clinically insignificant.

Second, we observed neither benefit nor harm from WGS on USPSTF guideline-concordant care. Most patients were already meeting these guidelines at study baseline, but we found no evidence that WGS enhanced or detracted from preventive care. Third, WGS neither worsened nor improved self-rated health, anxiety, or depression scores among FH+WGS patients, compared to FH patients. Many patients reported health behavior changes in response to either FH or FH+WGS results, although the appropriateness of these changes requires further examination. Fourth, experts judged that PCPs' management of MDR results was appropriate in eight of 11 cases. Instances of inappropriate management were so judged because of under-evaluation of the variant's disease risk or miscommunication about its significance, not because of concerns about safety or unnecessary or harmful follow-up evaluation.

The results of this study do not support the use of WGS in primary care but suggest that, if a healthy adult undergoes WGS, some of the resulting increased utilization may be clinically appropriate. Furthermore, they challenge the common notion that PCPs are unprepared to make appropriate medical decisions about complex sequencing results(7–9), although PCPs may need support in managing specific variants. Indeed, many MDR cases judged as appropriately managed resulted in referrals to genetics professionals. As the demand for genetics professionals exceeds supply, these preliminary data suggest that PCPs can be trusted to recognize when to refer a patient with WGS for genetics consultation. The recommendations generated by our panelists may help guide non-geneticist physicians faced with managing a genome variant identified in an asymptomatic patient. While our study examined WGS in a generally healthy adult population, these results may generalize to patients for whom specialists order clinical sequencing for a primary indication but who then return to their PCPs for management of any secondary findings identified in the process.

Strengths of the present study include its randomized design, use of validated instruments, and use of EHR data to assess medical care. However, there are important limitations to note. The small sample size of this trial limited the statistical power to detect between-group differences and restricted the range of clinically significant variants observed. Because much of the benefit of WGS in ostensibly healthy individuals might be its ability to detect rare but treatable monogenic disorders, such as familial cancer syndromes, larger trials are needed to determine the impact of WGS as a screening tool on the health and healthcare of patient populations. Moreover, it is imperative that future studies feature greater ancestral, geographic, and socioeconomic diversity than the current pilot trial, if the observed benefits and risks of sequencing are to be generalizable(38). The use of a standardized FH collection tool as our control intervention may not represent typical practice. This and the possibility of contamination among FH and FH+WGS patients treated by the same PCP may have biased the difference in downstream utilization and costs towards the null, as evidenced by the additional clinical actions prompted by FH alone. Although we measured all medical care documented in the EHR, including notes and results from outside providers, our analyses do not account for any outside medical care not recorded in the EHR. This study did not analyze the potential benefits of WGS to patient-participants' family members, often proposed as a driver of the clinical utility of WGS(39, 40). Studies will need longer follow-up to determine the clinical impact of all types of WGS results (*e.g.* pharmacogenomic, carrier status, and MDR), particularly if studying younger cohorts in whom MDR variants might not yet manifest. We hope our experience informs the design and outcomes assessment of the several research studies and clinical programs that are preparing for the large-scale return of genomic results to more diverse groups of participants, patients, and their providers in academic and non-academic settings.

In conclusion, we found that about one in five generally healthy patients undergoing WGS in a primary care setting had a new molecular diagnosis, while only one in 25 had a new clinical diagnosis. Although some PCPs may be able to manage the results appropriately, WGS may prompt additional clinical actions without evidence of short-term distress or clinical utility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Text Box

Expert recommendations for the primary care management of a genetic variant in an ostensibly healthy patient

1. Consult resources such as Online Mendelian Inheritance in Man (OMIM), GeneReviews, and the medical literature for more information about conditions of concern.
2. Obtain additional personal and family health history to target potential phenotypic associations with the variant, keeping in mind the possibility of variable expressivity and reduced penetrance.
3. As appropriate, based on the disease severity and patient and family circumstances, consider evaluating the variant through relevant physical examinations, laboratory testing, imaging, and specialist referral.
4. Consider genetics consultation, including genetic counseling for implications for family members.
5. It may be reasonable to evaluate a variant of uncertain significance (VUS). Counsel the patient that its classification may change over time.

