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.

Primary Funding Source: National Institutes of Health.

Ann Intern Med. 2017;167:159-169. doi:10.7326/M17-0188 **Annals.org**

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This article was published at Annals.org on 27 June 2017.

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

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). Many health care systems are moving toward more widespread adoption of clinical sequencing. Compared with simpler gene- or gene panel–based testing, whole-genome sequencing (WGS) brings additional complexity in the 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. Sequencing is still predominantly the province of genetics specialists, but its expansion in this era of limited health care resources, including access to genetics professionals, evokes concern. The main considerations are whether nongeneticist physicians and primary care physicians (PCPs) can manage genomic information appropriately (7–9) and the degree to which clinical integration of genomics enables early disease detection and prevention or leads to anxiety and unnecessary and costly follow-up (10, 11).

Although the risk–benefit ratio of sequencing is probably favorable in specific clinical contexts, the risks and costs of sequencing might outweigh its benefits for generally healthy persons. To examine this balance, we developed a process to perform clinical WGS, interpret the resulting variants, issue a WGS report that nongeneticist physicians could use, and measure downstream clinical outcomes. To provide early empirical evidence about the risks and benefits of integrating sequencing

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into primary care, we conducted a pilot randomized controlled trial of family health history (FH) alone versus FH and WGS.

METHODS

Study Design and Participants

The MedSeq Project is a pair of pilot randomized controlled trials of WGS in 2 clinical contexts: subspecialty care for patients with cardiomyopathy and primary care for generally healthy adults. This article 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 e-mail outreach and presentations at staff meetings to recruit a convenience sample of 9 PCPs from 1 academic network of outpatient practices in Boston, Massachusetts. Each PCP helped MedSeq Project staff recruit approximately 10 of his or her patients until we reached the prespecified sample of 100 patients (see Supplement, available at Annals.org). Eligible patients were recruited at ages 40 to 65 years, had no history of cardiovascular disease or diabetes mellitus, and were deemed generally healthy by their 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 have a sham blood draw (FH group) or a blood draw for WGS (FH + WGS group) (Figure). 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.

