

Applying Existing Ethical Principles to Personal Medicine

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Abstract

While areas such as gene therapy have fallen short of its initial promises as a byproduct of the Human Genome Project, personal medicine (which will be used interchangeably with pharmacogenomics) is more promising. The development of hundreds of thousands of biomarkers along with the technologies to rapidly and inexpensively perform genetic screening has laid the foundation for personal medicine. Just as the Human Genome Project itself has been burdened with ethical implications, so has personal medicine. However, society has been evolving practices regarding genetic and clinical information which are poised for their application to personal medicine. In this article, three topics with ethical implications: (1) privacy concerns, (2) economic considerations, and (3) potential malpractice litigation, are discussed along with the application of existing ethical principles to each.

FUTURE PERSPECTIVE

In the next five to ten years, medicine will evolve more than it has in the past century. While physicians previously dealt with two phenotypes (man and woman), the Human Genome Project has allowed a stratification which would not have been considered 50 years ago. Medicine will become more "personal." Each patient is a unique collection of genetic materials and it is well known that genetics play roles in nearly every major chronic disease. Previously, genetics and disease was limited to single gene disease such as cystic fibrosis; but now genetics has been proven to be factors in nearly every major medical subspecialty. With the ability of the physician to apply personal medicine comes ethical considerations. Here three major issues: privacy, economics, and litigation are discussed with an emphasis of how a foundation for their treatment has been laid.

BACKGROUND

Pharmacogenomics, commonly referred to as "personal medicine," has been heralded as the most promising medical advancement in the development of modern medicine. It has also been used as an example of a byproduct of the Human Genome Project. However, as in most scientific advances, the potential for harm can be as great as the potential for benefit. Some believe this may be true of pharmacogenomics.

The discomfort with pharmacogenomics is centered on the potential abuse of human genetic information. Since the

inception of the Human Genome Project, a minimum of 5% of total research funding has been earmarked for the Ethical, Legal, and Social Issues (ELSI) Program of the National Institutes of Health (NIH). Genetic discrimination is the most common fear resulting from the Human Genome Project.

Pharmacogenomics is the first example of the potential open use of genetic information for general health care. While there has been limited diagnostic testing based on genotype (a person's genetic complement of one or more genes), pharmacogenomics will be the first full scale use of genetic information across the health care industry. Major ethical implications of the use of pharmacogenomics are discussed in this paper with an emphasis on how such implications may not pose a significant threat to patient populations.

In 1865 Gregor Mendel, an Austrian Monk, is regarded to have written the first scientific paper in the field of genetics [1]. In that seminal work, Mendel demonstrated the inheritance of traits across generations of pea plants. It took nearly 40 years for the scientific community to appreciate the importance of Mendel's findings. However, once Mendel's work was "rediscovered," the new field of genetics gained momentum. Between 1900 and the 1950s genetic research focused primarily on the basic understanding of the molecular basis of genetics. This included Watson and Crick's discovery of the structure of DNA and the work of Hershey and Chase which demonstrated the molecular role of DNA in the development of genetic traits. Ultimately, the

Human Genome Project was started in 1989 as an international endeavor to broadly understand the genetic architecture of humans [2].

It is a common misconception that the Human Genome Project originated with the U.S. NIH. In actuality, the Human Genome Project was an extension of research authorized by the U.S. Atomic Energy Commission (which later became the U.S. Department of Energy) in a follow-up to the use of nuclear weapons in World War II. At that time, it was known that radiation had an effect on DNA. This was demonstrated in the offspring of patients who were in the vicinity of Hiroshima and Nagasaki at the time of the bombings. There was a Presidential directive given to the Atomic Energy Commission to undertake a study in the results of radiation on the nuclear bombing survivors and to extend that work into a better understanding of human genetics. It was not until 1989 that the NIH formalized a collaboration with the DOE and several international scientific organizations which resulted in the Human Genome Project.

The goals of the Human Genome Project were to map, sequence, and determine the function of all human genes [3]. In 2000 a joint announcement from the public Human Genome Project consortia and Celera, a private company which focused on sequencing the human genome for profit, heralded the “completion” of the draft DNA sequence of the human genome [4, 5]. This announcement was quickly misinterpreted by the press that the “Human Genome Project has been completed.” The excitement in the scientific community for the completion of the draft DNA sequence no doubt contributed to the failure of the scientific community to adequately explain to the public that the announcement represented a single step in the project, not its completion. While the goals of the Human Genome Project focused on steps leading to an overall understanding of human genetics; the driving force of the project was to better human health by relating disease to genetic factors. One extension of this to treatment resulted in the field of pharmacogenomics.

