Ethical Issues in Pharmacogenetics

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articlehighlights

Pharmacogenetics promises drugs specific to an individual's condition. However, it poses some ethical concerns:

- *invasion of medical privacy*
- *unequal distribution of benefits*
- *discrimination because it involves genetic tests*
- *research/business conflict-of-interest*

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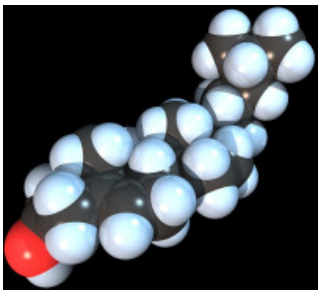
Drugs can be developed for individuals.

Pharmacogenetics is the study of how genes influence an individual's response to drugs. Though the field would seem to be brand new, it is really half a century old. In the 1950's, scientists first identified deficiencies in enzymes that explained adverse reactions to drugs and that they could be inherited.



Molecular model of cholesterol. Genetic tests may determine a patient's response to new medication. Source: Wikiemdia Commons; Illustrator: RedAndr.

For example, early research showed that 10% of African American men serving in the Korean war became anemic after ingesting an anti-malarial drug, which rarely, if ever caused problems for Caucasian soldiers. To pinpoint the cause, it took years of study:

Trial and error used to determine drug development.

- The anemic reaction was determined to be caused by a variation of the G6PD gene, and the variation was found to be common among people of African descent but not so among Caucasians.
- It was later discovered that the normal form of the gene makes an enzyme that helps protect red blood cells against certain chemicals. Lacking that protective effect, those with the variant form are vulnerable to deleterious effects.
- Since that time, numerous other enzyme variants have been identified and found to cause adverse reactions. Such adverse effects were identified, until recently, by trial and error methods. Specifically, drugs were administered, and an individual's metabolism of that drug was tracked by recording the amount of by-product in their urine.

Genomic mapping eliminates trial and error drug trial methods.

The Human Genome Project has enabled us to identify the molecular composition of the enzymes in question so that we can study correlations between genotypic (gene trait) and phenotypic (physical trait) variability. These advances will increasingly enable us to detect individuals who are likely to experience adverse reactions to medicines without having to use potentially dangerous methods of trial and error.

In coming years, we are likely to learn that particular single nucleotide polymorphisms (SNPs) are associated with sensitivities or resistances to chemical compounds in the environment. Scientists are now rushing to not only identify common SNPs, but to determine what drug effects can be correlated to them.

Pharmacogenomics is a recent offshoot of pharmacogenetics. Its scope is broader; for example, it attempts to understand not only the molecular composition of genetic variants associated with drug response but also the behavior of those variants, including how those genes affect drug receptor sites.

Ethical Issue #1: "Good" or "Bad" Allocation of Scarce Resources?

Many believe that pharmacogenomics, like other new fields spawned by the Human Genome Project, represent a misallocation of resources. Rather than

Critics say that genomic mapping is a waste of money and time.

embark on learning how genes indicate a predisposition to disease and developing cures and enhancements, or experimenting with ways to change the human germ cell, global efforts should be spent on solving more urgent problems facing humanity, such as global famine or accessibility to potable water.

Others contend that pharmacogenomics, in particular, offers enormous potential for clinical benefits to patients as well as economic benefits for health care delivery. The arguments in favor include:

Every year, adverse reactions to drugs possibly kill 100,000 American patients.

- In the U.S. alone, adverse drug reactions are thought to KILL about 100,000 hospitalized patients annually. It is believed that many of these reactions are due to genetic variants and thus many of these deaths can be avoided by testing people for adverse drug response before giving them drugs. The science and technology for such tests, however, are in their infancy.

Over 2 million people have serious reactions to medication.

- Another 2.2 million incur serious, but non-fatal, reactions. Physicians, in view of their Hippocratic oath, are obligated to do no harm. Can this obligation be fulfilled when the information available to physicians about how particular medicines will fare in their patients is so meager? At present, physicians, generally have no way of knowing in advance whether the drug they prescribe will or will not cause an adverse effect in their patients.

'One-size- fits-all' medication can be dangerous.

- This situation is further compounded by the fact that most adverse drug reactions result from the fact that medicines are "a one-size-fits-all." In other words, although medicines are taken in different dosages depending on symptoms, patient age, weight and other clinical factors, these criteria may not be adequate to ensure that a particular medicine will be safe and effective for a particular individual. Until recently, there has been no alternative to either developing or prescribing medicines. Pharmacogenomics promises to take the guesswork out of developing and prescribing safe and effective drugs.

Ethical Issue #2: What is a fair distribution of burdens and benefits in developing the field of pharmacogenomics?

Monies and people (as research subjects and as researchers) will develop the field to the point that customized medicine will be possible. Who will benefit?

