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A One-Page Summary Report of Genome Sequencing for the Healthy Adult

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Abstract
As genome sequencing technologies increasingly enter medical practice, genetics laboratories must communicate sequencing results effectively to nongeneticist physicians. We describe the design and delivery of a clinical genome sequencing report, including a one-page summary suitable for interpretation by primary care physicians. To illustrate our preliminary experience with this report, we summarize the genomic findings from 10 healthy participants in a study of genome sequencing in primary care.

Introduction

The clinical implementation of genomic medicine has begun and is widely anticipated to bring exciting medical benefits. Whole-exome and whole-genome sequencing, hereafter referred to as genomic sequencing (GS), is becoming increasingly useful in the diagnosis and treatment of rare diseases [1–3] and cancer [4–6] and is currently used predominantly by genetics specialists or subspecialty practitioners [1]. In anticipation of the more widespread introduction of clinical sequencing to general medicine practice, we are conducting a randomized clinical trial studying the impact of GS, with attendant incidental findings, in both the specialty care of a hereditary illness and the primary care of healthy adults. In order to study the impact of GS and its clinical outcomes in this context, we have refined an interpretive pipeline for the filtration and analysis of any medically relevant variants discovered in an individual genome [7] and designed a report to communicate these results effectively to nongeneticist physicians. Here, we describe this report and our early experiences delivering GS results to primary care physician participants via a Genome Report (fig. 1; online suppl. Appendix, see www.karger.com/doi/10.1159/000370102), along with the genomic results from the first 10 healthy participants.

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The Challenge of Genomic Screening in Healthy Individuals

GS of individuals without a suspected genetic illness is currently not recommended [8] but may eventually be utilized in population-based genomic screening for the practice of preventive medicine [9, 10]. Under this model, knowledge gained from GS might guide heightened surveillance in the face of increased genetic predisposition, reveal pharmacogenomic information that could maximize drug efficacy and minimize adverse effects, or be used for reproductive planning. As one of the NIH-funded centers in the Clinical Sequencing Exploratory Research Consortium [11], we are conducting the MedSeq Project to develop such processes and to explore the risks and benefits of sequencing healthy adults [12]. A significant challenge for genomic screening with GS is to identify, distill, and report the variants that have clinical significance for a healthy individual.

Molecular laboratories have developed standards and ontologies for analyzing and communicating the clinical significance of genetic variants found during GS of individuals with a suspected genetic disease [13, 14]. After automated filtration and manual curation, geneticists reporting on GS may convey a variant's clinical significance by using a variant classification schema such as 'benign', 'likely benign', 'variant of uncertain significance (VUS)', 'likely pathogenic', or 'pathogenic'. Because many variants fall into the uncertain category, some laboratories will further subclassify VUS into subcategories such as 'favor benign' or 'favor pathogenic'. While efforts for standardization are under way, there is as yet limited consensus on the validity and evidence for pathogenicity that a variant should have before being reported to physicians and patients. If a laboratory identifies a VUS in a gene related to the reason for clinical sequencing, it will likely choose to report that finding to the ordering physician, despite the inherent uncertainties. For example, a VUS in the cardiac β-myosin heavy chain *(MYH7)* gene will likely be reported when the patient has familial hypertrophic cardiomyopathy.

However, when sequencing is performed in healthy individuals without a specific reason for genomic testing, the scenario more closely resembles screening tests used in preventive medicine, which are generally held to higher standards of validity and utility. For example, one might argue that a VUS in the *MYH7* gene should be reported to the patient with familial cardiomyopathy, because additional testing might determine whether the variant segregates with disease in the family. By contrast, whether this variant should be reported to the generally healthy individual without a personal or familial history of cardiomyopathy is a much more difficult question, absent studies with long-term follow-up that can help elucidate the pathogenicity of the variant as well as the penetrance of pathogenic variants in an unselected population.