It has been well-known since 1955 that genetic variation has a role in drug metabolism [6]. From 1960 to 1999, 1134 papers were published on pharmacogenomics [7]. In 2005 the first drug developed to treat a particular subgroup, Bidil, was released [8-12]. Since then, the completion of the HAPMAP project has laid the foundation for easier investigation into the relationship of genetics with human responses to medications. The HAPMAP project has resulted in a collection of more than 3,000,000 genetic markers and

the tools to quickly assay any particular individual [13]. For a cost of less than a fraction of one-cent per marker, scientists can determine which makers are present in a particular patient. This may be followed by an examination of the statistical association of certain markers with medication response. Thus, as pharmaceutical companies develop new drugs, there is a tool to “tailor” the prescription of those drugs to patients with a certain genetic make-up in order to maximize the success of the treatment. This is the goal of pharmacogenomics.

DISCUSSION

Having presented the background of pharmacogenomics, this manuscript will now deal with three ethical issues of this field. Though this list is not exhaustive, some major issues are: (1) privacy concerns, (2) economic considerations, and (3) potential litigation. First, it is useful to examine the landscape of both case law and statutes as related to this topic.

FEDERAL AND STATE CASE LAW AND STATUTES

Presently, neither U.S. case law nor statutes addressing pharmacogenomics at either the federal or state levels exist. In fact, Congress has been slow to adopt legislation regarding basic information security and discrimination as it relates to human genetics. On October 14, 2003 the Senate unanimously passed S.1053, the Genetic Information Non-Discrimination Act of 2003. This bill would have provided fundamental protection for the release of genetic information and its use for discrimination. However, the bill failed in committee in the House of Representatives.

On February 17, 2005 the Senate passed bill S.306, the Genetic Information Non-Discrimination Act of 2005. Nearly identical to the 2003 bill, and supported by President George W. Bush, the bill was introduced into the House of Representatives (H.R.1227) on March 10, 2005. The bill has yet to pass.

It is reasonable to expect that the legal provenance of pharmacogenomics may begin with its relationship to genetic privacy and potential discrimination. In fact a major concern of bioethicists is the inappropriate use of genetic information for discriminatory purposes. Therefore, it is likely that the courts and legislature may address these issues prior to those directly dealing with personal medicine.

Even the Food and Drug Administration has commented on the immaturity of pharmacogenomics as a discipline in

reference to formal regulation. The FDA has stated “Because the field of pharmacogenomics is rapidly evolving, in many circumstances, the experimental results may not be well established specifically to be suitable for regulatory decision making.” [14]. The FDA echoes the overall government’s reluctance to presently weigh in on the issue of pharmacogenomics. However, opinions regarding the ethical implications of personal medicine are increasingly being presented in the scientific literature. As previously stated, three of these will be discussed below.

1. PRIVACY CONCERNS

One could argue that the central dogma of ethical considerations of any aspect of human genetics is composed of: consent, privacy, and confidentiality [15]. Since the inception of the Human Genome Project, research funding for ethics related to these three areas has been continuous. What is different today from earlier stages of the Human Genome Project, is that there is now a forum within which most patients may come into contact with genetic issues. Previously, genetics has been used to screen for particular diseases, either pre- or post-natal. Genetics has been used in most cases to confirm a particular disease rather than treat it. Huntington’s disease is an example of an illness which can be diagnosed years before symptoms present themselves; however, the diagnosis does not result in a treatment advantage to the patients. Some patients have stated that the genetic test serves more like a “death sentence” confirming a particular end.

Alternatively, genetic testing may provide some limited utility to patients. The presence of a particular set of genetic alleles in women may conform to an increase in the rate of breast cancer in that group of 5-10% compared to controls [15]. In this case, a physician can take more exhaustive measures in cancer screening for those women in a particular class of patients.

Each of the above cases has implications for privacy. Both methods could be used against the patient (e.g., withdrawal of insurance) even though the patients do not presently manifest any symptoms indicative of a disease. Another widely used example of genetic discrimination is the refusal of a bank to issue a mortgage to an individual based on his or her genetic profile.

