**Annals of Internal Medicine** ORIGINAL RESEARCH

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

## A Pilot Randomized Trial

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

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

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

**Setting:** Academic primary care practices.

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

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

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

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

**Limitation:** Limited sample size and ancestral and socioeconomic diversity.

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

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For author affiliations, see end of text.

* 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.

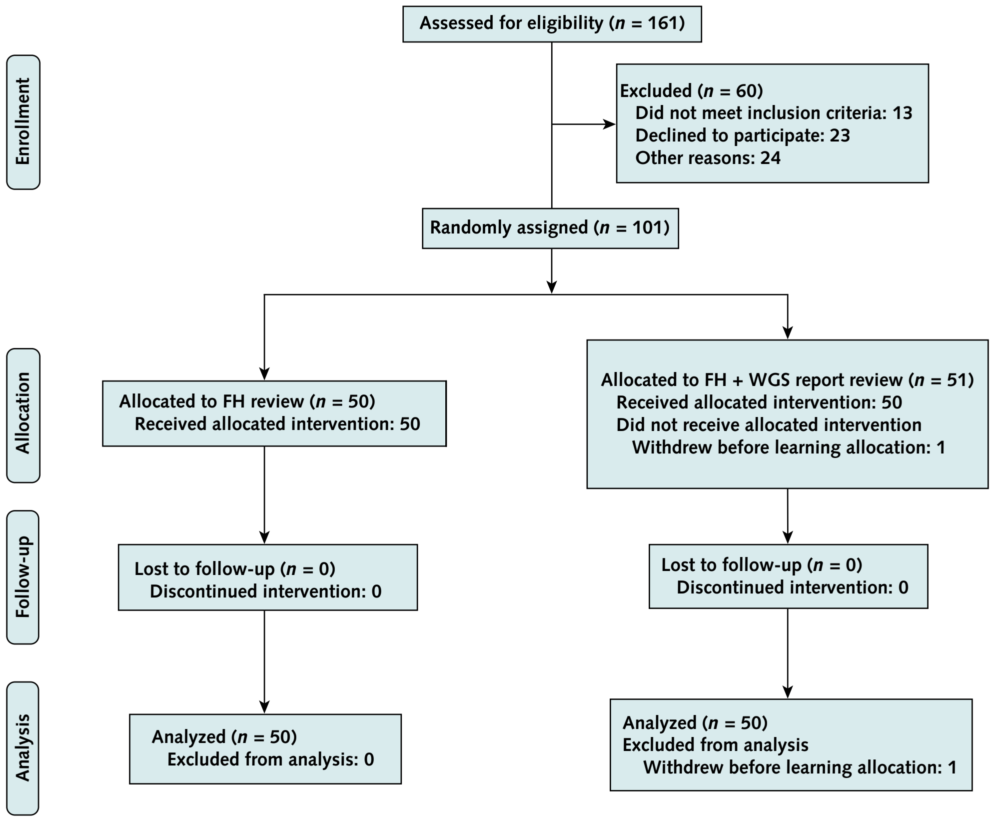
### Physician Education and Support

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).

## 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**.

***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.

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)<br>c.285G>A (p.Trp95X) | P | Autosomal recessive | Evaluation: Elicited additional ophthalmic history<br>Recommendation: To discuss results with ophthalmologist<br>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<br>Education: No evidence of porphyria; medications that precipitate porphyria symptoms<br>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<br>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<br>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)<br>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<br>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<br>Education: Sons are not at risk; no evidence of chondrodysplasia punctata<br>*(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<br>*(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<br>*(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)<br>c.845G>A (p.Cys282Tyr) | P | Autosomal recessive | Already receiving medical care | – | – |
| *HFE* | Hereditary hemochromatosis (cardiovascular) | c.845G>A (p.Cys282Tyr)<br>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*<br>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 |
| | $\text{HbA}_{1c}$ | Polygenic risk: T2DM | Yes |
| | $\text{HbA}_{1c}$, blood glucose, and lipid panel | Polygenic risk: T2DM, CAD<br>FH: T2DM, CAD | Yes |
| | $\text{HbA}_{1c}$ 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; $\text{HbA}_{1c}$ = hemoglobin $\text{A}_{1c}$; 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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**Reproducible Research Statement:** *Study protocol, statistical code, and data set*: Available from Dr. Vassy (e-mail, jvassy@partners.org).

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**Supplementary Material**

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* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

## Supplementary Methods

### Study Design

The MedSeq Project is a pair of pilot randomized controlled trials of whole genome sequencing (WGS) in two clinical contexts: subspecialty care for patients with cardiomyopathy and primary care for generally healthy adults (1). This manuscript describes the results of the primary care trial, in which we recruited 9 primary care physicians (PCP) from one academic network of outpatient practices, each of whom recruited approximately 10 of his or her patients from December 2012 to August 2014 until the prespecified sample of 100 patients was reached. Eligible patients were aged 40 to 65 years, had no history of cardiovascular disease or diabetes mellitus, and were deemed generally healthy by the PCP. Charlson comorbidity scores were calculated from International Classification of Diseases codes (2). Each enrolled PCP gave study staff a list of potentially eligible patients, sometimes after introducing the study personally to their patients (3). Study staff mailed identified patients a study brochure and informational letter, after which they called patients up to two times to assess eligibility and formally invite them to participate. Patients who expressed interest in participating at the end of the phone screen were scheduled for a baseline visit, at which they signed an informed consent form, completed a baseline survey, and reported their family health history (FH) using an adaptation of the U.S. Surgeon General's "My Family Health Portrait" web tool (4). Patients were then randomly assigned in a 1:1 ratio to have their PCP receive only the pedigree resulting from this tool (FH arm) or the combination of the pedigree and an interpreted WGS report (FH + WGS arm). Study staff enrolled patients and randomly assigned them to the two arms by drawing from sealed envelopes. Patients were each followed for six months, and the observation period for the last patient ended in March 2016.

### Genome Sequencing, Interpretation, and Reporting

Sequencing was performed in the Clinical Laboratory Improvement Amendments (CLIA)-certified and College of American Pathologists (CAP)-accredited Illumina Clinical Services Laboratory (San Diego, CA) on the Illumina HiSeq platform following standard validation protocols. 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. The CLIA-certified and Joint Commission-accredited Partners Laboratory for Molecular Medicine (LMM) performed sequence realignment, variant calling, and annotation as described previously, following standard validation protocols (5). Annotated variants were first filtered based on validated quality metrics from GATK to exclude variants with quality by depth (QD) scores <4 or Fisher strand bias (FS) scores > 30. Variants were then filtered to include 1) variants with a minor allele frequency (MAF) <5% in European-American (EA) or African-American (AA) chromosomes from the NHLBI Exome Sequencing Project (ESP) (6) classified as disease causing (DM) or possible disease causing mutations (DM?) in the Human Gene Mutation Database (HGMD) (7) or as pathogenic or likely pathogenic by the LMM; 2) nonsense, frameshift, and canonical splice-site (+/−1,2) variants with a MAF <1% in EA or AA chromosomes from the NHLBI ESP from a list of 4,631 disease-associated genes curated by expert review of many sources of gene-disease relationships including Online Mendelian Inheritance in Man (OMIM) (8), ClinVar (9), and HGMD; and 3) pharmacogenomic variants for metformin, clopidogrel, warfarin, simvastatin, and digoxin metabolism. As described earlier (5), molecular geneticist in the LMM classified variants based on allele frequency, genetic and functional evidence, and computational analysis into five categories: benign, likely benign, uncertain significance (VUS), likely pathogenic, and pathogenic. In addition, a subset of VUS were subclassified as “uncertain significance: favor benign” or “uncertain significance: favor pathogenic”. As previously described, parallel analytic pipelines were used to calculate multiplicative polygenic risk scores, derived from 161 published risk alleles and normalized with the population median, for eight cardiometabolic traits: abdominal aortic aneurysm, atrial fibrillation, coronary heart disease, type 2 diabetes, hypertension, obesity, platelet aggregation, and QT prolongation (11).

The format and content of the genome report and cardiac risk supplement delivered to PCPs have been described previously (5, 12) and are shown in this Supplement. The report contained the following sections: monogenic disease risk, carrier risk, pharmacogenomic associations, polygenic risk estimates for cardiometabolic traits, and polygenic predictions of untreated lipid profiles. In the monogenic and carrier risk sections, only variants with substantial evidence for causing or contributing to Mendelian genetic disease were reported, including all pathogenic (P), likely pathogenic (LP), and uncertain significance: favor pathogenic (VUS:FP) variants. Variants were included in the monogenic disease risk (MDR) section of the report if they signified disease risk for the patient him or herself, 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. Each reported variant was confirmed by Sanger sequencing before reporting. The genome report’s first page summarized the findings, while subsequent pages gave more detail about their evidence and clinical interpretations. For the eight cardiometabolic traits, the cardiac risk supplement included the population prevalence of the phenotype, the proportion of phenotypic variation explained by common variants, the patient’s polygenic relative risk and percentile rank of relative risk (11). The report did not include recommendations for clinical management. Genome reports were delivered directly to the PCP in advance of a dedicated audio-recorded clinical visit, during which each patient met with his or her PCP to discuss the study reports (pedigree alone or pedigree plus genome report). The reports were uploaded to the electronic health record (EHR) after these disclosure visits.

