Atherosclerosis 253 (2016) 225–236

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Implementing genomics and pharmacogenomics in the clinic: The National Human Genome Research Institute's genomic medicine portfolio

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ARTICLE INFO

Article history:
Received 31 May 2016
Received in revised form
19 August 2016
Accepted 23 August 2016
Available online 26 August 2016

Keywords:
Genomics
Pharmacogenomics
Clinical care

ABSTRACT

Increasing knowledge about the influence of genetic variation on human health and growing availability of reliable, cost-effective genetic testing have spurred the implementation of genomic medicine in the clinic. As defined by the National Human Genome Research Institute (NHGRI), genomic medicine uses an individual's genetic information in his or her clinical care, and has begun to be applied effectively in areas such as cancer genomics, pharmacogenomics, and rare and undiagnosed diseases. In 2011 NHGRI published its strategic vision for the future of genomic research, including an ambitious research agenda to facilitate and promote the implementation of genomic medicine. To realize this agenda, NHGRI is consulting and facilitating collaborations with the external research community through a series of "Genomic Medicine Meetings," under the guidance and leadership of the National Advisory Council on Human Genome Research. These meetings have identified and begun to address significant obstacles to implementation, such as lack of evidence of efficacy, limited availability of genomics expertise and testing, lack of standards, and difficulties in integrating genomic results into electronic medical records.

The six research and dissemination initiatives comprising NHGRI's genomic research portfolio are designed to speed the evaluation and incorporation, where appropriate, of genomic technologies and findings into routine clinical care. Actual adoption of successful approaches in clinical care will depend upon the willingness, interest, and energy of professional societies, practitioners, patients, and payers to promote their responsible use and share their experiences in doing so.

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1. Introduction

Growing understanding of the role of genetic variants in human health and disease, and improved technologies for measuring these variants rapidly at large scale, have opened the door to increased use of genomic information in clinical care [1]. While individual, high-impact genetic variants, such as the cystic fibrosis conductance transmembrane regulator (*CFTR*) ΔF508 variant in cystic fibrosis and the beta hemoglobin (*HBB*) β6 glutamic acid to valine substitution in sickle cell anemia, have long been known to clinical medicine, the advent of high-throughput assay techniques has enabled consideration of much larger numbers of genes and variants in an individual in a more multi-factorial, truly genomic, approach. Although some have argued that the difference between "genetics" and "genomics" is merely two letters, and the terms do tend to be used interchangeably, "genetics" as often used refers to the study of heredity with a focus on a specific and limited number of genes with known function in disease. "Genomics," in contrast, refers to the totality of an individual's genetic make-up, their "genome," and has become much more prominent clinically as technologies and understanding have advanced. Here the focus will largely be on "genomics," though in any given clinical setting involving a specific disease or drug, emphasis will necessarily sharpen to one or a few individual genes or variants within them.

"Genomic medicine," another core concept for consideration here, has been defined as the use of an individual patient's genotypic information in his or her clinical care [2]. While this definition encompasses both Mendelian and multigenic complex diseases, emphasis is shifting to assaying and using multiple variants simultaneously in clinical care for the reasons noted above—an expanding knowledge base and improved measurement techniques that permit a more holistic approach to incorporating genomic findings into patient care.

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http://dx.doi.org/10.1016/j.atherosclerosis.2016.08.034
0021-9150/Published by Elsevier Ireland Ltd.