Designer drugs may be too costly at first for all to benefit.

- The availability of this new technology may be costly initially, and thus accessible only to those wealthy enough to pay for both the test and the designer drug best suited to them. Yet, the cost will likely diminish so as to become affordable to most. However, will lower costs influence a person to submit to the required genetic testing, thus creating threats, if not violations, to one's autonomy (the basic tenet of bioethics)?

Commercialization of research results may lead to conflict of interest.

- Researchers who have investments in companies competing in their field may be in a conflict of interest if they are conducting research for such a company. Substantial concerns about conflicts of interest as both a threat to quality research as well as to the well being of research subjects have abounded for decades.[1]

- A recent study found that policies governing conflicts of interests at major medical institutions varied considerably in both disclosure requirements and the nature of permitted academic-industry relationship, thereby opening a door to the possibility that an interest in financial gain could overpower an interest in either achieving valid research or protecting the well-being of subjects.[2]

Participants do not always benefit from successful outcomes of drug trials.

- Further, there are several examples in the history of medical research where the patient population standing to benefit from advances (i.e., people who have donated their time, bodies, and hearts to research, though compensated per standard National Institute of Health [NIH] terms), did not receive the anticipated medical benefits because new therapies were unaffordable, when they became commercially available, or not covered by insurers, as these two examples illustrate:

    - Numerous sufferers of Gauchier Disease, who helped companies developed safe and effective treatment (clinical research), were denied access to treatments by insurance companies by refusing to cover the high cost therapies. The patients couldn't afford to pay costs out of their own pocket.

    - A Canavan's Disease Support Group has been instrumental in

helping a company develop treatment by raising research funds as well as supplying researchers with willing research participants. The group is suing research facilities not for financial return on investment but for the opportunity to play an active role in furthering research/treatment goals.[3]

Ethical Issue #3: Will individualized medicine be used ethically?

Knowing if a person will respond to a drug in ways that are safe and effective for that individual will enable patients to avoid medications that are dangerous or ineffective for them.

Gene profiling is not the only factor in creating designer drugs.

This is not to say that genes are the only key to cures. Environment plays a role, too. Dietary and lifestyle behaviors are likely to still affect the safety and efficacy of medicines for particular individuals. As well, variation in drug response is not limited to micro polymorphisms. Environmental factors also play a role (such as sun exposure, drug/drug interaction, drug/food interaction). However, scientists are poised to uncover why the metabolism of particular individuals absorbs and dispels pharmaceuticals in a particular manner.

Consider the following *hypothetical* clinical scenario as illustrating some of the ethical issues that can arise in clinic:

Not all physicians will take advantage of new testing methods.

- A 42 year old man of Scandinavian descent presents to his physician with a general feeling of malaise.
- Five years previously he was diagnosed with high serum cholesterol, which he attempted to control with a regimen of exercise and dietary regulation, with no success. His physician then prescribed for him a drug therapy.
- Before agreeing to take the prescribed medication, the patient retrieved volumes of information from the Web, including but not limited to peer-reviewed journal articles about his condition and his physician's first choice drug.
- After six months of therapy there was only a modest lowering of cholesterol levels, so the medication was changed. After nine months on the second medication, there was still no marked effect.
- By the time the patient was able to see his physician again, a newer therapy had become available. This new drug had become the physician's favorite. The physician advised the patient to switch to this new drug, and the patient was eager to try it. Three weeks later, the patient came to see the physician to complain of continued malaise.

The patient may have been better served if he had undergone the following genetic tests, the results of which could have provided valuable management information:

Genetic testing can provide an array of diagnostic results.

- Test 1: a pre-dispositional test to determine whether the patient has a polymorphism associated with plaque development leading to coronary heart disease.
- Test 2: a test to see whether the patient has a polymorphism associated with a non-response to the medication (the newest medicine). A positive test 2 indicates that the patient lacks an enzyme needed to metabolize the drug. The absence of the enzyme means that the drug is dispelled from the body without absorption.
- Test 3: a test to see whether the patient has a polymorphism which indicates the presence of an enzyme responsible for metabolizing the dosage too slowly, making the drug in that dosage toxic to the patient.
- The rationale sequence of testing is 1-3.

If the patient tests negative, meaning that he does not have the polymorphism associated with plaque development, then his high cholesterol poses no health risk and medication to lower cholesterol levels are not indicated. If the patient tests positive, meaning that he does have the polymorphism, then he is predisposed to coronary heart disease (CAD) by virtue of being a plaque maker. In this case, cholesterol-lowering medication is indicated.

Ethical Issue #4: Whose right predominates?

The father of a research subject opened a letter addressed to his child and

learned that his child had enrolled in a genetic research study.

Whose privacy was invaded — the father's or the child's?