## Appropriateness of Primary Care Management of Sequencing Results

We used an adaptation of the RAND/UCLA Appropriateness Method (13) to measure the appropriateness of PCP management of WGS results. This validated methodology synthesizes evidence review and expert opinion to rate the appropriateness of specific clinical management strategies. For each patient in the FH + WGS arm who received a MDR result previously unknown to them (*n*=11), we prepared a clinical vignette describing the patient’s family and past medical history, the variant(s) identified, and the immediate clinical actions the PCP took as a result. Information for each vignette came from the audio-recorded disclosure visit, the PCP checklist, and EHR review. We recruited 11 academic geneticist-clinicians not affiliated with the study to serve as expert panelists to review the appropriateness of how PCPs managed these variants. Panelists were physicians trained in internal or family medicine with additional specialized training and expertise in genetics, most commonly a medical genetics fellowship. Panelists individually accessed the 11 vignettes through a web-based survey and rated the clinical management in each using the validated 9-point RAND Appropriateness Scale (RAS), ranging from 1 (extremely inappropriate) to 9 (extremely appropriate). The RAS instructs respondents to define appropriateness as follows: “Management is considered to be appropriate if the expected health benefit (*e.g.,* increased life expectancy, relief of pain, reduction in anxiety, improved functional capacity) exceeds the expected negative consequences (e.g., mortality, morbidity, anxiety, pain, time lost from work) by a sufficiently wide margin that the procedure is worth doing, exclusive of cost” (13). The panelists’ median responses were used to categorize the management of each vignette as inappropriate (1-3), neither inappropriate nor appropriate (4-6), or appropriate (7-9). Disagreement among the panelists about the appropriateness of the management of a vignette was measured quantitatively with disagreement indices, calculated using interpercentile ranges adjusted for symmetry (13). Disagreement indices indicated that the panelists agreed on how to rate the appropriateness of the PCPs' overall management for all 11 vignettes in this study. At the end of the 11 cases, the survey asked each panelist to answer the following question: "Now that you've read these cases, what would you consider to be core components of future guidelines for a primary care physician managing a variant in an ostensibly healthy patient?" The study staff synthesized the panelists' free-text responses to generate a set of six recommendations. These were presented to the panelists during a follow-up telephone meeting, during which they had the opportunity to discuss the recommendations as a group. After this meeting, panelists individually submitted their recommendations for revisions to the study staff, who synthesized them to generate the final list of five recommendations (see main manuscript).

## Routine Health Maintenance

United States Preventive Services Task Force (USPSTF) Grade A guidelines identify health care measures that are highly recommended due to their net benefit, while Grade D guidelines recommend against measures without net benefit or with a risk of harm. To examine the potential impact of WGS on evidence-based preventive healthcare, we used EHR review to determine each patient's concordance with applicable USPSTF Grade A and D recommendations (Supplement Table 4) at the date of the disclosure visit and then 6 months later. Prior to April 2016, the USPSTF recommended against the use of aspirin for cardiovascular disease (CVD) prevention in women younger than 55 years and men younger than 45 years (Grade D), while recommending aspirin for higher-risk men aged 45-79 and women aged 55-79 (14). We used clinical characteristics from the EHR to assign each patient participant a baseline CVD risk, using the Framingham Heart Study risk equations (15) and considered patients with 10-year CVD risk ≥10% to be high-risk. All six-month observation periods concluded before April 2016.

## Healthcare Utilization and Costs

Healthcare utilization and associated costs were assessed at two times: immediately after the disclosure visit (immediate attributable utilization/costs) and 6 months after disclosure (6-month utilization/costs). Immediate attributable utilization was determined from clinical actions reported on a checklist the PCP completed after each disclosure visit. The checklist asked the PCP to identify any clinical actions recommended as a result of the study reports for each patient, grouped as laboratory tests, imaging tests, cardiology tests, and referrals. For each action, the PCP identified which specific FH and/or WGS result(s) prompted the recommendation. EHR review and administrative data from the Partners Research Patient Data Registry (RPDR) (16) were used to determine six-month utilization and to confirm whether immediately attributable actions were completed by the patient.

Review of the EHR was used to determine counts of clinical actions (PCP visits, specialty visits, laboratory tests, cardiac tests, and imaging studies) during the 183 days after the disclosure visit, excluding services provided during inpatient care. The observation period for the last patient ended in March 2016. For clinical actions documented as completed in the EHR but lacking specific Current Procedural Terminology (CPT) or Healthcare Common Procedure Coding System (HCPCS) codes from the RPDR, we imputed CPT codes as shown in

Supplement Table 6 based on consensus opinion of the investigators. New patient and established patient visits to specialists without CPT codes were imputed as 99203 and 99215, respectively, the mode of the CPT codes observed in RPDR for these types of visits.

Centers for Medicare and Medicaid Services (CMS) price weights for 2015 were used to assign costs for the immediate attributable and 6-month utilization, adapting methods and assumptions used to estimate the costs of ambulatory care provided by the Department of Veterans Affairs (17). Analyses included facility costs, professional costs, vaccines covered under Medicare Part B, and clinical diagnostic laboratory tests. Facility costs were assigned to outpatient services based on the CMS Hospital Outpatient Prospective Payment System, while professional costs were assigned based on the CMS Physician Fee Schedule payments for services provided in a facility setting (18, 19). Where CMS payment information was available for a code only in prior years, costs assumed a 3% increase per year. Costs for the single instance of inpatient care were assigned according to the CMS Acute Care Hospital Inpatient Prospective Payment System, with payment assigned to the appropriate Diagnosis-Related Group for care provided specifically at Brigham and Women's Hospital, Boston, MA.

**Supplement Table 1. Characteristics of primary care physician (PCP) participants in the MedSeq Project**

| | | | | | Enrolled patients (*n*) | | |
|---|---|---|---|---|---|---|---|
| **PCP** | **Sex** | **Age** | **Race** | **Genetics training beyond the typical medical school curriculum** | **Total** | **FH-only** | **FH+WGS** |
| 1 | Male | 64 | White | No | 16 | 9 | 7 |
| 2 | Female | 65 | White | No | 16 | 8 | 8 |
| 3 | Female | 53 | White | No | 9 | 4 | 5 |
| 4 | Male | 64 | Asian | Yes* | 9 | 5 | 4 |
| 5 | Male | 56 | White | No | 14 | 7 | 7 |
| 6 | Female | 45 | Black | No | 16 | 8 | 8 |
| 7 | Female | 57 | White | No | 4 | 2 | 2 |
| 8 | Female | 41 | White | No | 6 | 2 | 4 |
| 9 | Male | 39 | White | No | 10 | 5 | 5 |

*Participant responded that he had previously taken a continuing medical education course in genetics for PCPs.

**Supplement Table 2. Carrier status variants reported to 50 generally healthy adult patient participants in the MedSeq Project**

| Patient | Gene | Associated disease | Variant (Nucleotide) | Variant (Protein) | Classification |
|---|---|---|---|---|---|
| 1 | *MMACHC* | Methylmalonic aciduria and homocystinuria cblC type | c.271dupA | p.Arg91LysfsX14 | P |
| 1 | *SPATA7* | Leber congenital amaurosis | c.94+2T>C | | LP |
| 3 | *CFTR* | Cystic fibrosis | c.3846G>A | p.Trp1282X | P |
| 3 | *PFKM* | Glycogen storage disease 7 | c.237+1G>A | | P |
| 5 | *ERCC5* | Xeroderma pigmentosum | c.3238C>T | p.Arg1080X | LP |
| 7 | *CUBN* | Imerslund-Gräsbeck syndrome | c.6928_6934delGAGGTTA | p.Glu2310CysfsX3 | P |
| 7 | *RAB27A* | Familial hemophagocytic lymphohistiocytosis | c.259G>C | p.Ala87Pro | VUS:FP |
| 10 | *ABCA4* | Stargardt disease | c.5882G>A | p.Gly1961Glu | P |
| 10 | *CNGA3* | Achromatopsia | c.1669G>A | p.Gly557Arg | VUS:FP |
| 10 | *MPO* | Myeloperoxidase deficiency | c.2031-2A>C | | P |
| 11 | *DUOX2* | Hypothyroidism | c.3847+2T>C | | P |
| 13 | *BTD* | Biotinidase deficiency | c.1330G>C | p.Asp444His | P |
| 13 | *PYGL* | Glycogen storage disease 6 | c.25_44dup | p.Ser15ArgfsX21 | P |
| 13 | *SPG7* | Spastic paraplegia type 7 | c.1529C>T | p.Ala510Val | P* |
| 13 | *WFS1* | Wolfram syndrome | c.124C>T | p.Arg42X | P |
| 16 | *COL7A1* | Epidermolysis bullosa dystrophica | c.7557+1G>T | | LP |
| 23 | *CLRN1* | Usher syndrome type III | c.528T>G | p.Tyr176X | P |
| 23 | *CYP1B1* | Primary congenital glaucoma | c.171G>A | p.Trp57X | P |
| 23 | *NLRP7* | Recurrent hydatidiform mole | c.337_338insG | p.Glu113GlyfsX7 | P |
| 23 | *KCNQ1* | Jervell and Lange-Nielsen syndrome | c.826delT | p.Ser276ProfsX13 | LP |
| 23 | *NAGA* | Alpha-N-acetylgalactosaminidase deficiency | c.479C>G | p.Ser160Cys | LP |
| 30 | *HFE* | Hereditary hemochromatosis | c.845G>A | p.Cys282Tyr | P |
| 31 | *CYP1B1* | Primary congenital glaucoma | c.1103G>A | p.Arg368His | P |
| 31 | *ABCA4* | Stargardt disease | c.5882G>A | p.Gly1961Glu | P |
| 31 | *SP110* | Hepatic veno-occlusive disease with immunodeficiency | c.877A>T | p.Lys293* | LP |
| 32 | *C2* | C2 deficiency | c.841_849+19del | | LP† |
| 32 | *KHDC3L* | Hydatidiform mole, recurrent | c.334C>T | p.Gln112X | LP |
| 38 | *BEST1* | Autosomal recessive bestrophinopathy | c.602T>C | p.Ile201Thr | LP |
| 38 | *ARSB* | Mucopolysaccharidosis type VI | c.1450A>G | p.Arg484Gly | LP |
| 38 | *DUOX2* | Congenital hypothyroidism | c.2895_2898del | p.Phe966Serfs*29 | P |
| 49 | *ALOX12B* | Autosomal recessive congenital ichthyosis | c.1562A>G | p.Tyr521Cys | P |