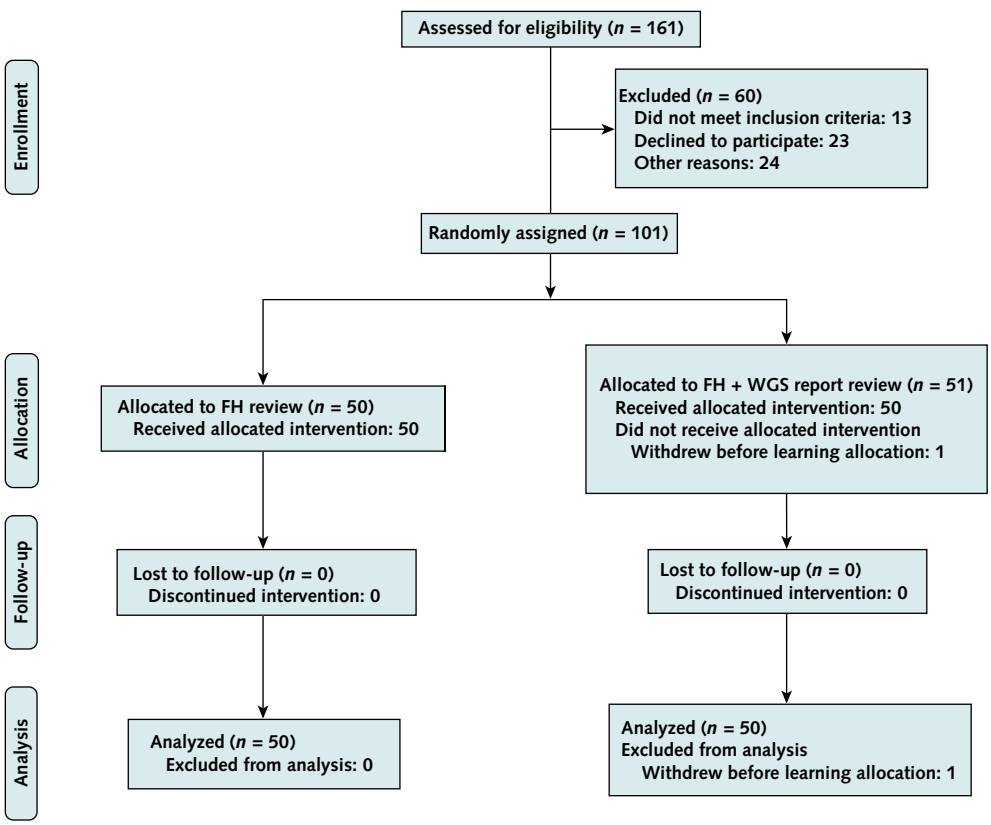
Physician Education and Support

Before enrolling patients, PCP participants had a brief educational course consisting of 4 hours of case-based online modules and two 1-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 staffed by medical geneticists and genetic counselors affiliated with the study to ask questions about patients' results. If consulted, genome resource center staff assisted the PCPs with result interpretation but did not make clinical recommendations. Result disclosure did not otherwise include genetic counselors or geneticists.

WGS, Interpretation, and Reporting

Whole-genome sequencing was performed in the Clinical Laboratory Improvement Amendments–certified Illumina Clinical Services Laboratory (San Diego, California), as described in the Supplement and previously (15). Raw data files were analyzed in the Partners

Figure. Study flow diagram of primary care patient participants in the MedSeq Project.



FH = family history; WHS = whole-genome sequencing.

Laboratory for Molecular Medicine. Molecular geneticists classified variants, which had been selected for possible clinical relevance from a curated list of 4631 disease-associated genes, into 5 categories: benign, likely benign, variant of uncertain significance (VUS), likely pathogenic (LP), and pathogenic (P), described further in the **Supplement**. A subset of VUS was 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 **Supplement**. They included sections for MDR, recessive carrier risk, pharmacogenomic associations, and polygenic risk estimates for 8 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 men) 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 or her randomization status and to discuss the reports before they were uploaded to the electronic health record (EHR).

Table 1. Baseline Characteristics of 100 Primary Care Patient Participants of the MedSeq Project

Variable	FH Only (*n* = 50)	FH+WGS (*n* = 50)
Mean age (range), *y*	55 (41–68)*	55 (41–66)
Sex, *n (%)*		
Male	20 (40)	22 (44)
Female	30 (60)	28 (56)
Median Charlson comorbidity score (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 (35)	8 (16)
$100 000–$149 999	8 (17)	7 (14)
≥$150 000	22 (48)	34 (69)
Highest educational attainment, *n* (%)		
High school or lower	5 (10)	1 (2)
Some college or associate's degree	6 (12)	2 (4)
College graduate	21 (42)	14 (28)
Master's or doctoral degree	18 (36)	33 (66)

FH = family history; WGS = whole-genome sequencing.
* In a protocol deviation, 1 patient was recruited at age 68 y.
† Calculated from International Classification of Disease codes (23).
‡ 2 participants did not respond.
§ 5 participants did not respond.

Outcomes

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

Patient surveys both at baseline and 6 months after the disclosure visit included the 14-item Hospital Anxiety and Depression Scale (18) and self-reported health status on a 5-item Likert scale ranging from "poor" to "excellent" (19). The 6-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 were "diet," "exercise," "use of vitamins or herbal supplements," "use of medications," and "other."

To assess how PCPs managed MDR results, we used the validated RAND/UCLA Appropriateness Method (21), described further in the **Supplement**. An external panel of 11 academic clinician-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 affected guideline-concordant primary care, we used EHR review at 6 months to determine each patient's concordance with U.S. Preventive Services Task Force guidelines, further described in the **Supplement**.

