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The Economic, Ethical, and Social Implications of the Pharmacogenomics Movement

I. Introduction to Pharmacogenomics

While the term "pharmacogenetics" has been in existence for roughly 50 years, developments in discovering genetic variants associated with differential drug reactivity have increased with parallel genome-wide testing's rise to prominence, a more recent phenomenon. As such, the term "pharmacogenomics" is now used to capture the field's scope of the entire human genome[1]. Since the dawn of the Human Genome Project in 1990, the promise of elucidating a genetic explanation to disease foreshadowed a paradigm shift in medical practice leading toward a more precise means of practicing medicine.

In 1997, the National Institutes of Health added the National Human Genome Research Institute (NHGRI) to its panel of centers constituting the NIH. The significance of incorporating NHGRI into this national consortium was significant in that it demonstrated widespread support for the notion that diseases and traits originate from a genetic basis, and that these would ultimately confer clinical benefit. Given estimations that only 50% of patients have the expected response to their medications, pharmacogenomics stands to increase the efficacy and safety of drug administration[2]. For example, research suggests that 50 common drugs are metabolized the cytochrome isoenzymes, CYP2D6 and CYP2C19; therefore, varying expressivity of these genes have widespread implications on drug reactivity[3]. Projects such as the International HapMap Consortium, initiated in 2002, have facilitated this process of discovering the 0.1% of the genome that is unique across humans and contributes to differences in drug response,

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[1] Pray, L. D. (n.d.). *Pharmacogenomics: Delivering on the promise*. Retrieved from http://www.insightpharmareports.com/uploadedFiles/Reports/Reports/Pharmacogenomics/Sample_Pages.pdf
[2] National Institutes of Health, National Human Genome Research Institute. (2014). *About nhgri: A brief history and timeline*. Retrieved from website: http://www.genome.gov/10001763
[3] Wilson, J. F. (2001). http://www.nature.com/scitable/content/population-genetic-structure-of-variable-drug-response-97417. *Nature Genetics*, *29*, Retrieved from http://www.nature.com/scitable/content/Population-genetic-structure-of-variable-drug-response-97417

pathogenesis, and reactivity to other factors influencing health. Adding to the significance of haplotype discovery is the potential to reveal variants found commonly in individuals with a specific continental ancestry[4]. From a broader perspective, these discoveries could also serve to reduce healthcare costs and create a market for gene variation-specific pharmaceuticals for groups carrying alleles whose association to drug response is known.

In the face of great potential that this emerging field carries to revolutionize medicine, there lies a lingering fear that these discoveries will lead to "race-based" medicine, wherein a person's race would be used as a proxy for their continental ancestry. A 2008 review of pharmacogenomics and race identified precedent for this phenomenon in a clinical trial for Enapril, an angiotensin-converting enzyme (ACE) inhibitor for heart failure patients. This study revealed Enapril to be more effective in Caucasian patients than in African American patients which ultimately led to significant decrease in the number physicians electing to offer this life-saving class of treatment to their African-American patients.[5] The problems that arise from this leap between patients' reported race to the physician's decision to adjust their clinical practice fall along methodological and ethical lines: while research supports that race is a first approximation for determining continental ancestry--a genetically defined category--the prevalence of mixed-race ancestry adds complexity to genetic heritage that isn't necessarily accounted for through observing racial phenotypes. This shortcoming is further compounded when physicians impute self-reported race as a rough estimation for predicting drug response, as this introduces an additional layer of imprecision. Parker and Satkoske use the term "slippage" to describe the information gap associated with inferring genotype and ancestry from self-reported

[4] The International HapMap Consortium. (2004). Integrating ethics and science in the international hapmap project. *Nature Review*, *5*, Retrieved from http://hapmap.ncbi.nlm.nih.gov/downloads/HapMapEthics.pdf
[5] Hunt, S. (2008). Pharmacogenetics, personalized medicine, and race. *Nature Education* , *1*(1), 212. Retrieved from http://www.nature.com/scitable/topicpage/pharmacogenetics-personalized-medicine-and-race-744

race, and speak to a greater question of how informative the current state of pharmacogenomics is in the quest toward personalized medicine[6].