Interpreting GS Results of Healthy Individuals

As part of the MedSeq Project, we are performing GS in patients who have been identified by their primary care physicians as having no major medical conditions. We are communicating the results of GS to nongeneticist physicians recruited from the primary care practices at our academic medical center, despite the challenges of interpreting and reporting identified variants and the concerns that the primary care workforce may not be prepared for the clinical integration of genomic information [15–18]. For each participant, whole-genome sequencing is performed in a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory and the resulting raw files of annotated high-quality variants are filtered based on their allele frequencies, previous disease associations in reference databases, genic locations, and predicted functional impacts. Variants are then manually classified by a review of genetic and functional evidence from the scientific literature as previously described [7]. At the end of this pipeline, the Genome Report for generally healthy individuals includes variants classified as 'likely pathogenic', 'pathogenic', or VUS subclassified as 'favor pathogenic'. In cases of uncertainty in how best to weight evidence for variant classification, the larger study team discusses the evidence as a group, careful to adhere to this systematic approach for variant classification and returning results. In this study, the laboratory interprets the GS data and issues the Genome Reports without any clinical knowledge about the patient. Given the low pretest probability of disease among healthy individuals, we do not report the vast majority of VUSs and none of the 'benign' or 'likely benign' variants. By reporting variants with at least some degree of evidence favoring pathogenicity, we aim to strike a balance between the risks of returning uncertain results and the potential clinical benefits for the generally healthy person undergoing genomic screening.

Communicating GS Results to Physicians

The molecular and clinical geneticists, genetic counselors, bioinformaticians, clinicians, and social scientists comprising the study team have been guided by two main

