6.4 Pharmacogenomics

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Educational Objectives

1. To identify ethical issues related to research ethics in a pharmacogenomic research context.
2. To identify important information to communicate to participants in pharmacogenomic studies.
3. To stimulate a reflection on the sensitive nature of pharmacogenomic information concerning large population group of similar ethnic ancestry.

Case

In the context of a clinical trial with Geneticeuticals, Dr. Smith is studying the role of genetic factors in cardiac disease and the available treatments options. He has recruited patients from his practice to participate in both a clinical trial and exploratory pharmacogenomic add-on study. Geneticeuticals financially supported Dr. Smith to conduct the study. However, he received no additional financial compensation per subject recruited.

In the trial, half of the participants are being treated with a new medication, drug "New," while the other half are being treated with a standard medication, drug "Old." Participants originating from North Africa, Central Europe and Japan are split relatively evenly between the study groups. The patient samples are being double-coded and, for the add-on pharmacogenomic research, studied in conjunction with pre-selected genetic markers to determine the efficacy of drug "New," which is produced by Geneticeuticals.

Before the samples were collected, the participants went through a detailed consent process during which Dr. Smith informed them of both the clinical and pharmacogenomic aspects of the study. The form included permission concerning the use of the samples, in an anonymized form, for "future pharmacogenomic researches about cardiovascular disease." The patients were also informed that because of the exploratory nature of pharmacogenomic aspects of the study and since the results of such a small study would need to be revalidated by other researches in a larger setting; results from that portion of the study would not be returned. They were given a signed copy of the consent form for their personal records.

The clinical study concluded with a finding that drug New was as effective (no better and no worse) than drug Old. The participants experienced no side-effects. However, the pharmacogenomic portion of the study revealed that drug New was metabolized more quickly than drug Old in a third of the Japanese participants and in three-quarters of the African participants. For these participants, a higher dose of drug New was needed to produce the same effect as a smaller dose of drug Old; they would therefore have to take drug New two additional times per day in order for it to be as effective as drug Old. While a higher dose is not necessarily worse for the patient, some may prefer to take an equally effective lower-dose treatment.

Questions

1. Was the consent process sufficient? Consider this question in light of the potential for conflicts of interest, the inclusion of a pharmacogenomic add-on study in the clinical trial and the consent to future research.
2. Should Dr. Smith inform his patients of the results of the pharmacogenomic add-on study? Consider this in terms of the value of the information for the patient, their expectations and their right to know.
3. Are the ethnicity-related exploratory results relevant for publication of the study? How should they be communicated?

Discussion

Q1. Was the consent process sufficient? Consider this question in light of the potential for conflicts of interest, the inclusion of a pharmacogenomic add-on study in the clinical trial and the consent to future research.

While the process of obtaining informed consent in this case was acceptable in some respects, errors were made
that could compromise the process.

The first of these errors concerns the role of Dr. Smith in participant recruitment and the informed consent procedure. The Tri-Council Policy Statement, created by the three major research funding bodies in Canada—the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada—cautions against the participation of a patient's clinical doctor in recruiting patients for experimental studies. In article 2.2, it is explained that the since the doctor-patient relationship is one of trust and confidence, a patient may feel unduly influenced to participate in a study on the advice of their doctor. Because of the possible degree of trust and dependency within a doctor-patient relationship, the voluntary nature of the informed consent could be compromised.

Furthermore, since Dr. Smith was being paid to conduct the study by the producer of the drug being tested, this could be further classified as a conflict of interest between the desire to make an additional income and the duty to provide the most effective care for participants. In article 4.1, the Tri-Council requires that a doctor's interests in a research study—in this case, that the study was being funded by the new drug’s producer be fully disclosed to the research ethics board. The participants could also have been given information about Dr. Smith's relationship with the pharmaceutical company Genetecuticals and the nature of their financial arrangement in the consent form. Depending on the importance of a financial conflict, there can sometimes be sufficient ground for an Ethics Committee to reject a study, even when full disclosure has been made by the researcher (e.g. researcher is one of the administrator of the company whose product is being tested).