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|---|---|---|---|---|---|
| 49 | *BTD* | Biotinidase deficiency | c.1330G>C | p.Asp444His | P |
| 49 | *C8B* | C8 deficiency, type II | c.1282C>T | p.Arg428X | P |
| 49 | *CYP1B1* | Primary congenital glaucoma | c.1103G>A | p.Arg368His | P |
| 49 | *POLG* | POLG-related mitochondrial disorders | c.1399G>A | p.Ala467Thr | P |
| 49 | *ITGB4* | Epidermolysis bullosa with pyloric atresia | c.2783-2A>G | | LP |
| 58 | *SLC6A19* | Hartnup disorder | c.517G>A | p.Asp173Asn | P |
| 79 | *HFE* | Hereditary hemochromatosis | c.187C>G | p.His63Asp | P |
| 82 | *BBS10* | Bardet Biedl syndrome | c.1091delA | p.Asn364Thrfs*5 | P |
| 83 | *CHRNE* | Congenital myasthenic syndrome | c.1033-2A>T | | P |
| 97 | *GJB2* | Nonsyndromic hearing loss | c.101T>C | p.Met34Thr | P |
| 97 | *HFE* | Hereditary hemochromatosis | c.187C>G | p.His63Asp | P |
| 97 | *NEK8* | Renal-hepatic-pancreatic dysplasia 2 | c.47+1delG | | VUS:FP |
| 99 | *SERPINA1* | Alpha-1 antitrypsin deficiency disorder | c.1096G>A | p.Glu366Lys | P |
| 99 | *USH2A* | Usher syndrome type II | c.920_923dupGCCA | p.His308fs | P |
| 99 | *CAPN3* | Calpainopathy | c.1468C>T | p.Arg490Trp | P |
| 99 | *FOXRED1* | Mitochondrial complex I deficiency | c.611_614dupGAGT | p.Ala206SerfsX15 | LP |
| 100 | *DNAH11* | Primary ciliary dyskinesia | c.8746C>T | p.Gln2916X | P |
| 100 | *EYS* | Retinitis pigmentosa | c.6528C>A | p.Tyr2176X | P |
| 100 | *GNRHR* | Isolated hypogonadotropic hypogonadism | c.317A>G | p.Gln106Arg | P |
| 100 | *COG4* | Congenital disorder of glycosylation | c.529C>T | p.Arg177X | LP |
| 100 | *USH2A* | Usher syndrome | c.10073G>A | p.Cys3358Tyr | LP‡ |
| 109 | *SPG7* | Spastic paraplegia type 7 | c.1529C>T | p.Ala510Val | P§ |
| 109 | *BTD* | Biotinidase deficiency | c.1330G>C | p.Asp444His | P |
| 109 | *EIF2B2* | Leukoencephalopathy with vanishing white matter | c.599G>T | p.Gly200Val | LP |
| 109 | *MPDZ* | Congenital hydrocephalus | c.4906C>T | p.Arg1636X | LP |
| 114 | *HFE* | Hereditary hemochromatosis | c.845G>A | p.Cys282Tyr | P |
| 114 | *GBE1* | Glycogen storage disease IV | c.691+2T>C | | P |
| 114 | *USH2A* | Usher syndrome type II | c.920_923dupGCCA | p.His308GlnfsX16 | P |
| 114 | *ANO5* | ANO5-Related Muscle diseases | c.2272C>T | p.Arg758Cys | P |
| 126 | *TG* | Congenital hypothyroidism | c.5184C>A | p.Cys1728X | P |
| 126 | *C6* | Complement component 6 deficiency | c.1786C>T | p.Arg596X | LP |
| 132 | *ACE* | Renal tubular dysgenesis | c.12_31del | p.Ser5AlafsX31 | P |
| 132 | *PAH1* | Phenylketonuria | c.691T>C | p.Ser231Pro | P |
| 143 | *HFE* | Hereditary hemochromatosis | c.187C>G | p.His63Asp | P |
| 143 | *TH* | Segawa syndrome | c.283delG | p.Ala95ArgfsX6 | P |
| 143 | *MRAP* | Familial glucocorticoid deficiency | c.3G>A | p.Met? | P |

| | | | | | |
|---|---|---|---|---|---|
| 143 | *SLC4A11* | Corneal endothelial dystrophy 2 | c.554_562delinsC | p.Arg185ProfsX4 | P |
| 144 | *GJB2* | Hearing loss | c.109G>A | p.Val37Ile | P |
| 144 | *HFE* | Hereditary hemochromatosis | c.187C>G | p.His63Asp | P |
| 144 | *CYP21A2* | Congenital adrenal hyperplasia | c.844G>T | p.Val282Leu | P\|\| |
| 144 | *CACNA2D4* | Retinal cone dystrophy | c.1882C>T | p.Arg628X | VUS:FP |
| 147 | *PAH* | Phenylketonuria | c.1208C>T | p.Ala403Val | P |
| 151 | *TCTN3* | Orofaciodigital syndrome 4 | c.877C>T | p.Gln293X | P |
| 151 | *SERPINA1* | Alpha-1 antitrypsin deficiency disorder | c.1096G>A | p.Glu366Lys | P |
| 151 | *SLC6A19* | Hartnup disorder | c.517G>A | p.Asp173Asn | P |
| 157 | *DBH* | Dopamine beta-hydroxylase deficiency | c.339+2T>C | | P |
| 157 | *UBR1* | Johanson-Blizzard syndrome | c.4107T>A | p.Cys1369X | P |
| 173 | *SERPINA1* | Alpha-1 antitrypsin deficiency disorder | c.1096G>A | p.Glu366Lys | P |
| 173 | *FANCF* | Fanconi anemia | c.690delT | p.Gly231GlufsX7 | LP |
| 175 | *SGCG* | Limb girdle muscular dystrophy type 2C | c.195+4_195+7del | | P |
| 175 | *PKHD1* | Polycystic kidney disease | c.9559delT | p.Ser3187LeufsX33 | P |
| 175 | *PLCE1* | Nephrotic syndrome | c.1845_1846insA | p.Gly616ArgfsX52 | P |
| 184 | *COL17A1* | Junctional epidermolysis bullosa | c.2435-6_2440del | p.? | LP |
| 184 | *MUTYH* | MUTYH-associated polyposis | c.536A>G | p.Tyr179Cys | P |
| 185 | *TNXB* | Ehlers-Danlos-like syndrome due to tenascin X deficiency | c.4996C>T | p.Arg1666X | VUS:FP |
| 186 | *ABCC2* | Dubin-Johnson syndrome | c.3741+1G>A | p. ? | P |
| 186 | *MUT* | Methylmalonic acidemia | c.1207C>T | p.Arg403X | P |
| 187 | *USH2A* | Usher syndrome type II | c.2276G>T | p.Cys759Phe | P |
| 187 | *CYP24A1* | Infantile hypercalcemia | c.1039C>T | p.Gln347X | LP |
| 188 | *HFE* | Hereditary hemochromatosis | c.187C>G | p.His63Asp | P |
| 188 | *ABCC6* | Pseudoxanthoma elasticum | c.3306+1del | p.? | P |
| 196 | *IDUA* | Mucopolysaccharidosis type I | c.208C>T | p.Gln70X | P |
| 196 | *MRAP* | Familial glucocorticoid deficiency | c.3G>A | p.Met1? | P |
| 196 | *ABCA4* | Stargardt disease | c.5882G>A | p.Gly1961Glu | P |
| 196 | *HSD17B3* | 17 beta-hydroxysteroid dehydrogenase 3 deficiency | c.277+4A>T | p.? | P |
| 196 | *NEK1* | Short rib-polydactyly syndrome type II | c.3107C>G | p.Ser1036X | LP |
| 196 | *SLC7A9* | Cystinuria | c.1399+4_1399+7del | p.? | VUS:FP |
| 196 | *GFPT1* | Limb-girdle myasthenia syndrome | c.*22C>A | p.? | VUS:FP |
| 199 | *GJB2* | Hearing loss | c.109G>A | p.Val37Ile | P |
| 199 | *CFTR* | Cystic fibrosis | c.2909G>A | p.Gly970Asp | LP |
| 199 | *RPGRIP1L* | Joubert syndrome | c.3299_3300dup | p.Ala1101SerfsX34 | LP |
| 199 | *PAPSS2* | Brachyolmia | c.1662_1666del | p.Phe555SerfsX15 | LP |