Table 1

Baseline characteristics of 100 primary care patient-participants of the MedSeq Project

	FH-only *n*=50	FH+WGS *n*=50
Age (years), mean (range)	55 (41-68)	55 (41-66)
Gender, *n* (%)		
Male	20 (40)	22 (44)
Female	30 (60)	28 (56)
Charlson comorbidity score, median (range)	0 (0-1)	0 (0-0)
Race, *n* (%)		
White	44 (88)	45 (90)
Other	6 (12)	5 (10)
Ethnicity, *n* (%) *		
Hispanic	3 (6)	2 (4)
Non-Hispanic	46 (94)	47 (96)
Annual household income, *n* (%) †		
<$99,999	16 (32)	8 (16)
$100,000–$149,999	8 (16)	7 (14)
$150,000 or more	22 (44)	34 (68)
Highest educational attainment, *n* (%)		
High school or lower	5 (10)	1 (2)
Some college or associates degree	6 (12)	2 (4)
College graduate	21 (42)	14 (28)
Masters or doctoral degree	18 (36)	33 (66)

Charlson comorbidity scores were calculated from International Classification of Disease codes(41).

Abbreviations: FH, family history; WGS, whole genome sequencing.

* Two patients did not respond.

† 5 participants did not respond.

Table 2

Primary care management of monogenic disease risk (MDR) variants and new clinical diagnoses among 50 generally healthy adult patients in the MedSeq Project

Gene	Associated disease (organ system)	Variant: nucleotide (protein)	Classification	Inheritance	Primary care physician management	Median RAND Appropriateness Score	New clinical diagnosis
RDH5	Fundus albipunctatus (nervous)	c.285G>A (p.Trp95X) c.285G>A (p.Trp95X)	P	Autosomal recessive	Evaluation: Elicited additional ophthalmic history Recommendation: To discuss results with eye doctor Education: Any future children would carry this variant	9	Yes
PPOX	Variegate porphyria (integumentary)	c.199delC (p.Leu67X)	P	Autosomal dominant	Evaluation: Asked about skin symptoms Education: No evidence of porphyria Recommendation: To let future providers know about result Education: Medications that precipitate porphyria symptoms Evaluation: Referral to medical geneticist with porphyria expertise	8	Yes
ANK2	Ankyrin-B related cardiac arrhythmia (cardiovascular)	c.4373A>G (p.Glu1458Gly)	LP	Autosomal dominant	Evaluation: Electrocardiogram Education: No evidence of ankyrin-B related arrhythmia Evaluation: Referral to a cardiovascular geneticist	7	No
COL2A1	Spondyloepiphysea l dysplasia congenital (skeletal)	c.4316C>T (p.Thr1439Met)	LP	Autosomal dominant	Education: Reassurance about variant's health impact Education: Daughter has a 50% chance of inheriting the variant	7	No
KCNQ1	Romano-Ward syndrome (cardiovascular)	c.826delT (p.Ser276ProfsX13)	LP	Autosomal dominant	Evaluation: Electrocardiogram Evaluation: Referral to a cardiologist Recommendation: To notify primary care physician before any new medication	7	No
PDE11A	Primary pigmented micronodular adrenocortical disease (endocrine)	c.171delT (p.Thr58ProfsX41)	VUS: FP*	Autosomal dominant	Education: Reassurance about variant's health impact Education: Symptoms of Cushing syndrome	7	No
TNNT2	Hypertrophic cardiomyopathy (cardiovascular)	c.832C>T (p.Arg278Cys)	VUS: FP	Autosomaldominant	Evaluation: Referral to cardiovascular geneticist	7	No
HFE	Hereditary hemochromatosis (cardiovascular)	c.845G>A (p.Cys282Tyr) c.187C>G (p.His63Asp)	P	Autosomal recessive	Education: No evidence of clinical significant disease Evaluation: Serum ferritin level Education: Each daughter has a 50% chance of carrying each variant	7	No**
ARSE	Chondrodysplasia punctata (skeletal)	c.410G>C (p.Gly137Ala)	VUS: FP	X-linked	Evaluation: Asked if children have skeletal or muscular problems Education: Sons are not at risk	4	No