We assessed health care use and associated costs immediately after the disclosure visit (immediately attributable use or costs) and 6 months after the visit (6-month use or costs). Immediately attributable use 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 or WGS results. For each action reported, the checklist asked the PCP to identify which specific FH or WGS results prompted the action. We used data from both the Research Patient Data Registry (22) and EHR review to determine 6-month use and to confirm whether immediately attributable actions from the checklist were completed by the patient. Counts of clinical actions during the 6 months after the disclosure visit were determined from EHR review and billing codes from the Research Patient Data Registry. We determined 6-month costs using Centers for Medicare & Medicaid Services price weights from 2015 (**Supplement**). The **Supplement** pro-

Table 2. Primary Care Management of 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	PCP Management	Median RAND/UCLA 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 ophthalmologist 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; referral to medical geneticist with porphyria expertise Education: No evidence of porphyria; medications that precipitate porphyria symptoms Recommendation: To let future providers know about result	8	Yes
ANK2	Ankyrin-B–related cardiac arrhythmia (cardiovascular)	c.4373A>G (p.Glu1458Gly)	LP	Autosomal dominant	Evaluation: Electrocardiography; referral to cardiovascular geneticist Education: No evidence of ankyrin-B–related arrhythmia	7	No
COL2A1	Spondyloepiphyseal dysplasia congenital (skeletal)	c.4316C>T (p.Thr1439Met)	LP	Autosomal dominant	Education: Reassurance about variant's effect on health; daughter has a 50% chance of inheriting the variant	7	No
KCNQ1	Romano–Ward syndrome (cardiovascular)	c.826delT (p.Ser276ProfsX13)	LP	Autosomal dominant	Evaluation: Electrocardiography; referral to cardiologist Recommendation: To notify PCP 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 effect on health; symptoms of Cushing syndrome	7	No
TNNT2	Hypertrophic cardiomyopathy (cardiovascular)	c.832C>T (p.Arg278Cys)	VUS:FP	Autosomal dominant	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 clinically significant disease; each daughter has a 50% chance of carrying each variant Evaluation: Serum ferritin level	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; no evidence of chondrodysplasia punctata *(Panelists judged the PCP's decision not to evaluate this variant as neither appropriate nor inappropriate, given its VUS classification.)*	4	No

Continued on following page

Table 2–Continued

Gene	Associated Disease (Organ System)	Variant: Nucleotide (Protein)	Classification	Inheritance	PCP Management	Median RAND/UCLA Appropriateness Score†	New Clinical Diagnosis
F5	Factor V Leiden thrombophilia (cardiovascular)	c.1601G>A (p.Arg534Gln)	Risk allele‖	Multifactorial	Education: Each child carries at least 1 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
LHX4	Combined pituitary hormone deficiency (endocrine)	c.452-2A>C	P	Autosomal dominant	Education: Any future child would have a 50% risk for inheriting variant *(Panelists noted that this information is correct but thought the PCP 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	–	–

LP = likely pathogenic; MDR = monogenic disease risk; P = pathogenic; PCP = primary care physician; VUS = variant of uncertain significance; VUS:FP = variant of uncertain significance: favor pathogenic.
* MDR variants signified 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 men) disease or biallelic P, LP, or VUS:FP variants in a gene associated with autosomal recessive disease.
† Rated by a panel of 11 clinician-geneticists on the RAND/UCLA Appropriateness Scale, categorized as inappropriate (1–3), neither inappropriate nor appropriate (4–6), or appropriate (7–9).
‡ 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 levels but elevated transferrin saturation.
‖ Defined here as a variant that has a stronger association with disease (e.g., odds ratio >2) than typical common complex variants but does not exhibit a classic Mendelian inheritance pattern.

vides additional details about the measurement of use and costs.

Statistical Analysis

The sample size was based on the number of specimens that could be sequenced and not on statistical considerations. One enrolled patient was randomly assigned to the FH + WGS group but withdrew from the study before learning his allocated intervention; we present the results from the 50 FH and 50 FH + WGS patients who received their allocations. Sensitivity analyses for 6-month counts and costs were done by limiting the data to actions with billing codes obtained from the Research Patient Data Registry (22). Exact 95% CIs were calculated with R version 3.2.2, statistical language.

