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1000 Genomes on the Road to Personalized Medicine

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The recently announced 1000 Genomes Project is an international collaboration to sequence 1000 individuals in an effort to produce the most complete catalog of human genetic variation to date. Building on the International HapMap Project, the 1000 Genomes Project will utilize new sequencing technologies to catalog genetic variants that are present in the human population across most of the genome at a rate of 1 percent or greater frequency. Investigators will not only look for single letter changes in the genome (called single nucleotide polymorphisms or SNPs), but will also look for differences in structural variants in the genome (segments of the genome that have been rearranged, deleted, or duplicated) (1). The first phase of the Project will involve three pilot studies. The first will sequence the genomes of two nuclear families (an adult child and both parents) at deep coverage (20x). The second will sequence the genomes of 180 people at low coverage (2x). The third will sequence the coding regions (exons) of about 1000 – 2000 gene regions in 1000 people at deep coverage (20x) (2).

The 1000 Genomes Project represents a major step forward on the road to personalized genomic medicine. By creating an important scientific resource, the Project will help advance understanding of the complex relationship between genetic variation and human health and disease. The promise of personalized genomics is not new; it was almost twenty years ago that the New York Times published an article that predicted: “In the not-so-distant future, we can expect to walk into a physician's office for an annual physical and walk out with a blueprint of our genetic inheritance - and with the knowledge of the most likely cause of our own death.” (3) In the past year, individual genome sequencing has become possible (4–5) but it is still a long way from becoming a routine part of medical care. In order to achieve its fullest potential, the 1000 Genomes Project, like other large scale sequencing projects that came before it, will have to be carefully designed to ensure adequate protection and respectful treatment of research participants. In addition to addressing the research ethics issues involved, however, this new initiative creates an opportunity to reflect on the larger health system challenges that will have to be addressed before the knowledge that is gained through genome research can be integrated into routine clinical care.

Current State of Genomic Research

The Human Genome Project took 13 years and $2.7 billion to complete (6). It is now possible to sequence an individual genome in a few months for less than $1 million (7). It is expected that new sequencing technologies will continue to reduce the time and cost of sequencing significantly, driving down the projected cost of the 1000 Genomes Project from $500 million to $30–50 million (1). The pace at which technology has advanced has enabled a tremendous growth in genome research; both large scale sequencing projects aimed at building shared resources as well as a variety of genome-wide association studies and pharmacogenomic

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research aimed at increasing our understanding of the functional significance of genetic variation.

Research Ethics: Data Sharing and Privacy Considerations

Although there are many ethical issues associated with the conduct of genome research, a major ethical and policy debate has centered around the tension between the desire to maximize the scientific utility of genomic data and the importance of protecting research participants' privacy. Efforts to advance research and encourage international collaboration have led to the adoption of broad data sharing policies in genome research (8–9), while concerns about individual privacy and the importance of maintaining public trust has raised questions about the appropriate limits to public data release (10–12). This debate has resurfaced in the context of the 1000 Genomes Project, raising the question of whether and under what circumstances individual genome data should be shared in publicly accessible databases.

The decision of whether or not to release data into publicly accessible databases will depend on the purpose of the project, the type and amount of information involved, and the desire of the research participant and, in some cases, her close genetic relatives (Table 1). For many large-scale sequencing projects, such as the Human Genome Project, the International HapMap Project, the Human Microbiome Project, and the 1000 Genomes Project, the primary purpose of the research is to create a shared resource that is easily accessible and can be used to develop research hypotheses. Open access is a fundamental component of these projects and should be provided with appropriate informed consent. Individuals who do not wish to have their genetic information shared in a publicly accessible database should not participate in these studies. Generally, only genotypic information should be released. Since these studies are not typically sufficiently powered to show a disease association, the increased risk to privacy that is created by including phenotypic information may not be justified.

If creating a shared resource is not the primary purpose of the study then the decision about public data broadcast should be left to the individual research participant (13). Where phenotypic information is included, data should generally be released into databases with restricted access. This is consistent with the new NIH Data Sharing Policy for Genome Wide Association Studies (GWAS), which calls for the release of all data from NIH-funded or supported GWAS into dbGap, a restricted database (14). Since DNA may reveal information not just about the individual from whom it came but also about her close genetic relatives, the decision to publicly release DNA data, especially if linked to other personal identifiers, may require a more family-centered approach to informed consent. At the very least, individuals who choose to publicly broadcast their genetic and clinical information, such as participants in the Personal Genome Project (15) should be informed of the potential risks to themselves as well as their close genetic relatives and encouraged to make a family decision about data sharing.

The Future of Personalized Genomic Medicine: Health System Challenges

While individuals are not yet able to "walk into a physician's office for an annual physical and walk out with a blueprint of [their] genetic inheritance" (3), they are able, for less than $1000, to purchase an electronic report of their genetic susceptibility to dozens of common and complex diseases. Personal genome companies like 23andMe, Navigenics, and deCODEme are significantly speeding the translation in genome research from bench to bedside. These companies communicate the latest scientific discoveries directly to the public, providing consumers a personalized assessment of their genetic susceptibility to disease. However, most of these companies warn that they do not provide medical services and consumers are directed to their health care provider to answer questions or concerns (16). There are persuasive arguments for why physicians should not provide detailed analysis of these test results

(including concerns about their analytic validity, clinical validity, and clinical utility) (17). David Hunter and colleagues suggest that physicians should respond to patient inquiries about risk estimates obtained from personal genome companies with "a general statement about the poor sensitivity and positive predictive value of such results," noting that a "detailed consumer report may be beyond most physicians' skill sets." (17) However, failure to address specific patient concerns may adversely affect the physician-patient relationship and could result in exposure to legal liability as we learn more about genetic associations and preventive health strategies. Thus, as patients become more familiar with these services, physicians should be prepared to answer more sophisticated consumer-driven questions about genetics and genomics research. This will require additional education for most physicians (18) and training on how best to counsel patients about the dangers of genetic determinism, the meaning of probabilities, and the acceptance of uncertainty.

As we begin to reap the benefits of projects like the 1000 Genomes Project and better understand the complex relationship between genetic variation and human health, the expectation for physicians to analyze, interpret, and explain genetic test results to patients will intensify. This will present many challenges to our health care system (19). For example, our current reimbursement system is not structured to compensate health professionals for providing this type of educational service to their patients. Reform that focuses only on the inclusion of personal genome testing and procedure-driven treatment will not be sufficient. Advances in genome research, combined with an industry-driven market for genetic information is sure to speed the path to individually-tailored therapeutics, but as medical treatments become more personalized so too must medical *care*.

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Table 1

Data Sharing in Genome Research

	Type of Information		
		Genotype Only	**Genotype + Phenotype**
Amount of information	Whole Genome Information	Public access with specific consent for data sharing	Controlled access with specific consent for data sharing
	Individual Gene Variants or Aggregated Data	Public access with general consent for future use	Controlled access with general consent for future use