Gene	Associated disease (organ system)	Variant: nucleotide (protein)	Classification	Inheritance	Primary care physician management	Median RAND Appropriateness Score	New clinical diagnosis
					Education: No evidence of chondrodysplasia punctata [*Panelists judged the physician's decision not to evaluate this variant as neither appropriate nor inappropriate, given its VUS classification.*]		
F5	Factor V Leiden thrombophilia (cardiovascular)	c.1601G>A (p.Arg534Gln)	Risk allele ***	Multi-factorial	Education: Each child carries at least one copy of the Factor V Leiden risk allele [*Panelists noted this as a miscommunication; each child has a 50% chance of inheriting the risk allele.*]	3	No
					Education: Risk of blood clots		
					Recommendation: Daughter might consider genetic testing if she takes oral contraceptive pills		
LHX4	Combined pituitary hormone deficiency (endocrine)	c.452-2A>C	P	Autosomal dominant	Education: Any future child would each have a 50% risk of inheriting variant [*Panelists noted that this information is correct but thought the physician should have done more to evaluate for pituitary hormone deficiency.*]	3	No
HFE	Hereditary Hemochromatosis (cardiovascular)	c.845G>A (p.Cys282Tyr) c.845G>A (p.Cys282Tyr)	P	Autosomal recessive	*Already receiving medical care*	–	–
HFE	Hereditary hemochromatosis (cardiovascular)	c.845G>A (p.Cys282Tyr) c.845G>A (p.Cys282Tyr)	P	Autosomal recessive	*Already receiving medical care*	–	–

Monogenic disease risk (MDR) variants signified disease risk for the patient him or herself, such as a single pathogenic (P), likely pathogenic (LP), or uncertain significance: favor pathogenic (VUS:FP) variant in a gene associated with autosomal dominant or X-linked (in males) disease or biallelic P, LP, or VUS:FP variants in a gene associated with autosomal recessive disease. Appropriateness of clinical management was rated by a panel of 11 geneticist-clinicians on the RAND Appropriateness Scale, categorized as inappropriate (1-3, red), neither inappropriate nor appropriate (4-6, yellow), or appropriate (7-9, green).

*This variant was reclassified from VUS:FP to VUS after the completion of the study and after appropriateness review by the external expert panel.

**Patient had normal serum ferritin but elevated transferrin saturation.

***Risk allele defined here as a variant that has a stronger association with disease (*e.g.* odds ratios greater than 2) than typical common complex variants, but does not exhibit a classic Mendelian inheritance pattern.

Table 3

Immediate attributable clinical actions by primary care physicians (PCP) after review of family history (FH) with or without whole genome sequencing (WGS) results

	Attributable action	Rationale	Six-month completion
Family history-only (*n*=50)			
Referrals	**6**		**3**
Genetic counseling		FH: Breast cancer	No
Genetic counseling		FH: Breast cancer	No
Genetic counseling		FH: Lung and esophageal cancer	No
Neurology		FH: Lewy body dementia	Yes
Colonoscopy		FH: Colorectal adenomata	Yes
Dermatology		FH: Melanoma	Yes
Laboratory tests	**4**		**3**
Lipid profile		FH: Hyperlipidemia	No
C-reactive protein, homocysteine, lipoprotein(a)		FH: Heart disease	Yes
Patients with any action, *n* (%)	**8 (16)**		**4 (8)**
Costs, mean / median (range)	$41 / $0 ($0-$1,063)		$31 / $0 ($0-$1,063)
Family history + WGS (*n*=50)			
Referrals	**7**		**3**
Genetic counseling		Carrier variant: *COL7A1* Cardiac VUS: *NEBL*	No
Medical genetics		Monogenic risk *PPOX*	Yes
Cardiovascular genetics		Monogenic risk: *KCNQ1*	Yes
Cardiovascular genetics		Monogenic risk: *TNNT2*	No
Cardiovascular genetics		Monogenic risk: *ANK2*	Yes
Ophthalmology		FH: Glaucoma	No
Nutrition		FH: CAD	No
Laboratory tests	**12**		**10**
Ferritin		Monogenic risk: *HFE*	Yes
Ferritin and iron		Carrier variant: *HFE*	Yes
Ferritin and iron		Carrier variant: *HFE*	No
Iron		Carrier variant: *HFE*	Yes
Hemoglobin A1c		Polygenic risk: T2D	Yes
Hemoglobin A1c, blood glucose, and lipid panel		Polygenic risk: T2D, CAD FH: T2D, CAD	Yes
Hemoglobin A1c and blood glucose		Polygenic risk: T2D	Yes
Imaging tests	**3**		**1**

