HHS Public Access

Author manuscript

Expert Rev Mol Diagn. Author manuscript; available in PMC 2018 July 10.

Published in final edited form as:

Expert Rev Mol Diagn. 2017 May ; 17(5): 415–418. doi:10.1080/14737159.2017.1309976.

The need to develop a patient-centered precision medicine model for adults with chronic disability

Susan M. Wolf[a], **Bharat Thyagarajan**[b], and **Brent L. Fogel**[c]

[a]Law School, Medical School, Consortium on Law and Values in Health, Environment & the Life Sciences, University of Minnesota, Minneapolis, MN, USA

[b]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA

[c]University of California-Los Angeles (UCLA), Departments of Neurology and Human Genetics, Los Angeles, CA, USA

Keywords

Exome sequencing; genomics; disability; neurology; ethics

Precision medicine aims to benefit patients through molecular understanding of each individual patient's pathological condition [1]. Expanding the availability of genomic medicine to all patients who can benefit is crucial to achievement of this goal. Yet work to date on whole exome and genome sequencing, especially in adults, has focused to a great extent on acute conditions such as cancer, with the goal of diagnosing, treating, and ideally curing the patient. While important and admirable, this focus ignores the large number of adults living with chronic, disabling genetic conditions that may persist and progressively worsen over a lifetime. Worldwide, disabling neurological disorders represent roughly 2% of the global burden of disease, a staggering percentage roughly on par with HIV and cancer (~5% each), heart disease and stroke (~4% each), and tuberculosis (~2%) [2]. Here we take a view of this problem from the perspective of the U.S. health system.

Over 56 million Americans or almost one-fifth of the population reported a disability in 2010 [3]. For many of these individuals, a genomic diagnosis has the potential to yield great benefits, but the nature and scope of these benefits will be different than for patients facing acute, treatable, illness that requires intense management over a shorter time frame with the hope of a cure. Current concepts of clinical utility, the actionability of genetic results, and clinical benefit are too narrow to serve this large population facing chronic and progressive disability [4]. Indeed, the narrowness of these concepts threatens to block access to genomic technologies for these patients. When payers evaluate the medical necessity and clinical utility of genomic testing in this population [5], they need to apply concepts of utility and

CONTACT Brent L. Fogel, bfogel@ucla.edu.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

benefit that work not just for the subset of patients facing acute illness, but for all patients. The promise of precision medicine rests on the capacity to yield benefit not only for those patients facing curable illness, but also for adults living with chronic disability.

A major challenge in the management of chronic disease arises from a difficulty in diagnosis. In adult patients it can be hard to ascertain whether a clinically heterogeneous phenotype is acquired or inherited without extensive evaluation [6]. In the case of neurodegenerative disease, previous standard methods of genetic testing have required laborious sequential sequencing of relevant genes either singly or in groups, at significant cost to the patient and payers [7,8], as there can be hundreds of individual genes that are capable of causing a given phenotype (Online Mendelian Inheritance in Man [OMIM] database; http://www.omim.org/). Recently, a significant percentage of genetic disorders have been identified in populations with sporadic and late-onset clinically heterogeneous phenotypes previously thought of as idiopathic [9–11]. A key to effectively establishing these diagnoses lies in the ability to collect from patients and clinically utilize large genomic datasets of biological relevance to disease pathogenesis [12,13]. Here we focus on the recent increased use of unbiased methods of diagnostic genomic testing, such as whole exome sequencing (WES), a technology with important applications to clinical medicine [14–17].

Whole exome sequencing allows rapid and cost-effective evaluation of essentially all 20,000 genes in the human genome for evidence of clinically relevant mutations, in a single analysis that is broadly applicable across the range of phenotypes associated with chronic disability, particularly from neurodegenerative causes [18,19]. A key ethical consideration with regard to WES is the possibility of identifying medically actionable secondary findings (e.g. a mutation in a cancer predisposing gene such as *BRCA1*). Patients must be appropriately counseled with regard to this possibility which, although small [20], is of significant clinical importance [18]. The American College of Medical Genetics and Genomics (ACMG) has issued guidance on analysis and disclosure of secondary findings in clinical sequencing [21,22].

Although results from exome sequencing can occasionally lead to unexpected options for cure [9], the clinical impact for the typical patient is much broader and not as dramatic, but no less as important. As an example, consider the patient who undergoes WES to identify the cause of a progressive familial neurodegenerative condition (e.g. amyotrophic lateral sclerosis, dementia, or Parkinson disease). This patient most likely will not be cured. However, the patient may realize tremendous benefit. Sequencing may end a diagnostic odyssey, which can last a decade or more in patients with neurological disorders. The patient's clinicians may improve symptomatic care through the elucidation of better options for pharmacologic and medical management and may recognize or initiate surveillance for other modifiable or treatable medical comorbidities. But that is just a small part of the benefits picture. Patients may see benefit in qualifying for enrollment in clinical trials, for sources of funding related to the documented disability (such as Social Security Disability Income), and for reasonable accommodations in the workplace. Patients may be able to share with family members' information on potential risk and the advisability of genomic analysis for relatives and their current (or future) children. There are still further dimensions of potential psychosocial benefit to patients, including understanding the cause of previously

puzzling symptoms, being able to explain their symptoms to others as they choose, and planning for progressive disability. Understanding their prognosis and the likely trajectory of their disease can be crucial to making informed choices about employment, living arrangements, and financial planning, all of which may significantly impact the quality and effectiveness of medical care received by the patient.