- The letter indicated that for the purpose of research the research facility had obtained some of the father's medical records. The father objected to what apparently was non-consensual disclosure of his medical information, even for the purpose of obtaining an informative family history to be used to provide optimal care for the son/daughter.

- Outraged, the father phoned the Office for Human Research Protections (OHRP),[5] of the U.S. Dept. of Health and Human Services, and protested that the researchers obtaining his family history without his explicit consent constituted a violation of his privacy rights. OHRP, apparently siding with the father, blocked the offspring from using the father's information and forbade any further attempts to obtain more information on grounds that an individual's (specifically his) right to privacy and autonomy is paramount.

Among the interesting and difficult issues in this case is the fact that it challenges us to think deeply about the weighted values we assign to first principles, namely the right to privacy. Whose right predominates in this case - the father's or the child's?

Laws exist to ensure medical privacy.

New federal medical privacy rules under HIPPA spell out the requirements to ensure privacy of all individuals. These rules, though scheduled to become practice February 2001, are facing strict opposition from several different sectors of the health care industry, primarily because of the cost and impracticalities involved in implementation. For numerous reasons, it is far from clear if these rules would support the father's claim, and if so how.[4]

Conclusion

In spite of our best efforts to anticipate and resolve ethical quandaries arising from the application of new genetic technologies, it is likely that unexpected conflicts will arise. Those discussed in this article are not intended as an exhaustive list.

Pharmacogenetics has fewer ethical issues than other medical biotechnologies.

The ethical issues here are remarkably similar to those standardly invoked in pre-dispositional testing discussions. Yet, arguably the stakes are lower here. The risk of psychological harm is, for the most part, far less substantial than testing for a late onset disorder like Huntington Disease, for which, effective treatment does not exist. Still, in the absence of guidance about what constitutes high and low stakes, ethically defensible decision making requires acknowledgement of the competing interests and a broad enough scope of concern to analyze how an apparent low risk can become a real high risk and vice versa.

Pharmacogenetics will ensure safer drugs.

Pharmacogenetics will permit gene profiling to answer questions about medicine responses, as well as enable researchers to design better and safer medicines. The science and its applications are real today and will be increasingly common in coming years. While the likelihood that individuals will be shut out from health insurance because they do not respond to a single drug or because a particular drug formula is toxic to them is extremely low, as would be employment exclusions (in hiring, promoting or job responsibilities), the issues underscore the importance of debating more widely the ethical use of pharmacogenetics.

Conclusion: The end product of this technology — individualized drugs — must be made easily available to all.

In the U.S., 45 million people lack any health insurance, and thus are at the mercy of hospitals' budgets for unrecoverable expenditures. Further, these individuals, and the many more millions of people with health insurance, have no access to sophisticated medical care due to limits imposed by insurers, especially for-profit managed care organizations and self-insured employers. Whether customized medicine will be available to all remains a large unknown. If history is a hint to how this new field will be used, we ought to act now to ensure that the benefits are available to ALL.

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learnmore links

Medical privacy issues
Philip Bereano examines invasion of privacy because of biotechnology.
http://www.actionbioscience.org/genomic/bereano.html

Health Privacy Project
An information resource to obtain the latest developments in health privacy issues.
http://www.healthprivacy.org

Medicines by design
A comprehensive overview of medical treatment in the future. You have several topics to choose from. Don't miss "A Visit to the Doctor, 2015."
http://publications.nigms.nih.gov/medbydesign/

Pharmacogenetics Research Network
Several resources are available. Check out the information and brochures, in English and Spanish in the right bottom corner of home page.
http://www.nigms.nih.gov/pharmacogenetics/

Pharmacogenetics research
Brief definition of pharmacogenetics and information about research in this scientific field.
http://www.nigms.nih.gov/pharmacogenetics/

Drugs and genes
A resource to learn about drugs and their interaction with genes.
http://www.pharmgkb.org/do/serve?id=home.welcome

Pharmacogenetics for children
"Drugs by Design" describes how researchers at a children's hospital use genetic testing of children to determine treatment. http://www.stjude.org/stjude/v/index.jsp?vgnextoid=8e6c0307f6e70110VgnVCM1000001e0215acRCRD&vgnextchannel=9f40c10e16be0110VgnVCM1000001e0215acRCRD

Brief summary of pharmacogenomics
Human Genome Project information with a brief definition and description of terms and potential benefits of pharmacogenomics.
http://www.ornl.gov/sci/techresources/Human_Genome/medicine/pharma.html

Drugs and medications
An extensive list of informational links, including pharmacogenetics, legal issues, and consumer advice.
http://www.noah-health.org/en/pharmacy/index.html

Pharmaceutical news
The Biotechnology Industry Organization's web site with news and other info. (For pharmaceutical news, choose "vaccines & therapeutics.") The second link takes you to their calendar of events.
http://science.bio.org
http://www.bio.org/events/

