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Pharmacogenomics: A Balancing Act

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With the increasing accessibility and affordability of sequencing our genomes, it becomes very relevant to ask questions about how this information can be applied to improve human health. Some might even say we have an ethical duty to invest in exploring this possibility. One emerging application of this research is in the area of pharmacogenomics, which Dr. Amalia M. Issa, Assistant Professor and Clinical Ethicist at Southern Illinois University School of Medicine, defines as the process of "identifying candidate genes and polymorphisms, correlating these polymorphisms with possible therapies, predicting drug response and clinical outcomes, reducing adverse events and selection and selecting dosing of therapeutic drugs on the basis of genotype" (Issa, 2002, p. 1). While this appears to be a novel and practical concept, it is important to think critically about the rhetoric surrounding the prospect of "saving the world" that the scientists seeking funding can purport. There are drawbacks and concerns surrounding pharmacogenomics, including a possible threat to the equal access to pharmaceuticals due to market supply and demand as well as insurance coverage. Some biological anthropologists, like Jonathan Marks, fear it is a means of reinstitutionalizing racism. Nonetheless, pharmacogenomics is an emerging field that pushes us to ask urgent questions regarding how, and in what way, we can use genetics to help improve pharmaceutical treatments.

Pharmacogenomics concerns the variations in the genes that produce enzymes, and how these differences affect drug metabolism in the body. Pharmacogenomics is commonly used interchangeably with another term: "pharmacogenetics" which applies more narrowly to the connection between drug response and single-nucleotide polymorphisms (SNP's). SNP's are variations in DNA at a single base that are found in at least 1% of the population (Debnath, 2009). Mousumi Debnath continues to explain that pharmacogenomics is "the whole genome application of pharmacogenetics, which examines the single gene interactions with drugs" (Debnath, 2009, p. 3). The overall goal of both disciplines is to "develop rational means to optimize drug therapy, with respect to the patients' genotype, to ensure maximum efficacy with minimal adverse effects" (Debnath, 2009, p. 3). One diagnostic tool that is being used to sequence genomes is called a DNA microarray. Debnath provides a detailed description of this process:

In a typical application, high-density nucleic acid samples, usually cDNAs or oligonucleotides, are delivered (or printed) by a robotic system onto very small, discrete areas of coated substrates(or chips) usually microscopic glass slides or membrane filters, and then immobilized to the substrate. The resulting microarray is then hybridized with a complex mixture of fluorescently labeled nucleic acids(probe) derived from a desired source. Following hybridization, the fluorescent markers are detected using high-resolution laser scanner. A pattern of gene expression is obtained by analyzing the signal emitted from each spot with digital imaging software.

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In 2009, one microarray could screen 100,000 single nucleotide polymorphisms in a patient's genome in a matter of hours (Debnath, 2009, p. 4)- and this technology is only increasing in speed and efficacy. Therefore the possibility of

having this technology in your doctor's office is becoming more and more likely. Already, DNA microarrays have been responsible for revealing numerous associations between specific gene loci

and complex diseases, such as breast cancer, type II diabetes, coronary artery disease, asthma, and bipolar disorder (Wiseman, 2009). This is why there is a sense of urgency in addressing the regulation and application of pharmacogenomic understandings.

Figure 1. Scientistists and scholars today are debating the medical benefits and the potential social risks of pharmacogenomics.

In addition to predicting a patient's response to drugs, there are many more theorized benefits to pharmacogenomic research, such as: the ability to develop "customized" prescriptions, to screen and monitor certain diseases, to develop more powerful vaccines, and to allow improvements in drug research and development (Debnath, 2009). If successful, this will likely lead to improved patient compliance due to an individual's increased confidence in a drug's effectiveness and decreased anxiety about adverse side effects. These benefits exemplify a shift to more "personalized medicine." As Adam Hedgecoe explains, this pull towards personalized medicine includes economic factors as well: "Most of the apparent drive towards personalized medicine comes from the need for reduced drug expenditure in the US healthcare system, driven by recent changes in the way heathcare is provided. This centers on managed care organizations" (Hedgecoe, 2004, p. 12). This is an important societal backdrop to keep in mind.