There are several mechanisms in place and under development which would greatly impede, if not eliminate, the chances of using information gathered as part of a pharmacogenomic testing procedure being used to patient’s

detriment. The most overarching control is HIPAA, The Health Insurance Portability and Accountability Act of 1996. HIPAA creates stringent criteria for the release of private health information. Any information gathered in a pharmacogenomic test would fall under HIPAA protection. In that way, genetic information would be no different than other diagnostic information (e.g., presence of the HIV antigen) which could have similar negative effects. While it is true that genetic information can have a future predictive value compared to a present diagnostic result (e.g., high cholesterol), the impact of genetics on most common and complex diseases (e.g., asthma, diabetes, heart disease, etc.) are much less than environmental factors.

In a clinical setting, the “Georgetown Mantra” has relevance in a broader perspective. The four principles: autonomy, beneficence, non-maleficence, and justice are generally applied to issues such as right to die[16]. One may argue that the issues surrounding personal medicine have their foundation in the principles in the “Georgetown Mantra.” While one might find guidance from principles from the “mantra” or from the Hippocratic Oath, these are only philosophical attempts to classify the role of the “healer.”

For privacy issues, HIPAA is not a panacea, but rather a start. Law, whether it is statutory or common law, has two components. The first component consists of the elements of the law (e.g., what constitutes drunk driving). The second component, usually more difficult to discover is the policy underlying the law (safety on the road). Conscientious judges know that the “letter of the law” must be coupled with the “policy under the law” and address such in their opinions through which the common law is created. One may look to published comments or legislative histories for an understanding of policy under statutory law.

Interestingly, in academic medicine HIPAA is increasingly being looked at in terms of the “letter of the law” rather than the policy behind it. Academic researchers struggle to perform their clinical trials while seeing HIPAA as a series of hurdles that are added to an already difficult task. This is not to say that an academic clinician has no regard for the privacy of his or her patients, but rather is institutionally mandated to comply with the law and not focus on the policy. Laws reflect society, and as society moves toward one in which medicine has important genetic components, laws such as HIPAA should evolve along with the science.

In addition to the privacy / confidentiality issues surrounding pharmacogenomic data, an issue often raised is consent.

Consent is usually discussed in terms of a patient's agreement to have his or her medical information and / or samples used for scientific investigation. Again, HIPAA provides the environment within which such information would be obtained. Additionally, the requirement that institutions conducting human subject research have Institutional Review Boards (IRBs) to oversee the ethical use of human subjects and data also provides a mechanism for protection.

The proposed development of large databases for pharmacogenomic research has raised some concern amongst ethicists [17]. The release of patient information into such databases might violate both the consent and privacy of the patients. Again, there are safeguards in place to minimize the chance of this occurring. First, all patients who participate in clinical studies must provide informed consent. The informed consent must state the manner and means by which the data will be used. Moreover, any data which might go into such a database would be anonymized. This procedure is not unique for pharmacogenomic data. The National Health Survey Act of 1956 resulted in the creation of the NHANES data set. The first three studies were conducted between 1959-1962, 1963-1965, and 1966-1970 with an addition five since 1970. Since 1959, 130,000 patients have been enrolled into the NHANES registry. The dataset contains detailed medical information on the patients and the data is made readily available to researchers for qualified research purposes. Patient confidentiality, however, is maintained as the data released is done in such a way as to prevent the identification of particular individuals. Surely, such a mechanism would be put in place for any national gene-drug interaction database. Thus, a model exists which can be deployed (and modified if necessary) to meet the ethical concerns of pharmacogenomics.

2. ECONOMIC CONSIDERATIONS

In 2005, the NIH budget for medical research was \$27.1 billion. While that funding level reflects the relatively flat budget imposed by the federal government, it nevertheless dwarfs those of other scientifically prominent nations. While medical (and biological) research is funded through other government programs (e.g., DOE, the National Science Foundation (NSF), the Centers for Disease Control and Prevention (CDC), etc.) the NIH budget is a good yardstick with which to measure other research investments, such as those made by the pharmaceutical industry. In 2005 the industry group PhRMA reported pharmaceutical research spending of \$39 billion. When combined with non-PhRMA

members, the total drug research expenditures exceeded \$51 billion, nearly twice that of NIH.

With expected sales in excess of \$1 billion for a "blockbuster" drug, there is considerable incentive for the pharmaceutical companies to invest in research. A common attack on pharmaceutical companies by patients is the high cost of drugs. Many fail to realize that the cost of bringing a drug to market today is in excess of \$880 million [18] and these research costs must be offset primarily during the remainder of the drug's patent. This enormous cost is principally due to the high rate of failure of drugs in clinical trials.