In this paper, I intend to demonstrate a need for pharmacogenomics in its potential to inform healthcare decisions; however, I hope to caution against blindly applying this knowledge to patients due to the potential for physicians to practice discriminatory medicine. Instead, I aim to offer a broader context in which pharmacogenomic data should be interpreted and applied to patients, namely as one component of many biopsychosocial determinants that shape our health.

II. The Emergence of Pharmacogenomics

Our ability to extract predictive insight from genomic information increases as technology for genomic analysis continues to develop. High-density analytic platforms such as microarray chips allow for a more informative view into an individuals genome, increasing the certainty with which we can make inferences based on these data. In the spirit of the broader view that today's analytical techniques afford us into the human genome, the term "pharmacogenomics" has also expanded to encompass higher-level biological systems influencing drug metabolism, such as pharmacokinetics (the individual's affect on the drug) and pharmacodynamics (the drug's affect on the individual)[7].

Continuing along this wave of expanding the boundaries of discovery is of vital importance for medicine, as pharmacogenomics will play an important role in refining medical practice. At present, many physicians must still determine drug doses for their patients on a case-by-case basis--this perfect balance is often achieved by a decidedly inexact process of trial and

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[6] Parker, L., & Satkoske, V. B. (2012). Pharmacogenetics, personalized medicine, and race. *Journal of Law, Medicine & Ethics* , *40*, Retrieved from http://www.nature.com/scitable/topicpage/pharmacogenetics-personalized-medicine-and-race-744

[7] Urban, T. J., & Goldstein, D. B. (2014). Pharmacogenetics at 50: Genomic personalization comes of age. *Science Translational Medicine*,*6*(226).

error. The random nature of this drug-tailoring method has repercussions on both cost and patient safety: the Institute of Medicine (IOM) reports that $765 billion of US dollars--nearly one third of every dollar spent on healthcare--are wasted annually, $130 billion of which are attributed to inefficiently delivered services.[8] This cost presents a clear burden to the US healthcare system and insurances companies, but most acutely affects the patient seeking treatment. This IOM report spells out a need for measures to guide physicians through the diagnostic process, a need that can be filled by pharmacogenomics. In economic support of this position, Stallings et al. modeled the cost impact of pharmacogenomics in asthmatic patients and demonstrated that an immediate cost of a $200 pharmacogenomic diagnostic test could save up to $567 per patient in forgone drug nonresponse costs. Furthermore, this report foresees these findings to be generalizable in many patient contexts, especially in patients suffering from prevalent illnesses.[9]

As was mentioned previously, efforts such as the HapMap Project have evolved to bolster this ultimate goal of applying genomic discoveries to medical contexts; in creating these databases, we can now confirm formerly under-supported hypotheses hinting at the existence of genetic differences across ancestral groups. To date, the HapMap Project has collected disease allele frequency data from samples of Yoruba, Japanese/Chinese, and United States descent and in so doing, is one of the first and largest efforts to address population stratification, a research design error that threatens to undermine data[4]. Published 10 years later in 2012, genomic findings from the 1000 Genomes Project not only added statistical power to genomic discoveries elicited by the HapMap but also, offered a higher resolution view to better understand conserved variants within populations. The project utilized the entire genome sequence of 1092 individuals