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 publish the finished manuscript.

Results

Participant Characteristics

Table 1 and Supplement Table 1 show the characteristics of the 100 patient participants receiving FH or FH + WGS results and the 9 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. We identified a range of 5 179 293 to 5 788 580 variants per patient in the FH + WGS group. Eleven FH + WGS patients (22% [95% CI, 12% to 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 pre-

Table 3. Expert Recommendations for the Primary Care Management of a Genetic Variant in an Ostensibly Healthy Patient

- Consult resources, such as Online Mendelian Inheritance in Man, GeneReviews, and the medical literature, for more information about conditions of concern.
- 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.
- 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.
- Consider genetics consultation, including genetic counseling for implications for family members.
- It may be reasonable to evaluate a variant of uncertain significance. Counsel the patient that its classification may change over time.

Table 4. Immediately Attributable Clinical Actions by PCPs After Review of FH With or Without WGS Results*

Variable	Attributable Action	Rationale	6-mo Completion
FH only (*n* = 50)			
Referrals, *n*	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, *n*	4	–	3
	Lipid profile	FH: Hyperlipidemia	No
	CRP, homocysteine, lipoprotein(a)	FH: Heart disease	Yes
Patients with any action, *n (%)*	8 (16)	–	4 (8)
Mean/median costs (range), *$*	41/0 (0–1063)	–	31/0 (0–1063)
FH+WGS (*n* = 50)			
Referrals, *n*	7	–	3
	Genetic counseling	Carrier variant: *COL7A1* Cardiac VUS: *NEBL*	No
	Medical genetics	Monogenic risk *PPOX*	Yes
	Cardiovascular genetics	Monogenic risk: *KCNQ1*	Yes
	Cardiovascular genetics	Monogenic risk: *TNNT2*	No
	Cardiovascular genetics	Monogenic risk: *ANK2*	Yes
	Ophthalmology	FH: Glaucoma	No
	Nutrition	FH: CAD	No
Laboratory tests, *n*	12	–	10
	Ferritin	Monogenic risk: *HFE*	Yes
	Ferritin and iron	Carrier variant: *HFE*	Yes
	Ferritin and iron	Carrier variant: *HFE*	No
	Iron	Carrier variant: *HFE*	Yes
	HbA_{1c}	Polygenic risk: T2DM	Yes
	HbA_{1c}, blood glucose, and lipid panel	Polygenic risk: T2DM, CAD FH: T2DM, CAD	Yes
	HbA_{1c} and blood glucose	Polygenic risk: T2DM	Yes
Imaging tests, *n*	3	–	1
	Abdominal ultrasonography	Polygenic risk: AAA, CAD	No
	Abdominal ultrasonography	FH: AAA	No
	Abdominal ultrasonography	FH: AAA	Yes
Cardiac tests, *n*	7	–	5
	ECG	Monogenic risk: *KCNQ1*	Yes
	ECG	Polygenic risk: QT	Yes
	ECG	Polygenic risk: CAD, QT	Yes
	ECG	Monogenic risk: *ANK2*	Yes
	ECG	Polygenic risk: QT	No
	Echocardiography	Polygenic risk: Atrial fibrillation	Yes
	Exercise stress test	Polygenic risk: AAA, CAD	No
Patients with any action, *n (%)*	17 (34)	–	12 (24)
Mean/median costs (range), *$*	68/0 (0–603)	–	38/0 (0–490)

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CRP = C-reactive protein; ECG = electrocardiogram; FH = family history; HbA_{1c} = hemoglobin A_{1c}; PCP = primary care physician; QT = QT interval prolongation; T2DM = type 2 diabetes mellitus; VUS = variant of uncertain significance; WGS = whole-genome sequencing.