The long-term success of precision medicine depends on recognizing the diversity of patients to be served. While researchers and funders have now recognized the urgent need to diversify study populations by race, ethnicity, and other factors poorly addressed by current genomic databases that are overly homogeneous [23], too little attention has been paid to chronic disability. Even the federal 'All of Us' Precision Medicine Initiative takes cancer as its 'near-term focus,' with 'a longer-term aim to generate knowledge applicable' more broadly [24]. Yet nearly all common neurological diseases, for example, show significant heritability [7] and WES is already showing marked utility in the diagnosis and management of the Mendelian forms of these conditions, in both familial and sporadic cases [9, 18, 25–28]. The benefits of sequencing in these patients extend far beyond simply generating a diagnosis and will guide clinicians in helping patients and families face the challenges of chronic and progressive disability over the full course of the disease [19].

Unfortunately, current concepts of clinical utility, actionability, and clinical benefit fail to fully recognize the broad value of this knowledge to the patient. The immediate consequence is that payers may be reluctant to reimburse costs of WES. The ACMG published a 2015 policy statement advocating a view of the clinical utility of genetic testing significantly broader than the view proposed by many payers that requires empirical demonstration of resulting change in treatment producing benefit [29]. Instead, the ACMG argued that assessment of clinical utility 'should take into account effects on diagnostic or therapeutic management, implications for prognosis, health and psychological benefits to patients and their relatives, and economic impact on health-care systems.' [29] While the ACMG policy notes potential benefit to patients with intellectual disability and autism spectrum disorder, the statement does not explicitly consider patients with other conditions that are chronically disabling. More recently, the Association for Molecular Pathology has recommended a patient-centered approach to defining clinical utility [30]. Patients facing chronically disabling conditions present a compelling case for this broader approach.

For patients with chronic disability, additional important domains of utility include being able to seek appropriate clinical services tailored to their precise condition and from clinicians well versed in genetic as well as phenotypic understanding of their disorder. Moreover, patients with incurable conditions may especially value access to the most effective management of their symptoms and disease progression. Indeed, these patients may seek the option to participate in research aiming to advance treatment and seek curative options. The current payer model may not fully value the impact of such efforts, but to the patient suffering with the chronic disease, the impact may be truly profound. Patients with chronic, lifelong, degenerative conditions often face decades of medical care. This increases the importance of early definitive diagnosis to avoid years of suboptimal care and fruitless testing at potentially great cost. Patients need to seek care, symptom management, rehabilitative services, and care planning fully informed by genomic analyses.

It is important to note that the average diagnosis rate for WES is approximately 25% and may vary between much lower rates for some conditions to nearly 60% for some familial and well-phenotyped neurological disorders [19], illustrating that WES is not expected to provide a definitive diagnosis for every patient. However, a significant percentage of patients may benefit from this knowledge. There is value even in the absence of a molecular diagnosis, including narrowing the differential diagnosis leading to more focused care and management, and avoiding empiric therapies that are unsupported by the sequencing results. Furthermore, as WES analysis is dynamic and continuously improving, diagnostic rates may increase as more information becomes available from the use of WES in broader populations and as new scientific information is applied to the reanalysis of patients previously undiagnosed by this technology [19,31].

A narrow focus on clinical utility, actionability, and benefit ignores the patient's capacity to take action based on genetic findings in order to better their care and quality of life. In the context of acute illness, focusing on the value of the genetic finding to prevent, treat, or cure a disease is understandable. However, in the context of chronic disabling conditions with a lifelong debilitating trajectory, the value of genetic findings to the patient assumes greater prominence. Even when such a condition cannot be prevented or cured, understanding the genetic basis for the condition, the prognosis, and the likely progression, can be crucial to a patient's care planning, support arrangements, and life choices.

Our society is growing progressively older and our population is requiring increasing care for chronic disabling conditions [32–36]. As we implement genomic testing and integrate sequencing into clinical care, we would be remiss to overlook the benefits to those who will be the longest affected. Important next steps in the clinical integration of genomics will involve quantifying the full effects of genomic testing on patients, with a particular emphasis on cost savings and quality of life. Developing evidence-based models for the successful use of genomic diagnostic testing to control payer costs while improving patient care over the entire course of the patient's disease (whether long or short) will be crucial. Precision medicine should serve all patients, including those with chronic debilitating disease.

Acknowledgments

Funding

Preparation of this article was supported by the National Institutes of Health (NIH), National Human Genome Research Institute (NHGRI) and National Cancer Institute (NCI) grant #1R01HG008605 (Wolf, Clayton, Lawrenz, Principal Investigators [PIs]) and NIH, NCI/NHGRI grant #1R01CA154517 (Petersen, Koenig, Wolf, PIs); funds from the Bob Allison Ataxia Research Foundation (Thyagarajan, PI), Institute of Translational Neuroscience (Thyagarajan, PI), and Department of Laboratory Medicine and Pathology at the University of Minnesota (Thyagarajan); and NIH grant #R01NS082094 (Fogel, PI). The views expressed are those of the authors and not necessarily the views of the funders.

This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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