[8] Institute of Medicine. (n.d.). *Us healthcare costs*. Retrieved from http://resources.iom.edu/widgets/vsrt/healthcare-waste.html
[9] Stalling , S. T., Huse, D., Finkelstein, S. N., Crown, W. H., Witt, W. P., Maguire, J., Hiller, A. J., Sinskey, A. J., & Ginsburg G.S. (2006). A framework to evaluate the economic impact of pharmacogenomics.*Pharmacogenomics*, Retrieved from https://cbi.mit.edu/wp-content/uploads/2011/04/Future_medicine_Stallings.pdf

across 14 different ancestry groups; thus, the 1000 Genomes project paints a more precise picture of intra-group variation[10]. Contributions from these projects allow for fine mapping of candidate loci associated with complex traits, such as drug metabolism and toxicity and adverse drug reactions. The literature already supports the notion that knowing the ancestral differences in allele frequencies is relevant to predicting drug response: Chung et al. discovered an association between B*1502 HLA allele carrier status and developing Stevens-Johnson syndrome, a disease causing skin necrosis, in patients treated with an anti-epileptic medication called carbamazepine; furthermore, carrier status was found at a higher frequency in Han Chinese patients. B*1502 HLA tests have since been widely implemented in Taiwan to prescreen for carbamazepine reactivity, saving the Taiwanese National Health Service roughly 1 billion USD annually in mis-prescribed carbamazepine costs and many patients from this disfiguring disease. In all, these efforts bring us closer to understanding the causal genetic variants implicated in these biological processes[5]. Projects such as the 1000 Genomes Project go even further to enhance our understanding of the rare genetic variants and variants with population-specific frequencies that regulate drug mechanisms.

III. Where does Pharmacogenomics Fit into the Picture of Medical Practice?

With an appreciation for the vast promise pharmacogenomics presents to improving the practice of medicine, it is reasonable to question the feasibility of transitioning pharmacogenomics from a theoretical topic of research into practice. There is already precedent for applying clinical interpretations of pharmacogenomics research into medical practice internationally, as evidenced by the previous example in Taiwan using the presence of the

[10] Stalling , S. T., Huse, D., & Finkelstein, S. N. (2011). An integrated map of genetic variation from 1,092 human genomes. *Nature*, *491*, 56-65. Retrieved from http://www.nature.com/nature/journal/v491/n7422/full/nature11632.html

B*1502 HLA to inform carbamazepine prescription. Moreover, the United Kingdom has paved the way for uniform integration of pharmacogenomic research into the clinical sphere, claiming the title as the first country to make the sequences of thousands of individuals available to healthcare professionals to use in clinical settings--the complete sequences of the 100,000 individuals in this patient population are set to become available in April of this year. However, before similar initiatives can be replicated in the US, the research and scientific community must be wary of limitations and potential pitfalls associated with the current state of pharmacogenomics research. This concern can be divided into two main categories: overstating the genetic penetrance of identified alleles, and making spurious between an individual's apparent race, haplotype blocks, and predicted response to therapy.

While there is abundant evidence of genetic bases for drug response, there are also methodological constraints to testing "pharmacogene" heritability that hinder researcher's ability to calculate the proportion of drug response phenotype that is attributable to genetics. In addition, maintaining such a narrow focus on pharmacogenomics runs the risk of ignoring important individual characteristics that play a role in determining one's drug response. Currently popular fields of study such as epigenetics--environmentally-induced genome modifications--are being examined with other "omics" (i.e. proteomics, metabolomics) to create a more comprehensive picture of biologically driven outcomes in order to combat this tunnel-vision perspective on determinants of health[11]. This argument does not discourage pharmacogenomics research so much as it suggests that interpreting pharmacogenomic data be reframed to also include discussions of additional explanatory variables.

[11] Gamazon, E., & Perera, M. (2012). Genome-wide approaches in pharmacogenomics: heritability estimation and pharmacoethnicity as primary challenges. *Pharmacogenomics*, *13*(20), 1101-1104. Retrieved from http://www.futuremedicine.com/doi/pdf/10.2217/pgs.12.88

Of ethical concern is the foreseeable scenario in which a physician uses their patient's race as a proxy for their continental ancestry to intuit information about their probable haplotype block and thus, predicted response to a given therapy. In such a case, researchers such as Parker and Satkoske call into question the use and potential abuse of pharmacogenomics in the possibility that "slippage" (as previously defined in the introduction) and systematic discrimination and stigmatization of racial groups will occur. Ideally, medical professionals would be spared the need to approximate genetic inheritance patterns because whole-genome sequencing would be widely accessible. In a current assessment of whole genome sequencing's cost, it is certainly a great feat this figure has experienced a dramatic decrease from $1 million in 2007 to as low as $1000 in seven years; however, the elusive "$100 Genome" is still years away and the inertia to reach these marginal cost reductions, sizable[12]. Furthermore, the infrastructural barriers to contracting this laboratory-caliber technology into use within a medical setting must also be acknowledged.