* Each PCP indicated the actions taken as a result of the study results (FH alone or FH + WGS) and identified the results prompting that action. Medical record review was used to confirm whether each action was completed within the subsequent 6 mo. No cardiac or imaging tests were ordered as a result of FH results in the FH group. **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).

viously 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 2 (4% [CI, 0.01% to 15%]) within the subsequent 6 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 funduscopy. A second patient with a pathogenic p.Leu67X variant in *PPOX*, associated with variegate porphyria, described occasional "odd rashes." A follow-up genetics consultation confirmed a subclinical porphyria phenotype based on dermatologic symptoms and a history of photosensitivity in the proband's mother and son, not reported on her pedigree. For the remaining 9 patients with a new MDR result, 6-month EHR review found no evidence of the predicted phenotypes from routine clinical evaluation. For example, a patient with an LP p.Ser276ProfsX13 variant in *KCNQ1* demonstrated no evidence of long QT syndrome on subsequent evaluation with resting electrocardiography 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 Medical Genetics and Genomics (24), but were classified as LP and VUS:FP, respectively.

All patients with WGS results had at least 1 carrier variant associated with a recessive condition (median, 2; range, 1 to 7) (**Supplement Table 2**). The **Supplement Figure** and **Supplement Table 3** show the distribution of reported pharmacogenomic and polygenic results, respectively. Overall, 48 patients (96% [CI, 85% to 99%]) received a pharmacogenomic result indicating atypical or nonstandard response to at least 1 medication. Six patients were receiving at least 1 of these medications at baseline (simvastatin, $n = 5$; metformin, $n = 1$), and no prescription change or adverse effect was documented during the 6-month observation period. The patient taking metformin (1500 mg per day for metabolic syndrome) received a pharmacogenomic result predicting decreased glycemic response to the drug, but she and her PCP decided not to increase the dose of metformin, choosing instead to use hemoglobin A_{1c} 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 6 of these patients, no additional management was recommended beyond history, physical examination, and counseling. Six variants in 5 patients prompted additional evaluation: 2 electrocardiograms (variants in *KCNQ1* and *ANK2*), 4 referrals to specialists (variants in *KCNQ1*, *PPOX*, *TNNT2*, and *ANK2*), and 1 serum ferritin level (2 variants in *HFE*). The external panel of geneticists judged that 8 cases (73% [CI, 39% to 99%]) had been managed appropriately and 2 cases (18% [CI, 3% to 52%]) inappropriately, 1 because of underevaluation of a pathogenic variant and 1 because of miscommunication about inheritance. The panel rated the management of 1 variant, p.Gly137Ala VUS:FP in *ARSE*, associated with chondrodysplasia punctata, as neither appropriate nor inappropriate. Panelists thought the PCP underevaluated the patient for subtle clinical manifestations of chondrodysplasia punctata, but they did not rate the management as inappropriate given the VUS categorization. After discussion, panelists generated the 5 general recommendations shown in **Table 3**. The proportions of patients with U.S. Preventive Services Task Force guideline–concordant care did not differ between the 2 groups at 6 months (**Supplement Table 4**).

Health Care Use and Costs After FH and WGS Results

Primary care physicians recommended at least 1 immediately attributable clinical action for 16% (CI, 8% to 30%) of FH patients and 34% (CI, 22% to 49%) of FH + WGS patients (**Table 4**). Even in these established PCP–patient dyads, discussion of FH alone prompted additional actions, such as a dermatology referral for an FH of melanoma and C-reactive protein testing for an FH of heart disease. In the FH + WGS group, referrals were often prompted by MDR results; in contrast, most additional laboratory and cardiac tests in the FH + WGS group were 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 to $1063) in the FH group and $68 (median, $0; range, $0 to $603) in the FH + WGS group.

Table 5. Health Care Use and Costs During 6 Months After PCP–Patient Discussions of FH With or Without WGS Results

Variable	FH Only ($n = 50$)		FH+WGS ($n = 50$)	
	Total	Per Patient	Total	Per Patient
Use, *n*				
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
Mean/median costs per patient (range), $	1142/548 (0–10 704)		1490/694 (0–15 026)	

FH = family history; PCP = primary care physician; WGS = whole-genome sequencing.