Personal medicine has been promoted by the pharmaceutical industry as a way in which to bring drugs, which would otherwise not make it to market, to patients with a genetic background conducive to positive drug response. From an economic standpoint, this benefits both the patient and the pharmaceutical company. Research funding for a drug which would normally be discarded results in a niche market of patients who might not otherwise receive a treatment.

However, arguments have been made that the economics of personal medicine may have an overall negative impact on patients. One argument is that pharmaceutical companies may create a drug which serves a large number of, but not all, patients with a particular illness. The pharmaceutical company might then find it fiscally irresponsible to continue research for the remaining subset of the patient population [19]. Thus, a pharmaceutical company might pre-maturely end drug development once a drug is effective in an economically viable population; whereas further drug development might produce a drug with a slightly broader range. While there are no examples of this occurring, drug companies regularly terminate entire research programs for lack of progress. Therefore, it is reasonable to assume that a pharmaceutical company will only continue to invest in drug discovery for a particular patient population so long as it continues to make economic sense.

Orphan drugs have continued to be both an ethical and policy issue regarding drug discovery. There are many diseases which could likely be treated with drugs but are not actively researched due to the small patient population. Public funding sources have attempted to fund orphan drug research, but is it unlikely that the amount of funding necessary to be effective in bringing an orphan drug to market could be obtained without funding from the pharmaceutical industry. Once a population is stratified in

such a way as to ensure FDA approval of a drug, one creates in essence an “orphan population” of those patients who do not fall within this economically feasible group which can be treated. However, the ethical principles which have been developed regarding orphan drugs and the policy considerations regarding them would be directly applicable to this effect of pharmacogenomics.

If one can stratify a population into subgroups based on their genetic profiles, clinical testing might show efficacy of a drug for a particular. Few would argue that it is not better to have a drug which treats a smaller patient population rather than continue research with the probability that continued drug failures would result in the termination of the entire research program. However, economic policies which promote and reward research resulting in drugs with broad efficacy may need to be examined as personal medicine evolves. In fact, the government could create financial incentives for pharmaceutical companies to continue research which would only help a small patient population.

Another argument against pharmacogenomics is the fear that the pharmaceutical companies would target research and marketing to groups with a high willingness to pay for treatment [20]. The recent release of numerous erectile dysfunction (ED) drugs demonstrates the use of research dollars to treat what some might argue is not a disease which merits significant research spending when compared to illnesses such as cancer [19]. In order for such an argument to stand, one would have to look at the entire landscape of drug pricing and drug purchase not only through the common funding sources in the U.S. (e.g., private health insurance, Medicaid, Medicare) but also internationally. Moreover, in order for this premise to be put into effect, one would need to apply a filter such as “Middle to upper-class white males are the most economically advantageous group to market to, therefore we will only screen white males.” Such a scenario is absurd. Personal medicine to date has been promoted as a screening process to remove patients from clinical trials to maximize success of the trial. By starting with the broadest possible population and then stratifying the population in order to maximize efficacy and minimize complications is a generally accepted strategy. In fact the first patient stratification resulting in a personal medicine drug, Bidil, was for the use of a subset of the population (black males) where the larger total patient population showed a lack of drug efficacy.

3. POTENTIAL LITIGATION

To understand the potential of litigation, it is helpful to have at least a cursory understanding of the drug development cycle. Once a potential drug has passed toxicity screening, efficacy studies are performed. A major economic driver for personal medicine is to increase the possibility that a given drug will be found effective in a patient population. Side effects of the medication are also examined. Thus, a new drug must be both efficacious as well as produce minimal complications.

The potential for litigation always exists for unanticipated complications manifested after the drug is approved and released into a large general patient population. The most notable recent examples of litigation regarding an unanticipated complication are the those lawsuits against Merck & Co. for their release of Vioxx. Rofecoxib, a nonsteroidal anti-inflammatory drug, commonly know as Vioxx, Ceoxx, and Ceeoxx, was recalled in 2004 because users had an increased risk of heart attack and stroke. Over 10,000 lawsuits have been filed against Merck & Co. The results of such litigation have been mixed. However significant money damages have been awarded. For example, in *Ernst v. Merck*, a Texas jury awarded the widow of Robert Ernst \$253.4 million in damages on August 19, 2005. The case is presently on appeal. However, In February 2006 a New Orleans jury in *Punkett v. Merck* found for the defendant. While there is much pending litigation regarding the use of this drug, it is useful to examine how such litigation could have an effect on pharmacogenomics.