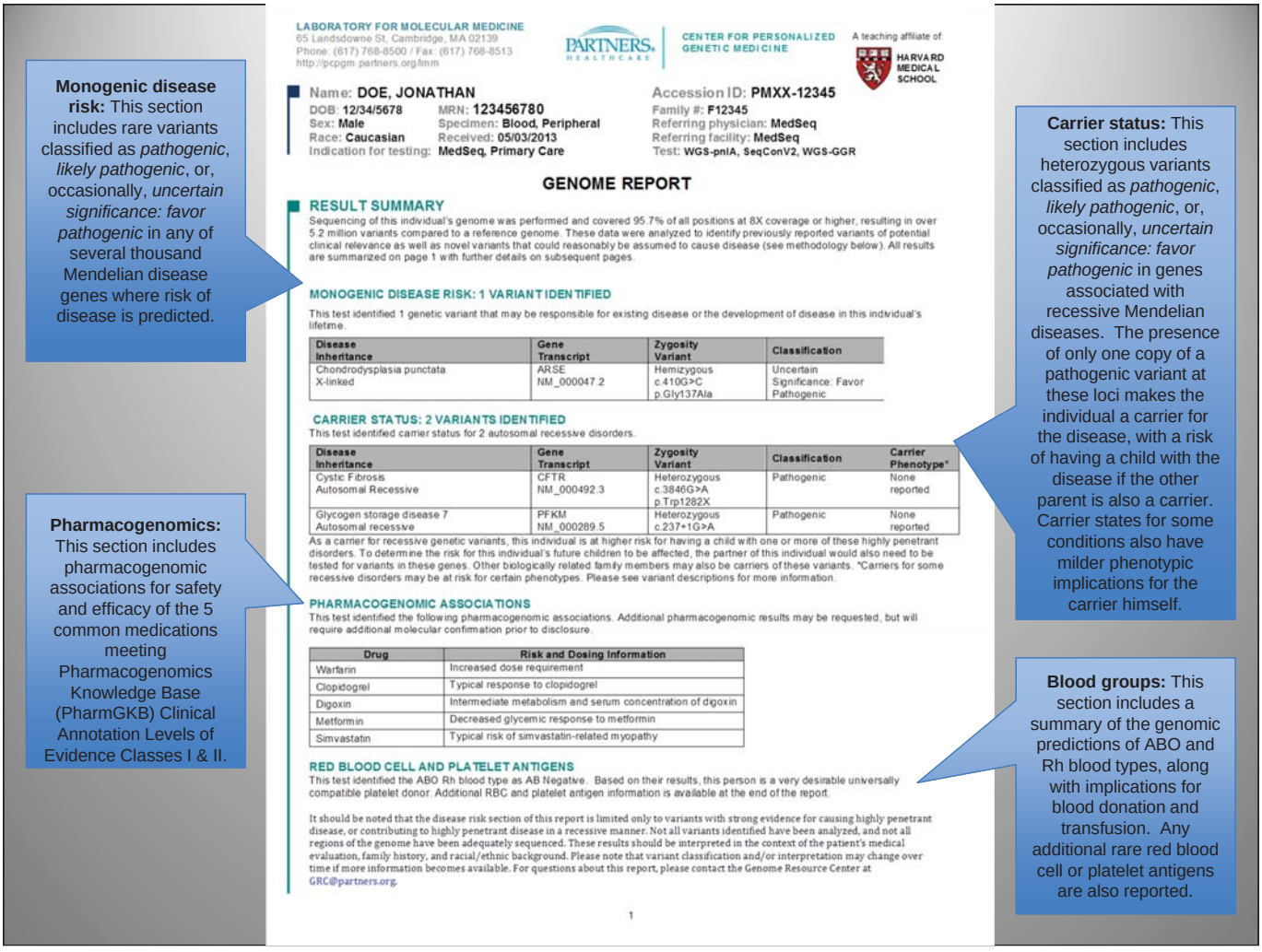

Fig. 1. Summary page of the Genome Report for GS results for a generally healthy individual.

principles in designing our Genome Report for healthy individuals. First, although genomic information has been heralded as a disruptive technology, we envision that its successful integration into medical practice will conform to standard clinical workflows: through providers to patients. The molecular laboratory sends the Genome Report, via the electronic health record, to the ordering physician. The report is written in medical terminology and not at a lay-person level, thus representing a different paradigm than direct-to-consumer genomics products. The second guiding principle is that GS reports must relay the most important findings concisely to busy physicians, but brevity must not mask complexity when it is present. The reports must be complete while still conveying a sense of prioritization, so that overwhelming amounts of test information and clinically uncertain results do not distract from the results in each report that may be most clinically significant for the patient. These guiding principles allow us to incorporate feedback flexibly to improve the Genome Report. For example, we eliminated the word 'Mendelian' from an earlier version of the report after nongeneticist physicians reported uncertainty in its meaning.

The first page of the Genome Report (fig. 1) is a summary of the key findings from the GS, while the subsequent pages give more detailed information. This format mirrors the precedent of prioritized information seen in other clinical reports. For example, a radiologist's full text of a chest X-ray report may describe in detail the radiographic appearance of the lungs, cardiac silhouette, ribs,

vertebrae, and overlying soft tissue. However, the 'Impression' section of the report, often set apart as separate text with bold lettering, might simply state 'No acute cardiopulmonary process' or 'Right middle lobe pneumonia'. The receiving physician often looks here first and then uses clinical judgment to determine whether the details in the full text of the report warrant further consideration. In our Genome Report, the first page is the genomic 'Impression' section, summarizing the identified variants that may cause monogenic disease or that indicate carrier status of autosomal recessive disorders. It also includes brief summaries of the implications of the patient's genome for blood donation and transfusion [19] and for the safety and efficacy of five medications commonly used in primary care meeting the Pharmacogenomics Knowledge Base Clinical Annotation Levels of Evidence Classes I and II criteria [20]: warfarin, clopidogrel, digoxin, metformin, and simvastatin. The subsequent pages of the Genome Report go on to define the precise variants identified and provide results and interpretation in greater detail (online suppl. Appendix), including a discussion of the scientific evidence favoring or disfavoring pathogenicity for each variant, references to relevant studies, information about the associated diseases, and risk to family members. This section also gives greater detail about the pharmacogenomic and blood antigen loci interrogated in each genome as well as the details and limitations of the sequencing and interpretation methodologies. Despite concerns that nongeneticist physicians are unprepared for genomic medicine [15–18], pilot testing among primary care physician participants of the MedSeq Project suggests that the Genome Report communicates clinical sequencing results effectively. Many physicians expressed the idea that the information is initially daunting but ultimately manageable, represented by one who stated: 'Although at first glance it is intimidating, I think if you get used to it, you probably can handle this.'