Table 5 shows health care use and costs in the 6 months after results disclosure. Six-month costs averaged $1142 (median, $548; range, $0 to $10 704) in the FH group and $1490 (median, $694; range, $0 to $15 026) in the FH + WGS group. **Supplement Table 5** shows the results of sensitivity analyses without costs of imputed billing codes. Within the FH + WGS group, the 6-month costs of the 11 patients with new MDR results averaged $2526 (median, $694; range, $0 to $15 026), whereas those of the 39 without new MDR results averaged $1198 (median, $694; range, $0 to $10 238).

Patient-Reported Outcomes

Table 6 shows the self-reported health, anxiety, and depression of patients at baseline and 6 months. At 6 months, 30% (CI, 17% to 45%) and 41% (CI, 27% to 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 (25), there is concern that its introduction into clinical care, particularly of generally healthy persons, might cause patient anxiety or harm and increase health care costs. Rigorous empirical evidence about these potential benefits and risks has been scant (26–28), but the development of clinical sequencing programs has continued in many health care systems. In this trial of WGS integrated into primary care settings, we found that about 1 in 5 generally healthy adult patients with WGS results had a previously unrecognized variant with potential risk for a Mendelian disease. Only about 1 in 25

Table 6. Patient-Reported Outcomes at Baseline and 6 Months After PCP–Patient Discussions of FH With or Without WGS Results

Variable	FH Only ($n = 50$)		FH+WGS ($n = 50$)	
	Baseline	6 mo*	Baseline	6 mo†
Perceived health, *n (%)*				
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 score (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 score (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, *n (%)*§				
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)

FH = family history; HADS = Hospital Anxiety and Depression Scale; PCP = primary care physician; WGS = whole-genome sequencing.
* 6 participants did not respond.
† 1 participant did not respond.
‡ 14-item scale with 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?"

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. Whole-genome sequencing did not seem to cause patient anxiety or depression, but considerable proportions of patients in both groups reported making health behavior changes related to the results they received. Both FH and WGS prompted medical decision making and new immediate clinical orders. We saw directions of effect consistent with increased 6-month health care use and costs due to WGS, but larger studies are needed to confirm these differences.

Determining whether WGS increases health care use and costs is important; however, a separate but critical first question is the value derived from WGS (29). Although the value of recessive carrier states to inform reproductive decisions and that of 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 occur within a short time frame. We attempted to assess this value in 4 ways. First, in examining the clinical courses of patients having WGS, we saw 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 such databases as the Human Gene Mutation Database and by certain submitters to ClinVar are determined not to be pathogenic upon expert review (30–35). 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. This allowed for variant classification using an approach consistent with current American College of Medical Genetics and Genomics standards and inclusion of only those variants meeting a rigorous evidence base for pathogenicity (36). The list of genes and variants considered reportable will probably 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 (37, 38). Indeed, the *PDE11A* variant (p.Thr58ProfsX41) reported to 1 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 will result in a clinical diagnosis while minimizing unnecessary follow-up for variants known to be clinically insignificant.

Second, we saw neither benefit nor harm from WGS on U.S. Preventive Services Task Force guideline–concordant care. Most patients were already meeting

these guidelines at 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 with 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 8 of 11 cases. Instances of inappropriate management were so judged because of underevaluation 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 pilot study do not support the use of WGS in primary care but suggest that, if a healthy adult has WGS, some of the resulting increased health care use 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 are readily able to recognize when to refer a patient with WGS for genetics consultation. The recommendations generated by our panelists may help guide nongeneticist physicians faced with managing a genome variant in an asymptomatic patient. Although 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. The small sample size limited the statistical power to detect between-group differences and restricted the range of clinically significant variants seen. Because much of the benefit of WGS in ostensibly healthy persons might result from its ability to detect rare but treatable monogenic disorders, such as familial cancer syndromes, larger trials are needed to determine the effect of WGS as a screening tool on the health and health care of patient populations. Moreover, future studies must feature greater ancestral, geographic, and socioeconomic diversity than the current pilot trial if the observed benefits and risks of sequencing are to be generalizable (39). 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 use and costs toward 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 patients' family members, often proposed as a driver of the clinical utility of WGS (40, 41). Studies will need longer follow-up to determine the clinical effect of all types of WGS results (for example, 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 outcome assessment of several research studies and clinical programs that are preparing for the large-scale return of genomic results to more diverse groups of patients and providers in academic and nonacademic settings.