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|---|---|---|---|---|---|
| 201 | *GJB2* | Non-syndromic hearing loss | c.167del | p.Leu56ArgfsX | P |
| 201 | *HFE* | Hereditary hemochromatosis | c.187C>G | p.His63Asp | P |
| 201 | *ASPA* | Canavan disease | c.854A>C | p.Glu285Ala | P |
| 201 | *CPT2* | Carnitine palmitoyltransferase II deficiency | c.338C>T | p.Ser113Leu | P |
| 201 | *GYS1* | Muscle glycogen storage disease type 0 | c.989_992del | p.Gly330AlafsX25 | LP |
| 203 | *CNGA3* | Achromatopsia | c.101+1G>A |  | LP |
| 203 | *HFE* | Hereditary hemochromatosis | c.187C>G | p.His63Asp | P |
| 203 | *ASPA* | Canavan disease | c.693C>A | p.Tyr231X | P |
| 203 | *NDUFAF3* | Mitochondrial complex I deficiency | c.180_181insT | p.Asp61X | VUS:FP |
| 204 | *HFE* | Hereditary hemochromatosis | c.845G>A | p.Cys282Tyr | P |
| 204 | *TTPA* | Ataxia with isolated vitamin E deficiency | c.19delC | p.Gln7SerfsX64 | P |
| 205 | *FANCA* | Fanconi anemia | c.987_990delTCAC | p.His330AlafsX4 | P |
| 205 | *NEB* | Nemaline myopathy | c.23848-1G>C |  | LP |
| 205 | *IFNGR1* | IFNGR1 deficiency | c.523del | p.Tyr175MetfsX2 | P |
| 206 | *IL36RN* | Generalized pustular psoriasis | c.338C>T | p.Ser113Leu | P |
| 206 | *C2* | C2 deficiency | c.1063C>T | p.Arg355X | VUS:FP |
| 206 | *MOCS2* | Molybdenum cofactor deficiency | c.539_540delAA | p.Lys180ArgfsX31 | LP |
| 209 | *ABCA4* | Stargardt disease | c.5882G>A | p.Gly1961Glu | P |
| 209 | *DHDDS* | Retinitis pigmentosa | c.124A>G | p.Lys42Glu | P |
| 209 | *HOGA1* | Primary hyperoxaluria, type III | c.944_946del | p.Glu315del | P |
| 209 | *BLM* | Bloom syndrome | c.2207_2212delinsTAGATTC | p.Tyr736LeufsX5 | P |
| 209 | *EDARADD* | Hypohidrotic ectodermal dysplasia | c.299_300insAAC | p.Cys100X | VUS:FP |
| 221 | *HFE* | Hereditary hemochromatosis | c.845G>A | p.Cys282Tyr | P |
| 221 | *KIF7* | Acrocallosal syndrome | c.2944G>T | p.Glu982X | P |
| 221 | *DHCR7* | Smith-Lemli-Opitz syndrome | c.452G>A | p.Trp151X | P |
| 221 | *GNPTAB* | Mucolipidosis II | c.3503_3504del | p.Leu1168GlnfsX5 | P |
| 222 | *GRM6* | Congenital stationary night blindness | c.2213_2219delCCAGAGG | p. Ala738GlyfsX81 | VUS:FP |
| 224 | *USH2A* | Usher syndrome type II | c.4405C>T | p.Gln1469X | P |
| 224 | *VWF* | von Willebrand disease type 2 N | c.2561G>A | p.Arg854Gln | P |
| 232 | *FLG* | Ichthyosis vulgaris | c.2143C>T | p.Gln715X | P |
| 232 | *SYNE1* | Spinocerebellar ataxia | c.3930_3931dup | p.His1311ProfsX30 | P |
| 242 | *MUTYH* | MUTYH-related attenuated familial adenomatous polyposis | c.1187G>A | p.Gly396Asp | P |
| 242 | *HFE* | Hereditary hemochromatosis | c.187C>G | p.His63Asp | P |

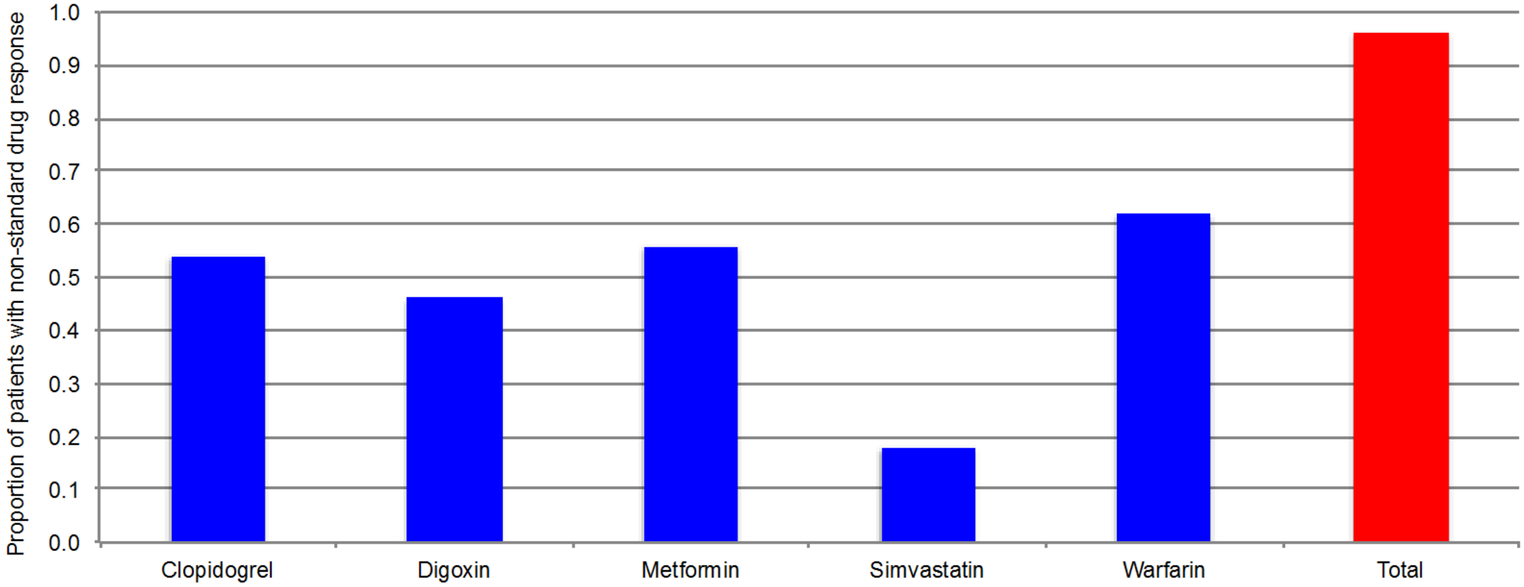
All variants were reported as having autosomal recessive inheritance and were reported with the pathogenicity classifications listed in the Table. After the observation period, some variant classifications were reclassified as indicated in the footnotes. Abbreviations: P, pathogenic; LP, likely pathogenic; VUS:FP, variant of uncertain significance, favor pathogenic. *Reclassified to LP June 2016. †Reclassified to P January 2017. ‡Reclassified to P January 2016. §Reclassified to LP June 2016. ||Removed from the genome report after reanalysis, when it was determined that the Sanger validation of the variant was unable to distinguish between the functional gene and multiple pseudogenes.

**Supplement Table 3. Polygenic risk estimates for cardiometabolic traits among 50 patients in the MedSeq Project**

| | | | **Patients, *n* (%)** | |
|---|---|---|---|---|
| | **Number of Loci Evaluated** | **Proportion of Variation in Phenotype Liability Explained by Common Genetic Variants** | **≤10th percentile** | **≥90th percentile** |
| Abdominal aortic aneurysm | 3 | Unknown | 5 (10) | 7 (14) |
| Atrial fibrillation | 11 | 10% | 6 (12) | 1 (2) |
| Coronary heart disease | 60 | <10% | 3 (6) | 10 (20) |
| Type 2 diabetes | 70 | 5-10% | 3 (6) | 11 (22) |
| Hypertension | 3 | <10% | 5 (10) | 4 (8) |
| Obesity | 7 | 1-2% | 9 (18) | 1 (2) |
| Platelet aggregation | 4 | 5-10% | 20 (40) | 6 (12) |
| QT prolongation | 3 | 7% | 16 (32) | 9 (18) |

Percentile rank of polygenic risk was calculated as described in Kong, *et al. Genet. Med.* 2015 (11).

**Supplement Figure: Primary care patients in the MedSeq Project (n=50) with an atypical or non-standard pharmacogenomic result for five common medications**



| Drug | Pharmacogenotype | Interpretation | *n* | % |
|---|---|---|---|---|
| Clopidogrel | *CYP2C19*: c.[-806C>T; 681G>A; 636G>A], *2/*2 | Significantly decreased response | 2 | 4 |
| | *CYP2C19*: c.[-806C>T; 681G>A; 636G>A], *1/*2 or *2/*17 | Decreased response | 11 | 22 |
| | *CYP2C19*: c.[-806C>T; 681G>A; 636G>A], *1/*1 | Typical response | 23 | 46 |
| | *CYP2C19*: c.[-806C>T; 681G>A; 636G>A], *1/*17 or *17/*17 | Increased response | 14 | 28 |
| Digoxin | *ABCB1*: c.3435T>C, TT | Decreased metabolism and increased serum concentration | 7 | 14 |
| | *ABCB1*: c.3435T>C, CT | Typical metabolism and serum concentration | 27 | 54 |
| | *ABCB1*: c.3435T>C, CC | Increased metabolism and decreased serum concentration | 16 | 32 |
| Metformin | *C11orf65*: c.175-5285G>A/T, GG | Decreased glycemic response | 16 | 32 |
| | *C11orf65*: c.175-5285G>A/T, GT | Typical glycemic response | 22 | 44 |
| | *C11orf65*: c.175-5285G>A/T, TT | Increased glycemic response | 12 | 24 |
| Simvastatin | *SLCO1B1*: c.521T>C, TT | Typical risk of myopathy | 41 | 82 |
| | *SLCO1B1*: c.521T>C,TC | Increased risk of myopathy | 9 | 18 |
| Warfarin | See caption | Decreased dose requirement | 4 | 8 |
| | | Standard dose requirement | 19 | 38 |
| | | Increased dose requirement | 27 | 54 |

The red bar indicates the proportion of patients receiving at least one atypical or nonstandard result among the five medications. The table summarizes the pharmacogenomic results for all 50 patients. Warfarin pharmacogenotype based on *VKORC1:* c.1639G>A and *CYP2C9:* c.[430C>T; 1075A>C]. An interpretation of "decreased dose requirement" was given for the following *VKORC1/CYP2C9* genotypes: G/A, *2/*3; A/A, *1/*3; A/A, *2/*3; A/A, *2/*2. An interpretation of "increased dose requirement" was given for G/A, *1/*1; G/G *1/*2; G/G *1/*1. All other genotypes were interpreted as "standard dose requirement."