Although we have designed the Genome Report with clarity in mind, we do not assume that it alone is sufficient to turn primary care physicians into proficient genomic medicine practitioners. Primary care physician participants of the MedSeq Project first underwent an orientation to genomics concepts, including inheritance patterns and pharmacogenomics, and to the format of the Genome Report. Comprised of two 1-hour in-person group classes and 4 h of self-paced online modules, these sessions are comparable in length to other continuing medical education opportunities that are a part of routine physician recertification. We also provide individualized support to physicians during the course of the study by offering the option to contact study-affiliated medical geneticists and genetic counselors for assistance in interpreting and managing their patients' GS results. We think this model of physician training and support will be scalable for an era when the genomics workforce will be insufficient to meet the clinical demand [21], and, as part of our research, we are collecting data on the use of these resources.

Sequences from the First 10 Healthy Patients

Table 1 shows the GS results reported for the first 10 primary care patient participants. A total of 211 unique variants were assessed and classified. After assessment, 70 (33%) of these were classified as benign or likely benign, 116 (55%) as VUS, and 25 (12%) as likely pathogenic or pathogenic. We have reported 3 variants associated with monogenic disease risk in 3 healthy participants. The first of these was a variant in the arylsulfatase E *(ARSE)* gene (fig. 1; table 1) previously observed in 2 males with chondrodysplasia punctata, an X-linked disorder of bone and cartilage development. Additionally, prior research indicated that the variant deleteriously impacted protein function. The same variant was identified in a male family member without the disease, though penetrance is known to be incomplete for the disorder. Given this limited scientific evidence, we classified and reported the *ARSE* variant as a 'VUS, favor pathogenic'. For a generally healthy adult, the clinical significance of this variant is unknown, but by virtue of its appearance on the Genome Report, the primary care clinician has the opportunity to review the patient's history and physical examination and to ask more directed questions about other family members.

Most variants reported in our healthy patients are associated with a carrier state for an autosomal recessive condition (table 1). These carrier states may be associated with milder phenotypic implications for the carriers themselves, which we include in the Genome Report. For example, in 1 individual we reported a pathogenic variant in the *WFS1* gene associated with Wolfram syndrome, a recessive neurodegenerative disease characterized by sensorineural deafness, type 1 diabetes mellitus, and pituitary gland dysfunction. However, carriers of *WFS1* variants may themselves demonstrate some degree of low-frequency hearing loss and impaired glucose metabolism. Although most patients have had at least 1 carrier variant, we are finding that primary care physicians and their healthy patients understand the extremely low likelihood that these carrier states will impact the health of the patients and their family members.

Table 1. GS results reported for the first 10 generally healthy participants in the MedSeq Project