In conclusion, we found that about 1 in 5 generally healthy patients receiving WGS results in a primary care setting had a new molecular diagnosis, and only 1 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.

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Disclaimer: The contents do not necessarily represent the views of the U.S. Department of Veterans Affairs (VA), the U.S. government, Harvard Catalyst, Harvard University and its affiliated academic health care centers, or the National Institutes of Health (NIH).

Acknowledgment: The authors thank 5AM Solutions (Rockville, Maryland) for their help in customizing the workflow of the My Family Health Portrait Web tool for this study. The authors thank the patient participants, physician participants, and genetics panelists of the MedSeq Project. Dr. Vassy affirms that he has listed everyone who contributed significantly to this work.

Financial Support: By grant U01-HG006500 from the National Human Genome Research Institute of the NIH. Dr. Vassy is an employee of the VA Boston Healthcare System and received support from NIH grant KL2-TR001100 and Career Development Award IK2-CX001262 from the VA Clinical Sciences Research and Development Service. Drs. Green and Rehm are also supported by NIH grants U19-HD077671, U01-HG008685, and U41-HG006834 and by funding from the Broad Institute of MIT and Harvard. Dr. Christensen is supported by NIH grant K01-HG009173. Dr. MacRae's work in this area is supported by NIH grant U01-HG007690 and by the Burroughs Wellcome Fund. This work was conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and National Center for Advancing Translational Sciences, NIH grant UL1-TR001102) and financial contribu-

tions from Harvard University and its affiliated academic health care centers.

Disclosures: Ms. Blout reports grants from the NIH during the conduct of the study. Dr. Lebo reports grants from the National Human Genome Research Institute during the conduct of the study. Dr. Machini reports grants from the NIH during the conduct of the study. Ms. Azzariti reports grant support from the National Human Genome Research Institute of the NIH during the conduct of the study. 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. Dr. Bates reports grants from EarlySense; personal fees from S.E.A. Medical Systems, EarlySense, QPID Health, Center for Digital Innovation (Negev), Enelgy, Valera Health, Intensix, and MDClone; and equity from S.E.A. Medical Systems, QPID Health, Enelgy, Valera Health, Intensix, and MDClone outside the submitted work. In addition, Dr. Bates has a patent for Medicalis with royalties paid to Brigham and Women's Hospital. Dr. Bates chaired the FDASIA workgroup, which has advised the U.S. Food and Drug Administration, the Federal Communications Commission, and the Office of the National Coordinator on the regulation of health care information technology including mobile technology, and also served as a member of the Health Information Technology Policy Committee. Dr. MacRae reports grants from the NIH during the conduct of the study. In addition, Dr. MacRae has a patent for gene testing in cardiomyopathies with royalties paid to Partners HealthCare. Dr. Murray reports personal fees from InVitae and Merck and grants from Regeneron outside the submitted work. Dr. Rehm reports grants from the NIH during the conduct of the study, payment for advisory board services from Genome Medical outside the submitted work, and employment at Partners HealthCare Laboratory for Molecular Medicine and The Broad Institute of MIT and Harvard (fee-based services) outside the submitted work. Dr. McGuire reports grants from MedSeq during the conduct of the study. Dr. McGuire is a consultant for Human Longevity outside the submitted work. Dr. Green reports personal fees from Illumina, Invitae, Helix, GenePeeks, Veritas, and Ohana and is a cofounder with equity in Genome Medical. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-0188.

Reproducible Research Statement: *Study protocol, statistical code, and data set*: Available from Dr. Vassy (e-mail, jvassy@partners.org).

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