**Supplement Table 4: Proportions of MedSeq Project patients receiving United States Preventive Services Task Force (USPSTF) guideline-concordant care at baseline and after 6 months**

| | **Family history-only** | | | | **Family history + WGS** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Baseline** | | **6 months** | | **Baseline** | | **6 months** | |
| **Grade A: Recommended due to high certainty of substantial net benefit** | | | | | | | | |
| Aspirin for men 45-79 years old and women 55-79 years old with a 10-year cardiovascular disease risk ≥10% | | | | | | | | |
| Among high-risk patients, n (%) | 3/3 | 100% | 3/3 | 100% | 3/3 | 100% | 2/3 | 67% |
| Among all patients, n (%) | 49/49 | 100% | 49/49 | 100% | 49/49 | 100% | 48/49 | 98% |
| Colorectal cancer screening with fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults 50-75 years old | | | | | | | | |
| Among patients ≥50 years old, n (%) | 31/33 | 94% | 31/33 | 94% | 33/38 | 87% | 34/38 | 89% |
| Among all patients, n (%) | 48/50 | 96% | 47/50 | 94% | 45/50 | 90% | 46/50 | 92% |
| Cervical cancer screening with cytology every 3 years or cytology and HPV testing every 5 years in women <65 years old with a cervix | | | | | | | | |
| Among women <65 years old with a cervix, n (%) | 24/27 | 89% | 23/27 | 85% | 22/26 | 85% | 23/26 | 88% |
| Among all women, n (%) | 27/30 | 90% | 26/30 | 87% | 23/28 | 82% | 25/28 | 89% |
| **Grade D: Recommended *against* due to moderate or high certainty of no net benefit or that harms outweigh benefits** | | | | | | | | |
| Aspirin for cardiovascular disease risk in men <45 years old and women <55 years old | | | | | | | | |
| Among low-risk patients, n (%) | 12/13 | 92% | 13/13 | 100% | 7/7 | 100% | 7/7 | 100% |
| Among all patients, n (%) | 49/50 | 98% | 50/50 | 100% | 49/49 | 100% | 49/49 | 100% |
| Prostate-specific antigen testing for prostate cancer screening | | | | | | | | |
| Among all men, n (%) | 15/20 | 75% | 15/20 | 75% | 11/22 | 50% | 18/22 | 82% |

**Supplement Table 5. Sensitivity analysis of healthcare utilization and costs during 6-month after family history with or without whole genome sequencing (WGS)**

| | | **Family history-only (*n*=50)** | | **Family history + WGS (*n*=50)** | |
|---|---|---|---|---|---|
| | | **Total** | **Per patient** | **Total** | **Per patient** |
| Utilization | Laboratory tests | 92 | 1.84 | 150 | 3.00 |
| | Imaging tests | 39 | 0.78 | 43 | 0.86 |
| | Cardiac tests | 4 | 0.08 | 16 | 0.32 |
| | PCP visit | 28 | 0.56 | 25 | 0.50 |
| | Non-PCP visits | 71 | 1.42 | 68 | 1.36 |
| Costs per patient, mean / median (range) | | $849 / $197 ($0-$10,704) | | $996 / $314 ($0-$14,178) | |

Healthcare utilization and costs limited to those actions with billing codes observed in the data set.

**Supplement Table 6: Imputed Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes**

| Clinical Action | Imputed Code |
|---|---|
| **Cardiology tests** | |
| Echocardiography | 93307 |
| Electrocardiogram | 93005 and 93010 |
| Exercise stress test | 93016, 93017, and 93018 |
| **Imaging tests** | |
| Two-view chest radiography | 71020 |
| Lumbar spine radiography | 72114 |
| Two-view shoulder radiography | 73030 |
| Wrist radiography | 73110 |
| Hip radiography | 73510 |
| Foot radiography | 73630 |
| Abdominal ultrasound | 76700 |
| Lower extremity Doppler ultrasound | 76882 |
| Computed tomography of upper extremity without contrast | 73200 |
| Computed tomography of thorax without contrast | 71250 |
| Magnetic resonance imaging of wrist without contrast | 73221 |
| Magnetic resonance imaging of foot without contrast | 73719 |
| Magnetic resonance imaging of lumbar spine without contrast | 72148 |
| Bilateral digital mammogram | G0202 and 77052 |
| Liver elastography | 91200 |
| Scanning computerized imaging of optic nerve | 92133 |
| **Laboratory tests** | |
| 25-hydroxyvitamin D | 82306 |
| Alanine aminotransferase | 84460 |
| Alpha fetoprotein | 82105 |
| Amylase | 82150 |
| *Anaplasma phagocytophilum* antibody | 86666 |
| Aspartate aminotransferase | 84450 |
| *Babesia divergen*s antibody | 87798 |
| *Babesia duncani* antibody | 87798 |
| *Babesia microti* antibody | 87798 |
| Bacterial blood culture | 87040 |
| Basic metabolic panel | 80048 |
| Beta human chorionic gonadotropin (blood) | 84702 |
| Beta-hemolytic *Streptococcus* throat culture | 87081 |
| *Borrelia burgdorferi* antibody | 86618 |
| Breast biopsy | 19100 |
| C-reactive protein | 86141 |
| Calcium | 82310 |
| Cancer screening with prostate-specific antigen test | G0103 |
| Collection of venous blood by venipuncture | 36415 |
| Colon biopsy pathology | 88305 |

| | |
|---|---|
| Complete blood count | 85025 |
| Comprehensive metabolic panel | 80053 |
| Creatine kinase | 82550 |
| Creatinine | 82565 |
| Cyanocobalamin | 82607 |
| Dermatology shave biopsy pathology | 11100 |
| *Ehrlichica chaffeensis* antibody | 87798 |
| *Ehrlichica ewingii* antibody | 87798 |
| *Ehrlichica muris-like* antibody | 87798 |
| Endometrial biopsy | 58100 |
| Endometrial biopsy pathology | 88307 |
| Erythrocyte sedimentation rate | 85652 |
| Ferritin | 82728 |
| Folic acid | 82746 |
| Follicle-stimulating hormone | 83001 |
| Glucose | 82947 |
| *Helicobacter pylori* antigen | 87338 |
| *Helicobacter pylori* urea breath test | 83013 |
| Hematocrit | 85014 |
| Hemoglobin A1c | 83036 |
| Hepatitis B surface antigen | 87340 |
| Hepatitis C nucleic acid detection | 87522 |
| Human immunodeficiency virus antibody | G0433 |
| Human papillomavirus nucleic acid detection | 87624 |
| Iron | 83540 |
| Lactate | 83605 |
| Lipase | 83690 |
| Lipid profile | 80061 |
| Lipoprotein(a) | 83695 |
| Liver panel | 80076 |
| Lymph node biopsy pathology | 88307 |
| Nasopharyngeal swab for influenza A&B | 87804 |
| Pap smear cytopathology | 88141 and 88175 |
| Variegate porphyria genetic testing | 83891 |
| Rheumatoid factor | 86431 |
| Testosterone | 84403 |
| Thiopurine metabolites | 80375 |
| Throat culture | 87070 |
| Thyroid-stimulating hormone | 84443 |
| Urinalysis | 81001 |
| Urine culture | 87086 |
| Urine microalbumin | 82043 |
| Urine pregnancy test | 81025 |

**Office visits**

| | |
|---|---|
| Acupuncture, new patient | 99203 |
| Cardiovascular genetics, new patient | 99205 |
| Dermatology, new patient | 99203 |

| | |
|---|---|
| Dermatology, established patient | 99215 |
| Gastroenterology, new patient | 99203 |
| Genetic counseling | 99213 |
| Gynecology, established patient | 99215 |
| Hand surgery, established patient | 99213 |
| Hematology-oncology, new patient | 99203 |
| Medical nutrition | 97802 |
| Neurology, new patient | 99203 |
| Ophthalmology, new patient | 99203 |
| Optometry, new patient eye exam | 92004 |
| Optometry, comprehensive vision evaluation, refraction, and contact lens evaluation | 92014 |
| Orthopedic surgery, new patient | 99203 |
| Orthopedic surgery, established patient | 99213 |
| Otorhinolaryngology, new patient | 99203 |
| Physical medicine and rehabilitation, established patient | 99215 |
| Physical therapy evaluation | 97001 |
| Physical therapy: hot/cold pack application | 97010 |
| Physical therapy: electrical stimulation | G0283 |
| Physical therapy: therapeutic ultrasound | 97035 |
| Physical therapy: exercise and tissue mobilization | 97110 and 97140 |
| Physical therapy: therapeutic activities | 97530 |
| Podiatry, established patient | 99213 |
| Primary care | 99213 |
| Radiation oncology, established patient | 99213 |
| **Procedures** | |
| Cryotherapy for acrochordon | 11200 |
| Nail debridement | 11720 |
| Destruction of up to four premalignant lesions | 17000 and 17003 |
| Finger tendon injections | 20550 |
| Colonoscopy with biopsy | G0105 and 45380 |
| Hysteroscopy, myomectomy, and ablation | 58558, 58561, and 58563 |
| Pulmonary function testing | 94060 |
| Intramuscular injection of medication | 96372 |
| Zoster vaccine | 90736 |
| Acupuncture | 97810 |
| Audiometry | 92557 |
| Dermatologic shave removal (x1) | 11300 |
| Dermatologic shave removal (x5) | 11300 (x4), 11305 |

These codes were imputed for clinical actions documented as completed in the electronic health record but without a corresponding code in the Research Patient Data Registry (RPDR). New patient and established patient visits to specialists were imputed as 99203 and 99215, respectively, the mode of the CPT codes observed in RPDR for these types of visits.