The cause of action introduced in the Vioxx litigation was that the drug company failed to adequately determine the drug’s side effects on the circulatory system. In order to find such side effects (which might be relatively uncommon) prior to release, the pharmaceutical company would need to examine large numbers of patients. The less frequent the complication, the more patients are needed before the complication might be seen. When pharmacogenomics is employed during the drug development process, the patient population is “striated” in such a way as to maximize efficacy in a relatively narrow group of patients. Thus, the number of patients needed to statistically show efficacy would be lower than those needed for a drug released to a general population. Thus, when examining a narrower population, one is less likely to find complications [21].

It is arguable that this reasoning is flawed. While an examination in a more striated patient population could

mask complications which might be seen in a more general population; the stratified population by its definition is predisposed to show the efficacy of a drug. While it is not a certainty that the similarities in efficacy would necessarily result in similarities for a lack of complications; there is no widely demonstrated evidence that the contrary argument is true.

The other major argument is that pharmacogenomics opens up areas of litigation in the area of medical malpractice. A concern among health care professionals is that once genetic markers have been linked to drug efficacy, failure to perform genetic tests could result in malpractice litigation [22]. While it is not inconceivable that the failure to perform a genetic test might form the basis of a cause of action for malpractice, the decision to perform any particular test is familiar territory for physicians. A duty of the physician is to balance the need and number of medical tests with their utility in providing information for diagnosis and treatment. The use, or lack of use, of a genetic test in the evaluation of a particular patient's treatment is another byproduct of the advances in modern medicine. It is reasonable that a physician should be cognizant of all the tools available for the benefit of the patient. Similarly, malpractice may fall into the areas of failure to warn of possible side effects and complications brought on by off-label uses.

While new litigation surrounding pharmacogenomics is possible, there is neither a convincing case that these possibilities are novel to the practice of medicine, nor that they would outweigh the potential benefits of personal medicine.

POLICY CONSIDERATIONS

As personal medicine continues to mature, there are several policy considerations which may exist. These include:

1. What is the government's role in protecting data used for personal medicine?
2. What regulatory elements are in place to minimize dangers to patients who are prescribed drugs developed through pharmacogenomics?
3. What legal protection will be provided to physicians?

These policy issues have begun to move to the forefront of consideration in areas where genetics intersects health care. A goal of public policy is to balance the rights of individuals

with the needs of society. In this case, the balancing test must address the benefit to patients who are prescribed effective personal drugs with the need to protect society from adopting norms which will negatively impact society's (a.k.a. government) interests in protecting the rights of its members.

Will society accept the potential of discrimination based on the release of genetic information in order to provide medical treatments for patients who would otherwise go untreated?

It is becoming clearer that the genetic "genie" has been released from its bottle. To prevent its use in the improvement of human health is unlikely and unwarranted. Society is focused on protecting its members from harm. Issues such as the balancing of society's interest in protecting and promoting human life versus euthanasia continue to develop, as will the balancing of issues surrounding personal medicine. For civilizations to continue to exist, proper policies concerning human life must be established. The fall of civilizations, such as the Roman Empire, has in many cases been preceded by a discounting of human life. While personal medicine has at its root the fundamental premise of promoting human life, there must be continued watchfulness on how its side-effects might erode the rights and needs of society by its new focus on how medical treatment may be delivered.

CONCLUSION

While the use of pharmacogenomics in medical treatment is unique to this era, there already exists a foundation for protecting society from its misuse. While some scientific advances may require the construction of new fundamentals upon which to begin to examine ethical issues, personal medicine does not. For example, if a drug were created which allowed a human to live forever, the ethics concerning unlimited lifespan and its effects on humankind would be a completely novel situation for this society to address. Conversely, the ethical issues which underlay personal medicine are an evolution, or arguably a mere extension, of those broader issues with respect to (a) health care privacy and (b) genetic discrimination. Much as a researcher builds on scientific findings in the furtherance of a research objective, the ethical issues related to personal medicine may be built upon those already existing and maturing.

This is not a situation where society will be "blind-sided" with policy considerations because of the adoption of personal medicine. Rather it is an opportunity to hone

existing public policy developed for the precursors of personal medicine to address any evolution in ethical considerations.

While much work remains to be done, the adoption of laws such as HIPAA (as a start) can readily be applied to this new paradigm of medicine. Issues such as a patient privacy, economic exploitation of patients, and the protection of physicians from onerous legal liabilities already exist in the absence of personal medicine. It is likely that society will effectively build upon its history and effectively adopt personal medicine and promote pharmacogenomic research while evolving solutions to protect against any negative implications brought. The genetic “genie” cannot be put back into its bottle.

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