1.1. Vision for the future of genomic research

The application of genomic information in clinical care has been an increasing focus of the research programs of the National Human Genome Research Institute (NHGRI) in the past several years. In 2011 NHGRI published its strategic vision for the future of genomic research [3], proposing an ambitious research agenda to facilitate and promote the implementation of genomic medicine. This vision is framed around five research domains, three of which (investigating genome structure, genome biology, and the genomic biology of disease) reflect fundamental technologic and basic science pursuits that have long been key components of the Institute's core mission. For the first time, however, the 2011 strategic vision extended NHGRI's research agenda to include genomics research to advance the science of medicine and improve the effectiveness of healthcare. These new emphasis areas differ from the disease-association, discovery-focused research that previously came to mind when considering the application of genomics to the study of health and disease. Specifically, genomic medicine at NHGRI would now move beyond demonstrating genotype-phenotype associations, typical of the Biology of Disease domain, to assess and demonstrate improved outcomes for patients and the healthcare system after using genomic information to guide clinical care (Table 1). In this way, NHGRI proposed to initiate concerted efforts to apply genomics for improving the prevention, diagnosis, and treatment of human disease and to evaluate its effectiveness in doing so. Many other genes and variants have been recommended for implementation since then, particularly in the pharmacogenomics realm [8,9].

Shortly after the 2011 strategic plan was made public, NHGRI consulted many of the nearly 30 Institutes and Centers comprising the U.S. National Institutes of Health to identify genomic research projects related to disease prevention, diagnosis, or treatment that were ready, or nearly ready, for implementation in actual clinical care. Few such projects were found, however, with most Institutes and Centers focused on projects falling more in the realm of genotype-phenotype association studies. Only a handful of studies involved examining the impact of using individual patients' genomic information in their medical care, and almost none focused on demonstrating the utility of genomics for actually improving the care of patients. This last domain encompasses much of what is referred to as “implementation research”— the study of methods that promote the systematic uptake of proven interventions into routine clinical care [5]. One project that did seem ready for clinical application was the implementation of a newly-developed targeted sequencing panel of 84 pharmacologically important genes in 9000 patients in the multi-site Electronic Medical Records and Genomics (eMERGE) network [6,7]. Of interest, the three drug-gene pairs that nearly all nine eMERGE sites agreed were ready for clinical implementation involved treatments for cardiovascular disease: *CYP2C19* variants and clopidogrel treatment for prevention of in-stent restenosis; *SLCO1B1* variants and simvastatin therapy; and *CYP2C9* and *VKORC1* variants for warfarin treatment in atrial fibrillation.

1.2. NHGRI genomic medicine working group and genomic medicine meetings

In parallel, NHGRI also consulted and facilitated collaborations with the external research community by convening a series of “Genomic Medicine Meetings” (Table 2), under the guidance and leadership of the Genomic Medicine Working Group of the National Advisory Council on Human Genome Research [10]. Although considerable doubt had been voiced during preparation of the 2011 strategic plan as to whether a critical mass of researchers actively

Table 1
Disease-related genomics research across three NHGRI research domains. Adapted from Ref. [4].

NHGRI domain	Biology of disease	Science of medicine	Effectiveness of healthcare
Common rubric	Discovery research	Clinical validation	Clinical implementation
General goal	Demonstrate genotype-phenotype associations	Assess outcomes after using genomic information to direct clinical care	Demonstrate improved healthcare with the use of genomic information
Specific examples	• Identify persons at increased risk of disease based on their genomic variants • Find all variants related to given phenotype or disease • Characterize variation in genes known to be related to disease or treatment response • Characterize phenotypic variation and effect modifiers in carriers of specific variants • Classify patients into subgroups with differing prognosis or treatment response (molecular taxonomy)	• Evaluate clinician and patient satisfaction with care after receipt of genomic information • Assess impact of reporting incidental findings on health behaviors, healthcare utilization, and psychological well-being • Identify causes of rare or undiagnosed diseases • Identify sources of infectious disease outbreaks and susceptibilities of infectious agents • Compare genome sequencing to enzymatic and other assays for modifiable metabolic disorders in newborns • Reclassify intermediate risk patients into high- and low-risk categories where differential interventions are available • Validate drug targets and develop improved therapeutic agents	• Educate clinicians and patients in clinical use of genomic information • Develop clinical informatics systems for reporting results of genomic analyses and providing decision support • Evaluate impact of using genomic variant information to individualize treatment • Incorporate genomic information into electronic medical records that can follow patients across care systems and throughout lifespan • Define clinically actionable genomic variants and disseminate that information and its relevant evidence base