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*****EXAMPLE REPORT*****

**Name: DOE, JOHN**
**Accession ID: PMXX-12345**

DOB: **01/23/1900**
MRN: **0123456789**
Sex: **Female**
Specimen: **Blood, Peripheral**
Race: **Caucasian**
Received: **05/03/2013**
Indication for testing: **MedSeq, Primary Care**
Family #: **F1234657**
Referring physician: **Dr. Med Seq**
Referring facility: **Brigham and Women's**
Test: **WGS-pnIA, SeqConV2, WGS-GGR**

# GENOME REPORT

## RESULT SUMMARY

Sequencing of this individual's genome was performed and covered 95.3% of all positions at 8X coverage or higher, resulting in over 5.2 million variants compared to a reference genome. These data were analyzed to identify previously reported variants of potential clinical relevance as well as novel variants that could reasonably be assumed to cause disease (see methodology below). All results are summarized on page 1 with further details on subsequent pages.

### A. MONOGENIC DISEASE RISK: 0 VARIANTS IDENTIFIED

This test did NOT identify genetic variants that may be responsible for existing disease or the development of disease in this individual's lifetime.

### B. CARRIER RISK: 3 VARIANTS IDENTIFIED

This test identified carrier status for 3 autosomal recessive disorders.

| Disease<br>Inheritance | Gene<br>Transcript | Zygosity<br>Variant | Classification | Carrier Phenotype* |
|---|---|---|---|---|
| B1. Congenital myasthenic syndrome<br>Autosomal recessive | RAPSN<br>NM_005055.4 | Heterozygous<br>c.264C>A<br>p.Asn88Lys | Pathogenic | None reported |
| B2. Cutis laxa, type IC<br>Autosomal recessive | LTBP4<br>NM_003573.2 | Heterozygous<br>c.254delT<br>p.Leu85ArgfsX15 | Pathogenic | None reported |
| B3. Joubert syndrome<br>Autosomal recessive | TCTN2<br>NM_02480.4 | Heterozygous<br>c.1877T>A<br>p.Leu626X | Pathogenic | None reported |

As a carrier for recessive genetic variants, this individual is at higher risk for having a child with one or more of these highly penetrant disorders. To determine the risk for this individual's future children to be affected, the partner of this individual would also need to be tested for variants in these genes. Other biologically related family members may also be carriers of these variants. *Carriers for some recessive disorders may be at risk for certain phenotypes. Please see variant descriptions for more information.

### C. PHARMACOGENOMIC ASSOCIATIONS

This test identified the following pharmacogenomic associations. Additional pharmacogenomic results may be requested, but will require additional molecular confirmation prior to disclosure.

| Drug | Risk and Dosing Information |
|---|---|
| C1. Warfarin | Increased dose requirement |
| C2. Clopidogrel | Increased response to clopidogrel |
| C3. Digoxin | Typical metabolism and serum concentration of digoxin |
| C4. Metformin | Increased glycemic response to metformin |
| C5. Simvastatin | Increased risk of simvastatin-related myopathy |

### D. RED BLOOD CELL AND PLATELET ANTIGENS

This test identified the ABO Rh blood type as A Positive. Additional blood group information is available at the end of the report.

It should be noted that the disease risk section of this report is limited only to variants with strong evidence for causing highly penetrant disease, or contributing to highly penetrant disease in a recessive manner. Not all variants identified have been analyzed, and not all regions of the genome have been adequately sequenced. These results should be interpreted in the context of the patient's medical evaluation, family history, and racial/ethnic background. Please note that variant classification and/or interpretation may change over time if more information becomes available. For questions about this report, please contact the Genome Resource Center at GRC@partners.org.

# DETAILED VARIANT INFORMATION

## A. MONOGENIC DISEASE RISK

This test did NOT identify genetic variants that may be responsible for existing disease or the development of disease in this individual's lifetime.

## B. CARRIER RISK

| Disease Inheritance | Gene Transcript | Zygosity Variant Classification | Variant Frequency | Disease Prevalence (Carrier Freq.) | References | Carrier Phenotype |
|---|---|---|---|---|---|---|
| B1. Congenital myasthenic syndrome<br>Autosomal recessive | RAPSN<br>NM_005055.4 | heterozygous<br>c.264C>A<br>p.Asn88Lys<br>Pathogenic | 13/8596<br>(0.01%)<br>European American | 1-9/1,000,000<br>(Unknown) | Ohno 2002,<br>Dunne 2003,<br>Richard 2003,<br>Muller 2003,<br>Banwell 2004,<br>Yasaki 2004,<br>Muller 2004,<br>Ioos 2004,<br>Cossins 2006,<br>Skeie 2006,<br>Milone 2009,<br>Brugoni 2010,<br>Bell 2011,<br>Alseth 2011 | N/A |

**VARIANT INTERPRETATION:** The Asn88Lys variant in RAPSN has been previously identified in many individuals with congenital myasthenic syndrome and has been shown to segregate with disease in several affected family members (Ohno 2002, Dunne 2003, Richard 2003, Muller 2003, Banwell 2004, Yasaki 2004, Muller 2004, Ioos 2004, Cossins 2006, Skeie 2006, Milone 2009, Brugoni 2010, Bell 2011, Alseth 2011). This variant has been identified in 0.01% (13/8596) of European American chromosomes by the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/; dbSNP rs104894299). Although this variant has been seen in the general population, its frequency is low enough to be consistent with a recessive carrier frequency. Functional studies indicate the Asn88Lys variant results in reduced co-localization with the acetylcholine receptor (AChR) (Cossins 2006). In summary, this variant meets our criteria to be classified as pathogenic (http://pcpgm.partners.org/LMM) based upon segregation studies and functional evidence.

**DISEASE INFORMATION:** Congenital myasthenic syndromes (CMSs) are characterized by fatigable weakness of skeletal muscle (e.g., ocular, bulbar, limb muscles) with onset at or shortly after birth or in early childhood; rarely, symptoms may not manifest until later in childhood. Cardiac and smooth muscle tissues are not involved. Severity and course of disease are highly variable, ranging from minor symptoms to progressive disabling weakness. In some subtypes of CMS, myasthenic symptoms may be mild, but sudden severe exacerbations of weakness or even sudden episodes of respiratory insufficiency may be precipitated by fever, infections, or excitement. Major findings of the neonatal onset subtype include: feeding difficulties; poor suck and cry; choking spells; eyelid ptosis; facial, bulbar, and generalized weakness. In addition arthrogryposis multiplex congenital may be present; respiratory insufficiency with sudden apnea and cyanosis may occur. Later childhood onset subtypes show abnormal muscle fatigability with difficulty in activities such as running or climbing stairs; motor milestones may be delayed; fluctuating eyelid ptosis and fixed or fluctuating extraocular muscle weakness are common presentations. From GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK1168/

**FAMILIAL RISK:** CMS is inherited in an autosomal recessive manner. A carrier of CMS has a 50% chance of passing on this variant to any children. The risk of this patient's child having CMS is dependent on the carrier status of the patient's partner. Two carriers have a 25% risk for having a child with CMS. This patient likely inherited this variant from a parent. Other biologically related family members may also be carriers of this variant.

| Disease Inheritance | Gene Transcript | Zygosity Variant Classification | Variant Frequency | Disease Prevalence (Carrier Freq.) | References | Carrier Phenotype |
|---|---|---|---|---|---|---|
| B2. Cutis laxa, type IC<br>Autosomal recessive | LTBP4<br>NM_003573.4 | heterozygous<br>c.254delT<br>p.Leu85ArgfsX15<br>Pathogenic | 1/5840<br>(0.01%)<br>European American | Unknown<br>(Unknown) | Urban 2009,<br>Callewaert 2013 | N/A |

**VARIANT INTERPRETATION:** The Leu85ArgfsX15 variant in LTBP4 has not been previously reported in individuals with autosomal recessive cutis laxa type I, but has been identified in 1/5840 of European American chromosomes by the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/). Although this variant has been seen in the general population, its frequency is low enough to be consistent with a recessive carrier frequency. This frameshift variant is predicted to alter the protein's amino acid sequence beginning at position 85 and lead to a premature termination codon 15 amino acids downstream. This alteration is then predicted to lead to a truncated or absent protein. Loss of LTBP4 function has previously been desribed in homozygous and compound heterozygous individuals with autosomal recessive cutis laxa type IC (Urban 2009, Callewaert 2013). In summary, this variant meets our criteria to be classified as pathogenic for autosomal recessive cutis laxa type IC (http://pcpgm.partners.org/LMM).