	Attributable action	Rationale	Six-month completion
Family history-only (*n*=50)			
Abdominal ultrasound		Polygenic risk: AAA, CAD	No
Abdominal ultrasound		FH:AAA	No
Abdominal ultrasound		FH:AAA	Yes
Cardiac tests	**7**		**5**
ECG		Monogenic risk: *KCNQ1*	Yes
ECG		Polygenic risk: QT	Yes
ECG		Polygenic risk: CAD, QT	Yes
ECG		Monogenic risk: *ANK2*	Yes
ECG		Polygenic risk: QT	No
Echocardiography		Polygenic risk: Atrial fibrillation	Yes
Exercise stress test		Polygenic risk AAA, CAD	No
Patients with any action, *n* (%)	**17 (34)**		**12 (24)**
Costs, mean / median (range)	$68 / $0 ($0–$603)		$38 / $0 ($0–$490)

Each PCP indicated the actions taken as a result of the study results (FH alone or FH+WGS) and identified the result(s) prompting that action. Medical record review was used to confirm whether each action was completed within the subsequent six months. No cardiac or imaging tests were ordered as a result of FH results in the FH-only arm. Table 2 lists the disease associations of the monogenic disease risk variants. The *COL7A1* gene is associated with dystrophic epidermolysis bullosa. The *NEBL* gene is associated with dilated cardiomyopathy, and the c.604G>A variant was reported as a part of a cardiac risk supplement to the MedSeq Project genome report.(12) Abbreviations: AAA, abdominal aortic aneurysm; CAD, coronary artery disease; CI, 95% confidence interval; ECG, electrocardiogram; QT, QT interval prolongation; T2D, type 2 diabetes mellitus; VUS, variant of uncertain significance.

Table 4

Healthcare utilization and costs during six months after primary care physician (PCP)-patient discussions of family history with or without whole genome sequencing (WGS) results

		Family historv-only (*n*=50)		Family history + WGS (*n*=50)	
		Total	**Per patient**	**Total**	**Per patient**
Utilization	Laboratory tests	186	3.72	271	5.42
	Imaging tests	44	0.88	58	1.16
	Cardiac tests	7	0.14	20	0.40
	PCP visits	37	0.74	35	0.70
	Non-PCP visits	108	2.16	124	2.48
Costs, mean / median (range)		$1,142 / $548 ($0-$10,704)		$1,490 / $694 ($0-$15,026)	

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Table 5

Patient-reported outcomes at baseline and six months after primary care physician (PCP)-patient discussions of family history with or without whole genome sequencing (WGS) results

		Family history-only (*n*=50)		Family history + WGS (n=50)	
		Baseline	6 months†	Baseline	6 months‡
Perceived health	Poor	0 (0%)	0 (0%)	0 (0%)	1 (2%)
	Fair	2 (4%)	1 (2%)	2 (4%)	0 (0%)
	Good	8 (16%)	10 (23%)	4 (8%)	7 (14%)
	Very good	24 (48%)	23 (52%)	21 (42%)	24 (49%)
	Excellent	16 (32%)	10 (23%)	23 (46%)	17 (35%)
HADS-anxiety	Mean (95% CI)	5.0 (4.2, 5.8)	4.8 (3.7, 5.9)	5.1 (4.2, 5.9)	4.9 (4.1, 5.7)
	Moderate/severe, *n* (%)	3 (6%)	2 (5%)	4 (8%)	2 (4%)
HADS-depression	Mean (95% CI)	1.8 (1.2, 2.4)	2.3 (1.5, 3.1)	1.8 (1.3, 2.4)	1.8 (1.1, 2.4)
	Moderate/severe, *n* (%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Health behavior*	Exercise		7 (16%)		13 (27%)
	Diet		9 (20%)		16 (33%)
	Supplements		4 (9%)		2 (4%)
	Medications		4 (9%)		6 (12%)
	Other		3 (7%)		1 (2%)
	Any change		13 (30%)		20 (41%)

The 14-item Hospital Anxiety and Depression Scale (HADS) consists of anxiety and depression subscales, where moderate or severe anxiety or depression is indicated by a subscale score ≥ 11.

*Responses to the question “Have you made any of the following health or wellness changes that were specifically motivated by the information you discussed with your doctor?”

†Responses missing from six participants.

‡Responses missing from one participant.