However, the risks of expanding personalized medicine sometimes feel more real than the hypothetical benefits. Four of the most prescient concerns are clinical-trial design, subject stratification, social risks, and economic considerations. Currently, when designing a clinical trial, investigators operate under the assumption that research participants have little inter-individual variability. This means that all participants are treated as being homogeneous. However, as we continue to learn more and more about the inherent differences in our genetic make-up and how this affects our response to certain drugs, this assumption seems more and more flawed. For example, in one study on the CYP2D6 polymorphism, there was wide variability in the metabolizer incidence: ranging from 0% to 100% (Issa, 2002). Such variability results in various interpretations, impacting suggested dosaging levels. Controlling for race and ethnicity may help explain such variance. However, as Issa speculates, this will "influence […] the progression of drug development research on the basis of pharmacogenomic profiling" (Issa, 2002, p. 303) which might not be beneficial to potential trial participants. This is due to the theory that during the process of profiling, some groups might be excluded or face unfair representation. In one Alzheimer's study, research subjects were selected based on their apolipoprotein E genotype

"Most of the apparent drive towards personalized medicine comes from the need for reduced drug expenditure in the US healthcare system"

because they might be less likely to respond to the treatment drug, tacrine. For those who were able to participate, there was a reduced risk of nursing-home placement (Issa, 2002). This example serves to show that as soon as genotyping becomes an inclusion or exclusion criteria, the opportunity to benefit for clinical trials might be allocated in a more concentrated manner.

Historically, sub-groups such as women, the elderly, and children have been underrepresented in clinical trials (Issa, 2002). A similar concern applies to trials using pharmacogenomics because, theoretically, the benefits of the new technologies could only be realized in a sub sect of the population with the particular SNP that the study drug is targeting. This would lead to the "orphan drug" syndrome: the narrowing of drug markets to only those diseases that impact people that would have the ability to pay for the drugs, leaving other common (but less profitable) potential therapies untouched. Similarly, if scientists discover a rare genetic predisposition in a small portion of the population, the profit incentive could lead to a possible "orphan population" syndrome where not only certain pharmaceuticals were not studied, but treatments for entire populations suffering from a particular disease might not be studied.

On the societal scale, we should not underestimate the burden of a "disease-label," or a negative stigma associated with a particular diagnosis, because it has broad implications on access to insurance, employment, and health care resources. One of the more important societal concerns is the threat of reductionist thinking, or that it is "all in the genes." As Issa and Marks both point out, this is a limited way to look at human beings. It is important to keep in mind the complex environmental interactions that contribute to making us who we are. Social determinates of health, such as income, education, and culture, are also closely linked to an individual's health status.

As an academic discipline, "Science and Technology Studies" provides an interdisciplinary framework for discussing the benefits and risks of pursing pharmacogenomic research. In "Terminology and the Construction of Scientific Disciplines: The Case of Pharmacogenomics," Adam Hedgecoe explores the social construction of technology, which serves as a critique on technological determinism, or the idea that humans are simply responding to the iron laws of physics (and by extension, genetics) that ground a wide range of advancing technologies. He explains how the name of a research topic could play a rhetorical role in building support for that research (Hedgecoe, 2003, p. 515). In this case, this is accomplished by building off the hype of the term "genomics" that was coined back in 1986 and spread quickly into the commercial market (Hedgecoe, 2003). It has allowed commentators to shape the regulatory structure that surrounds the debate, largely leading to an acceptance of the research trend and increased support for their projects. This concern, although real, is secondary to the importance of regulating the potential negative societal impacts of this research.

By using what we already know about trial designs and the drug development process, and an understanding of the implications of pharmacogenomic research, we can proactively regulate the research in such a way to prevent the orphan drug syndrome and disease stigma concerns that those like Issa have raised. If there is one thing that we can learn from the history of science and technology studies, it is that humans have an innate curiosity for the unknown as well as a hope that we may continue to improve our situation in life, resulting in advancing technologies despite a regulatory environment. It is important to help society realize the potential benefits to this new knowledge without letting it ignore other humanitarian concerns.

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