**DISEASE INFORMATION:** Cutis laxa, autosomal recessive, type IC is a form of cutis laxa with pulmonary manifestations. A characteristic of this subtype is the severity of associated malformations, including major congenital heart disease, severe pulmonary hypertension, thought to be the consequence of pulmonary artery stenosis, diaphragmatic hernia and multiple bladder diverticulae with vesicoureteral reflux were causative of life-threatening complications and short life span. Adapted from GeneReviews abstract: http://www.ncbi.nlm.nih.gov/books/NBK5200/

**FAMILIAL RISK:** Cutis laxa, autosomal recessive, type IC is inherited in an autosomal recessive manner. A carrier of cutis laxa has a

50% chance of passing on this variant to any children. The risk of this patient's child having Cutis laxa is dependent on the carrier status of the patient's partner. Two carriers have a 25% risk for having a child with Cutis laxa. This patient likely inherited this variant from a parent. Other biologically related family members may also be carriers of this variant.

| Disease Inheritance | Gene Transcript | Zygosity Variant Classification | Variant Frequency | Disease Prevalence (Carrier Freq.) | References | Carrier Phenotype |
|---|---|---|---|---|---|---|
| B3. Joubert syndrome<br>Autosomal recessive | TCTN2<br>NM_02480.2 | heterozygous<br>c.1877T>A<br>p.Leu626X<br>Pathogenic | Not previously reported | 1:80,00-1:100,000<br>(Unknown) | Sang 2011,<br>Shaheen 2011 | N/A |

**VARIANT INTERPRETATION:** The Leu626X variant in TCTN2 has not been previously identified in individuals with Joubert syndrome or in large population studies. However, this nonsense variant leads to a premature termination codon at position 626, which is predicted to lead to a truncated or absent protein. Loss-of-function variants in the TCTN2 gene, including another nonsense variant in this exon, have been previously reported in individuals with autosomal recessive ciliopathies including Joubert syndrome (Sang 2011) and Meckel-Gruber syndrome (Shaheen 2011). In summary, this variant meets our criteria to be classified as pathogenic.

**DISEASE INFORMATION:** Classic Joubert syndrome is characterized by three primary findings: (1) distinctive cerebellar and brain stem malformation called the molar tooth sign (MTS), (2) Hypotonia, and (3) Developmental delays. Often these findings are accompanied by episodic tachypnea or apnea and/or atypical eye movements. In general, the breathing abnormalities improve with age, truncal ataxia develops over time, and acquisition of gross motor milestones is delayed. Cognitive abilities are variable, ranging from severe intellectual disability to normal. The designation Joubert syndrome and related disorders (JSRD) is used to describe individuals with JS who have additional findings including retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyly, oral hamartomas, and endocrine abnormalities. Both intra- and interfamilial variation are seen.

**FAMILIAL RISK:** JS is inherited in an autosomal recessive manner. A carrier of JS has a 50% chance of passing on this variant to any children. The risk of this patient's child having JS is dependent on the carrier status of the patient's partner. Two carriers have a 25% risk for having a child with JS. This patient likely inherited this variant from a parent. Other biologically related family members may also be carriers of this variant.

## PHARMACOGENOMIC ASSOCIATIONS AND BLOOD GROUPS

### C. PHARMACOGENOMIC ASSOCIATIONS

<table>
<tr><th>Drug (Indication)</th><th>Summary</th><th>Variants Evaluated and Genotypes Identified</th><th>Interpretation</th><th>References (PMID)</th></tr>
<tr><td rowspan="2">C1. Warfarin (Anti-coagulation)</td><td rowspan="2"><b>Increased dose requirement</b></td><td><i>CYP2C9</i><br>rs1799853<br>rs1057910<br>Genotype: *1/*1<br>c.[430C;1075A];<br>c.[430C;1075A]<br><br><i>VKORC1</i><br>rs9923231<br>Genotype: GG</td><td>Patients with the CYP2C9*1/*1 genotype may require a higher dose of warfarin as compared to patients with other CYP2C9 genotypes. Patients with the VKORC1 GG genotype may require a higher dose of warfarin as compared to patients with the VKORC1 GA or AA genotypes. Patients with the combination of the CYP2C9*1/*1 genotype and VKORC1 GG genotype are predicted to require higher doses of warfarin compared to other patients. Refer to warfarindosing.org for dosing based on genotype and other clinical factors.</td><td>Johnson 2011</td></tr>
<tr><td colspan="3"><b><i>VKORC1/CYP2C9 genotype combination frequencies</i></b>
<table>
<tr><th>Dosing Group</th><th>VKORC1 rs9923231</th><th>CYP2C9 Genotypes</th><th>Approximate Frequency</th></tr>
<tr><td rowspan="2">Lower</td><td>AA</td><td>*1/*3, *2/*2, *2/*3, *3/*3</td><td>6%</td></tr>
<tr><td>GA</td><td>*2/*3, *3/*3</td><td>3%</td></tr>
<tr><td rowspan="3">Standard</td><td>AA</td><td>*1/*1, *1/*2</td><td>37%</td></tr>
<tr><td>GA</td><td>*1/*2, *1/*3, *2/*2</td><td>14%</td></tr>
<tr><td>GG</td><td>*1/*3, *2/*2, *2/*3</td><td><1%</td></tr>
<tr><td rowspan="2">Higher</td><td>GA</td><td>*1/*1</td><td>28%</td></tr>
<tr><td>GG</td><td>*1/*1, *1/*2</td><td>13%</td></tr>
</table></td></tr>
<tr><td>C2. Clopidogrel (Anti-coagulation)</td><td><b>Increased response to clopidogrel</b></td><td><i>CYP2C19</i><br>rs4244285<br>rs4986893<br>rs12248560<br><br>Genotype: *1/*17<br>c.[-806C(;)681G(;)636G];<br>c.[806C>T(;)681G(;)636G]</td><td>Patients with the CYP2C19 *1/*17 genotype may have ultrarapid metabolism of clopidogrel and increased response to clopidogrel as compared to patients with a *1/*1 genotype. Additional information and dosing recommendations for this result can be found at: http://www.pharmgkb.org/drug/PA449053.</td><td>Scott 2013</td></tr>
</table>

***CYP2C19 genotype frequencies***

| Metabolism | Genotypes | Frequency |
|---|---|---|
| Ultrarapid | *1/*17, *17/*17 | 5-30% |
| Extensive | *1/*1 | 35-50% |
| Intermediate | *1/*2, *1/*3, *2/17, *3/*17 | 18-35% |
| Poor | *2/*2, *2/*3, *3/*3 | 2-15% |

| | | | | |
|---|---|---|---|---|
| C3. Digoxin (Dysrhythmias, heart failure) | **Typical metabolism and serum concentration of digoxin** | *ABCB1*<br>rs1045642<br>Genotype: CT<br>*Genotype frequencies:*<br>CC: 22% **CT: 51%** TT:27% | Patients with the CT genotype who take oral digoxin may have typical metabolism and serum concentrations of digoxin as compared to patients with the CC and TT genotypes. | Aarnoudse 2008, Kurata 2002, Hoffmeyer 2000 |
| C4. Metformin (Type 2 diabetes mellitus) | **Increased glycemic response to metformin** | *C11orf65*<br>rs11212617<br>Genotype: GG<br>*Genotype frequencies:*<br>TT:37% TG:48% **GG:15%** | Patients with the GG genotype who have Type 2 Diabetes Mellitus and are treated with metformin may have an increased glycemic response as compared to patients with the TT genotype. An association with increased or decreased glycemic response to metformin was not seen in people diagnosed with impaired glucose tolerance in the absence of Type 2 Diabetes Mellitus. | Florez 2012, GoDARTS and UKPDS Diabetes Pharmacogenetics Study Group 2011 |
| C5. Simvastatin (Hyperlipidemia) | **Increased risk of simvastatin-related myopathy** | *SLCO1B1*<br>rs4149056<br>Genotype: CT<br>*Genotype frequencies*:<br>TT:68% **CT:30%** CC:2% | Patients with the CT genotype may have a higher risk of simvastatin-related myopathy as compared to patients with the TT genotype, and a lower risk as compared to individuals with the CC genotype. | Wilke 2012 |

## D. RED BLOOD CELL AND PLATELET ANTIGENS

### D1. SUMMARY

**ABO Rh Blood type: A Positive**

#### Rare RBC Antigens

No rare presence or absence of RBC antigens were identified.

#### Rare Platelet Antigens

No rare presence or absence of platelet antigens were identified.

### D2. DISCUSSION

These red blood cell (RBC) and human platelet antigen (HPA) predictions are based on published genotype to phenotype correlations for the alleles present. Some antigens have also been serologically determined using traditional blood typing methods.

During pregnancy or transfusion alloantibodies to blood group antigens and platelet antigens can form against foreign RBCs that contain immunogenic blood group and platelet antigens that the recipient is missing. These alloantibodies can cause clinically important complications during future transfusions and pregnancy.

#### Blood Production Transfusion

This individual does NOT have an increased risk of forming unusual RBC or platelet alloantibodies, since this test revealed a normal absence of low frequency antigens, normal presence of high frequency antigens, and no antigen gene rearrangements.

#### Blood Production Donation

Although this individual's results indicate that they do not have a rare donor antigen profile, they would still be a valuable RBC donor given the following uncommon changes (<40% of the population): c−, Fy(b−), and Jk(b−). If interested in becoming a RBC and/or platelet donor, this individual may contact the BWH donor recruitment supervisor (Malissa Lichtenwalter 617-632-3206, MLichtenwalter@partners.org) and mention that our testing found them to be ABO Rh Blood Type A Positive and RBC antigen c−, Fy(b−), and Jk(b−).