In lieu of technology that can be easily integrated into everyday healthcare use, it is therefore understandable that physicians would use these estimations, as there are no upfront monetary costs and it could confer economic and patient safety benefits as have already been described. But, not only does research show that these off-the-cuff estimations are often inconsistent[5], but also can lead to inequalities treatment as was seen in the aftermath following the ACE inhibitor study. Psychological theory sheds light on an existing tendency among physicians to stereotype their patients as both a necessity of facilitating effective medical practice, but also a dangerous unconscious process that fuels health disparities. As it stands, this relationship already carries an unfortunate legacy of mistrust and exploitation, particularly in

[12]Zimmerman, E. (2013, June 25). *The race to a $100 genome*. Retrieved from http://money.cnn.com/2013/06/25/technology/enterprise/low-cost-genome-sequencing/

African-Americans and among the Jewish community; therefore, without clear scientific evidence to support changes in treatment calls based on race alone, doing so could further damage a patient's ability to trust their physician. Researchers also worry that stratifying genomic bases for disease among continental ancestry groups will undermine the current view of race as a socially constructed identity as opposed to a biological one, thereby making way for scientific justifications to discriminate against patients for their biological differences. In a related concern, racial minorities are woefully underrepresented in genomic biobanks which means that the availability of pharmacogenomic data directly applicable to non-white patients is very limited compared to Caucasian patients--this disparity calls into the question the fairness of introducing these discoveries into healthcare settings at all, when minorities are at a clear disadvantage[6].

IV. Final Thoughts on the Current State of Pharmacogenomics

Despite these valid concerns, it is no secret that pharmacogenomics is the future of medicine. Indeed, this is burgeoning field reaching it's "inflection point" of significance, promising physicians the ability to personalize treatment regimens concordantly with their patients' biologically determined drug response[13]. At present, the Genomics and Targeted Therapy branch of the FDA has compiled a list of 155 drugs associated with human biomarkers modifying their reactivity, and this list will continue to grow as high-throughput data analytic techniques increase in efficiency. However, parallel efforts to discover pharmacogenes and to uncover more information about human variation through genomic analyses of geographical origin--like the prominent and recent 1000 Genomes Project--can be as much of a threat as an

[13] Steenhuysen, J. (2014, March 7). *the dawning of the age of genomic medicine, finally*. Retrieved from http://in.reuters.com/article/2014/03/06/genomics-future-idINDEEA250GI20140306

asset if the output is not interpreted in the appropriate context. There is evidence to support and dispute the reliability of self-reported race as an appropriate indicator of someone's continental ancestry and thus, biomarker profile[14]. The consensus among the research community seems to support more robust investigations on refining our understanding of genetic clusters and from here, examining the variable drug responses among these groups. Using an empirical approach to redefining clusters sharing similar allele frequencies both acknowledges an ancestral component to genomic inheritance and deemphasizes the use of common racial labels in this process. In this way, clusters can be used as a research tool to acknowledge human variation by adjusting for genetically-driven health disparities within different populations.[15] By moving beyond this mentality of race as an explanatory variable for drug response, the research community, pharmaceutical companies, and physicians alike will come closer to achieving truly precise medicine.

[14] Tang, H., Quertermous, T., & Risch, N. J. (2005). Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies. *American Journal of Human Genetics*,*76*(2), 268-275. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1196372/

[15] Ali-Khan, S. E., & Daar, A. S. (2005). Admixture mapping: from paradigms of race and ethnicity to population history. *HUGO Journal*, *4*(1-4), 23-34. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3051047/