See a Webcast of a Drug Discovery
Access the keynote presentation from the 2004 Drug Discovery Technology World Congress. Presenters represent the FDA, major drug companies, and universities.
http://www.drugdisc.com/section.asp

getinvolved links

Understanding gene testing
Before you accept to undergo gene testing, find out about the risks and benefits.
http://www.accessexcellence.org/AE/AEPC/NIH/gene20.html
http://www.accessexcellence.org/AE/AEPC/NIH/gene18.html

Medical Information Bureau
When applying for insurance, you may be authorizing the insurance company to check your records with MIB to verify that the information you have provided is accurate. Learn how to get a copy of your medical records from MIB.
http://www.mib.com/html/consumer_protection.html

Genetic Alliance
News, support groups, information on genetic conditions, as well as ethical, legal, and social issues. Also, a variety of ways to get involved (such as "action teams," "advocacy groups," and "e-mail discussion lists") on its membership page.
http://www.geneticalliance.org/

articlereferences

1. *Science Magazine*, Vol. 290, 8 Dec. 2000, p. 1873: "Studies trace patchwork of conflict policies," B. Agnew.
2. *The New England Journal of Medicine*, Vol. 343, 30 Nov. 2000: "Conflict-of-interest policies for investigators in clinical trials," Bernard Lo, Leslie E. Wolf, Abiona Berkeley.
3. *Science*, Vol. 290, 10 Nov. 2000, p. 1062: "Genetic Testing: Families Sue Hospital, Scientist for Control of Canavan Gene." Eliot Marshall.
4. U.S. Dept. of Health and Human Services. Office for Civil Rights - HIPAA. "Medical Privacy - National Standards to Protect the Privacy of Personal Health Information." http://www.hhs.gov/ocr/hipaa/
5. U.S. Dept. of Health and Human Services. "Code of Federal Regulations: Protection of Human Subjects." HHS (OHRP) home page: http://www.hhs.gov/ .

author glossary

Gene testing is a test that examines a sample of blood or other body fluid or tissue for biochemical, chromosomal, or genetic markers that indicate the presence or absence of genetic disease. **Human Genome Project** is an international research effort, led by the United States, to identify and order every base in the human genome. **Morphology** refers to the form and structure of organisms. **Single nucleotide polymorphisms (SNPs)** are micro-genetic differences between individuals. It is becoming increasingly known that these micro-differences explain a wide range of drug effects.

educatorresources

ActionBioscience.org original lesson

This lesson has been written by a science educator to specifically accompany the above article. It includes article content and extension questions, as well as activity handouts for different grade levels.

Lesson Title: ***Who Owns Rights To Pharmacogenetic Information?***
Levels: high school - undergraduate
Summary: This lesson examines potential benefits, risks, and ethical concerns of designer drugs. Students develop drug products for domestic animals, simulate a courtroom trial involving medical privacy, debate patenting of medical products, present DNA ownership views to a panel of indigenous peoples … and more!
Download/view lesson.
(To open the lesson's PDF file, you need Adobe Acrobat Reader free software.)

Other pharmacogenetics lessons

This lesson uses a 'case study' approach to investigate the applications of genetics to medicine. It explores one of the first examples of a pharmacogenetic test to enter mainstream clinical practice: Leukemia and the Thiopurine Methyltransferase (TPMT) Enzyme.
http://www.nwabr.org/education/pdfs/Pharmacogenetics/TPMT_LESSON.pdf

Useful links for student research

In addition to the links in the "learn more" section above:

» Issues in DNA sequence research
1) The Genetic Privacy Act 1995:
http://www.ornl.gov/sci/techresources/Human_Genome/resource/privacy/privacy1.html
2) Pharmacogenetics Research Network: http://www.nigms.nih.gov/pharmacogenetics
3) Pharmacogenetics in cancer research: http://www.pharmacogenetics.org
4) The Indigenous Peoples Council: http://www.ipcb.org

» Single nucleotide polymorphisms (SNPs)
Fact sheet about SNPs from the Human Genome Project Information office. Also, see links at end of fact sheet.
http://www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml

» The Promise of Pharmacogenomics
A primer on the topic, from the US National Center for Biotechnology Information.
http://www.ncbi.nlm.nih.gov/About/primer/pharm.html

» "Animal Genomics Is Food For Thought"
Online article (May 2002) in Red Herring examines designer drugs for animals.
http://www.redherring.com/Home/3660

» Glossaries
Cambridge Healthtech Institute offers numerous glossaries related to genomics. Free registration is required to access them. The second link is to their pharmacogenomics glossary.
http://www.genomicglossaries.com/content/gloss_cat.asp
http://www.genomicglossaries.com/content/pharmacogenomics.asp