### D3. RED BLOOD CELL ANTIGENS

| A | B | H | D | C | c | E | e | K | k | Jk(a) | Jk(b) | Fy(a) | Fy(b) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| + | - | + | + | + | - | - | + | - | + | + | - | + | - |

| M | N | S | S | Lu(a) | Lu(b) | Au(a) | Au(b) | Kp(a) | Kp(b) | Kp(c) | Di(a) | Di(b) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| + | - | - | + | [-] | [+] | [+] | [+] | [-] | [+] | [-] | [-] | [+] |

| Wr(a) | Wr(b) | Yt(a) | Yt(b) | Sc1 | Sc2 | Do(a) | Do(b) | Jo(a) | Hy | Co(a) | Co(b) | LW(a) | LW(b) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [-] | [+] | [+] | [-] | [+] | [-] | [-] | [+] | [+] | [+] | [+] | [-] | [+] | [-] |

| Cr(a) | Kn(a) | Kn(b) | Sl(a) | Vil | Yk(a) | KCAM | McC(a) | McC(b) | In(a) | In(b) |
|---|---|---|---|---|---|---|---|---|---|---|
| [+] | [+] | [-] | [+] | [-] | [+] | [+] | [+] | [-] | [-] | [+] |

| Ok(a) | MER2 | JMHK | JMHL | FORS |
|---|---|---|---|---|
| [+] | [+] | [+] | [+] | [-] |

## D4. PLATELET ANTIGENS

| 1a | 1b | 2a | 2b | 3a | 3b | 4a | 4b | 5a | 5b | 6bw | 7bw | 8bw | 9bw |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [+] | [-] | [+] | [-] | [+] | [+] | [+] | [-] | [+] | [+] | [-] | [-] | [-] | [-] |

| 10bw | 11bw | 12bw | 13bw | 14bw | 15a | 15b | 16bw | 17bw | 18bw | 19bw | 20bw | 21bw | 22bw |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [-] | [-] | [-] | [-] | [-] | [+] | [+] | [-] | [-] | [-] | [-] | [-] | [-] | [-] |

| 23bw | 24bw | 25bw | 26bw | 27bw |
|---|---|---|---|---|
| [-] | [-] | [-] | [-] | [-] |

Key: [+] presence of antigen predicted by genotyping; + presence of antigen predicted by genotyping and confirmed by serology; +* presence of antigen detected by serology, genotype prediction not available; [+w] weak presence of antigen predicted by genotyping; +w weak presence of antigen predicted by genotyping and confirmed by serology; +w* weak presence of antigen detected by serology, genotype prediction not available; [−] absence of antigen predicted by genotyping; - absence of antigen predicted by genotyping and confirmed by serology, -* absence of antigen detected by serology, genotype prediction not available; NC indicates no sequencing coverage, Dis indicates discordant. Rare (less than 5% population frequency) presence or absence of antigen is indicated in **red**.

## METHODOLOGY

Genomic sequencing is performed using next generation sequencing on the Illumina HiSeq platform. Genomes are sequenced to at least 30X mean coverage and a minimum of 95% of bases are sequenced to at least 8X coverage. Paired-end 100bp reads are aligned to the NCBI reference sequence (GRCh37) using the Burrows-Wheeler Aligner (BWA), and variant calls are made using the Genomic Analysis Tool Kit (GATK). Variants are subsequently filtered to identify: (1) variants classified as disease causing in public databases; (2) nonsense, frameshift, and +/-1,2 splice-site variants that are novel or have a minor allele frequency <1% in European American or African American chromosomes from the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/); and (3) rs11212617 (C11orf65; metformin), rs12248560 (CYP2C19; clopidogrel), rs4244285 (CYP2C19; clopidogrel), rs4986893 (CYP2C19; clopidogrel), rs28399504 (CYP2C19; clopidogrel), rs41291556 (CYP2C19; clopidogrel), rs72552267 (CYP2C19; clopidogrel), rs72558186 (CYP2C19; clopidogrel), rs56337013 (CYP2C19; clopidogrel), rs1057910 (CYP2C9; warfarin), rs1799853 (CYP2C9; warfarin), rs7900194 (CYP2C9; warfarin), rs9332131 (CYP2C9; warfarin), rs28371685 (CYP2C9; warfarin), rs28371686 (CYP2C9; warfarin), rs9923231 (VKORC1; warfarin), rs4149056 (VKORC1; simvastatin), and rs1045642 (ABCB1; digoxin). The evidence for phenotype-causality is then evaluated for each variant resulting from the filtering strategies above and variants are classified according to LMM criteria (http://pcpgm.partners.org/LMM). Only those variants with evidence for causing highly penetrant disease or contributing to disease in a recessive manner are reported. Before reporting, all variants are confirmed via Sanger sequencing or another orthogonal technology. The initial sequencing component of this test was performed by the Illumina Clinical Services Laboratory (San Diego, CA CLIA# 05D1092911) and the alignment, variant calling, data filtering, Sanger confirmation and interpretation were performed by the Laboratory for Molecular Medicine at the Partners Healthcare Center for Personalized Genetic Medicine (Cambridge, MA CLIA#22D1005307). This test has not been cleared or approved U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

## LIMITATIONS

It should be noted that this test does not sequence all bases in a human genome and not all variants have been identified or interpreted. Triplet repeat expansions, translocations and large copy number events are currently not reliably detected by genome sequencing. Furthermore, not all disease-associated genes have been identified and the clinical significance of variation in many genes is not well understood. It is recommended that genomic sequencing data is periodically reinterpreted, especially when new symptoms arise.

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*******EXAMPLE REPORT*******

Name: **DOE, JOHN**
DOB: **01/23/1900**
Sex: **Female**
Race: **Caucasian**
Indication for testing: **MedSeq, Primary Care**
MRN: **0123456789**
Specimen: **Blood, Peripheral**
Received: **05/03/2013**

Accession ID: **PMXX-12345**
Family #: **F1234657**
Referring physician: **Dr. Med Seq**
Referring facility: **Brigham and Women's**
Test: **WGS-pnIA, SeqConV2, WGS-GGR**

# CARDIAC RISK SUPPLEMENT

## RESULTS

### A. POLYGENIC PREDICTED FASTING LIPID PROFILE

The following lipid profile is predicted by known genetic factors, age, and gender and is not reflective of environmental, medication or other factors. These values are based on large epidemiologic studies and are not intended to substitute for measured values.

| | |
|---|---|
| LDL | 116 mg/dL |
| HDL | 47 mg/dL |
| Triglycerides | 140 mg/dL |

### B. ALLELES CONFERRING SMALL-MODERATE RISK MODIFICATION FOR 8 CARDIOVASCULAR PHENOTYPES

| | Contextual Data | | Patient Results | | | |
|---|---|---|---|---|---|---|
| **Phenotype** | **Population Prevalence of Phenotype for Age 54** | **Proportion of Variation in Phenotype Liability Explained by Common Genetic Variants** | **Number of Risk Loci Evaluated** | **Number of Total Risk Alleles Identified*** | **Polygenic Relative Risk**** | **Percentile Rank of Relative Risk**** |
| Abdominal aortic aneurysm | 1% | Unknown | 3 | 2/6 | 0.9 | 20-30th %ile |
| Atrial fibrillation | <1% | 10% | 11 | 6/22 | 0.6 | 10-20th %ile |
| Coronary heart disease | 6% (Age 40-59) | <10% | 60 | 57/120 | 1.4 | 60-70th %ile |
| Type 2 Diabetes | 13% (Age 45-64) | 5-10% | 70 | 69/140 | 1.4 | 60-70th %ile |
| Hypertension | 38% | <10% | 3 | 1/6 | 1.3 | 70-80th %ile |
| Obesity | 37% (Age 40-59) | 1-2% | 7 | 6/14 | 1.0 | 50-60th %ile |
| Platelet aggregation | Unknown | 5-10% | 4 | 0/8 | ≤0.6 | 0-10th %ile |
| QT prolongation | Unknown | 7% | 3 | 5/6 | 1.0 | 40-50th %ile |

*# of total possible risk alleles = # risk loci x 2 alleles per loci.
** As data utilized in this analysis were derived from non-longitudinal association studies, "Relative Risk from Common Genetic Variation" pertains to near-term risk of developing a phenotype (e.g. approximately 5 year risk), not lifetime risk. "Relative Risk from Common Genetic Variation" and "Percentile Rank of Relative Risk from Common Genetic Variation" values have been estimated using the 1000 Genomes European cohort.

## METHODOLOGY

Genomic sequencing is performed using next generation sequencing on the Illumina HiSeq platform. Genomes are sequenced to at least 30X mean coverage and a minimum of 95% of bases are sequenced to at least 8X coverage. Paired-end 100bp reads are aligned to the NCBI reference sequence (GRCh37) using the Burrows-Wheeler Aligner (BWA), and variant calls are made using the Genomic Analysis Tool Kit. Risk alleles identified at 161 loci involved in cardiac disease are determined and odds ratios are combined to provide overall assessment of risk for broad phenotypes. The technical component of this test as developed and its performance characteristics determined by the Illumina CLIA Lab (San Diego, CA CLIA# 05D1092911) and the interpretive algorithms and clinical reports were generated by the Laboratory for Molecular Medicine at the Partners Healthcare Center for Personalized Genetic Medicine (LMM, 65 Landsdowne St, Cambridge, MA 02139; 617-768-8500; CLIA#22D1005307). This test has not been cleared or approved by the U.S Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

## LIMITATIONS

It should be noted that the polygenic predicted values for lipid levels are based on large epidemiologic studies and may not apply to each individual patient (model from N. Stitziel and S. Sunyaev, personal communication). The summary risk assessments above, for small-moderate effect alleles, are based on combining individual risk allele data in ways that may not always apply to each individual patient.