Section of the Genome Report	Results		Classification
Monogenic disease risk (3 variants identified in 3 patients)	Gene	Disease	
	LHX4	Combined pituitary hormone deficiency	Pathogenic
	KCNQ1	Romano-Ward syndrome (a long QT syndrome)	Likely pathogenic
	ARSE	Chondrodysplasia punctata	VUS: favor pathogenic
Carrier status (22 variants identified in 10 patients)	Gene	Disease	
	MMACHC	Methylmalonic aciduria and homocystinuria, cblC type	Pathogenic
	CFTR	Cystic fibrosis	Pathogenic
	PFKM	Glycogen storage disease 7	Pathogenic
	CUBN	Imerslund-Gräsbeck syndrome	Pathogenic
	DUOX2	Hypothyroidism	Pathogenic
	ABCA4	Stargardt disease	Pathogenic
	MPO	Myeloperoxidase deficiency	Pathogenic
	BTD	Biotinidase deficiency	Pathogenic
	PYGL	Glycogen storage disease 6	Pathogenic
	SPG7	Spastic paraplegia type 7	Pathogenic
	WFS1	Wolfram syndrome	Pathogenic
	CLRN1	Usher syndrome type III	Pathogenic
	CYP1B1	Primary congenital glaucoma	Pathogenic
	NLRP7	Recurrent hydatidiform mole	Pathogenic
	SPATA7	Leber congenital amaurosis	Likely pathogenic
	ERCC5	Xeroderma pigmentosum	Likely pathogenic
	COL7A1	Epidermolysis bullosa dystrophica	Likely pathogenic
	KCNQ1	Jervell and Lange-Nielsen syndrome	Likely pathogenic
	NAGA	Alpha-N-acetylgalactosaminidase deficiency	Likely pathogenic
	SP110	Hepatic veno-occlusive disease with immunodeficiency	Likely pathogenic
	RAB27A	Familial hemophagocytic lymphohistiocytosis	VUS: favor pathogenic
	CNGA3	Achromatopsia	VUS: favor pathogenic
Pharmacogenomics			
Warfarin	2 patients with *decreased* predicted dose requirement 3 patients with *increased* predicted dose requirement		
Clopidogrel	2 patients with *increased* predicted anti-platelet response		
Digoxin	4 patients with *increased* predicted serum drug concentration 1 patient with *decreased* predicted serum drug concentration		
Metformin	5 patients with *decreased* predicted glycemic response		
Simvastatin	2 patients with *increased* risk of medication-related myopathy		
Blood groups	3 patients predicted to be *desirable platelet donors*		

The Future of the Genome Report

Our early experience in piloting the Genome Report has allowed us to optimize its format and content, including descriptive section header names understandable to primary care physicians and the appropriate distribution of details on the first versus the subsequent pages. More work remains, however. Communication today is instantaneous, and information is updated in real-time. Medical records, however, have generally not kept pace with state-of-the-art standards for communicating, displaying, and accessing information. At the same time, clinical data are becoming more complex, and the communication of results will need to become more dynamic and prioritized, allowing the physician and patient to access, digest, and use the data to variable degrees over time. One can imagine GS reports that have more creative dashboards for the clinician, and that incorporate hyperlinks to greater detail or to external references, allowing a physician to narrow or expand the focus of interrogating a

patient's genome. With the discovery of new disease genes, mutations, and clinically meaningful gene-gene and gene-exposure interactions, the genome report will need to reflect that new dynamism of genomic data. While our Genome Report provides an accessible summary of complex results using current clinical laboratory reporting and medical practices, it must eventually be adaptable to accurately and concisely communicate the full medical content contained within the genome. We are currently producing the Genome Report using the GeneInsight software suite [22], which is linked to a genomic knowledgebase, so that variant classifications remain up-to-date based on new scientific discovery. Through this process, the physician receives an alert message when a previously reported variant in a patient's genome has been reclassified on the basis of new knowledge (e.g. from 'VUS' to 'likely pathogenic'). One can also imagine a dynamic genome report that evolves to maintain relevance to the patient's individual clinical context over their life course, prioritizing carrier status during reproductive years and highlighting other genomic variants when newly abnormal clinical tests, physical findings, and medications are recorded. An active area of research is the role patients' preferences might play in shaping which GS results are reported and how. Regardless of the format that GS results take moving forward, physicians will need clear signposts to help them navigate their patients' genomes.

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Disclosure Statement

J.L.V., H.L.M., C.A.M., C.E.S., D.L., J.B.K., H.L.R., and R.C.G. are employed by Partners Healthcare, which is the sole owner of GeneInsight, LLC. The authors declare that they have no other conflicts of interest.

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Erratum

In the article by Jason L. Vassy et al., entitled 'A one-page summary report of genome sequencing for the healthy adult' [Public Health Genomics 2015;18:123–129, DOI: 10.1159/000370102], the name of the second author is wrong. The correct name is Heather M. McLaughlin.