The second consent-related oversight was including consent for the pharmacogenomic add-on study and for the clinical study in the same document. These consents should have been collected separately, on two different consent forms. Health Canada urges researchers studying pharmacogenomics to obtain separate informed consent in all cases where the pharmacogenomic testing is not absolutely essential to the study. In its guidance document for pharmacogenomics: Submission of Pharmacogenomic Information, it is explained that where there is "[Pharmacogenomic] testing as a sub-study that is not linked, but may be indirectly related to the main clinical trial" consent should be sought separately from consent to the main trial, either by using separate informed consent forms or by using the same form. The participant should have the ability to decline consent to the collection of samples for research use without prejudicing their participation in the main trial.” As such, Dr. Smith should have obtained separate consents from his participants to ensure that they were comfortable with participating in both aspects of the study.

The rather broad consent to future research in the cardiovascular field sought by Dr. Smith is arguably permissible. This type of consent is progressively becoming the norm as more flexible approaches to consent for future uses are being recognized as necessary and new ethical principles such as solidarity and citizenry are starting to emerge (Knoppers, B.M. and Ruth Chadwick, "Human genetic research: emerging trends in ethics?", 6 (2005) Nature Reviews/Genetics, 75-79.). In the leading case on informed consent in the research context, Halushka v. University of Saskatchewan, Justice Hall argued that the standard owed to research subjects is even higher than that owed to patients. However, in the presented case, participation in this future research presents no additional physical dangers to the patients because the samples to be used would already have been extracted. In addition, potential psychological dangers will be greatly reduced by anonymizing (removing identifiers) the samples. Moreover, while "blanket consent" to unlimited research for an unlimited amount of time is not acceptable, the consent in this case was limited to a specific class of research, which makes its broad nature more acceptable. However, Dr. Smith could have still given the participants other options, such as the ability not to consent to future use, or consent to a more limited future use, so as to ensure that they felt comfortable with the broad nature of the future consent that was obtained and fully understood the research project(s).

Q2. Should the Dr. Smith inform his patients of the pharmacogenomic results? Consider this in terms of the value of the information for the patient, their expectations and their right to know.

A major issue in pharmacogenomics, as well as in all genetic research, is the decision of whether, when and how to report results to participants. Many considerations influence this decision. First and most importantly, these include the scientific validity and clinical usefulness of the information; and, second, patient expectations and the right to know.

It has been proposed by Fernandez and colleagues in a seminal paper (Fernandez CV, Kodish E, Weijer C. Informing study participants of research results: an ethical imperative. IRB Ethics Hum Res 2003) that the communication of research results to participant was an ethical imperative funded on the principle of respect of the persons and on the relation of trust between participants and researchers that is necessary for the success of biomedical research. This might be true in the case of general results or information about a pharmacogenomic
study. However, in the case of individual results the emerging consensus is that these results should at a minimum meet the criteria of scientific validity, clinical significance, benefit (i.e. existence of prevention or treatment) and the absence of an explicit refusal to know before being communicated (Knoppers Bartha Maria; Joly Yann; Simard Jacques; Durocher Francine The emergence of an ethical duty to disclose genetic research results: international perspectives European Journal of Human Genetics (2006) 14, 1170—1178.).

Although the present study could generate information that may seem potentially relevant to the patient, because of its exploratory nature, it should be confirmed by other studies before it is shared. The exploratory nature of the project and its small sample size make it possible that the results could be contradicted by future independent studies. Many studies have shown that small preliminary trials are often proven wrong once they are applied in a wider setting; therefore, the results from these studies must be released with caution.5

Moreover, patients in this case were explicitly told not to expect the results of their pharmacogenomic tests. This supports the decision to not inform of the results. There is a policy consensus that the method or possibility of returning results should always be described in the consent process (E.g. PGx Working Group, Elements of informed consent for pharmacogenetic research; perspective of the pharmacogenetics working group).

The exploratory nature of the pharmacogenetic research results, their low informational and clinical value, the fact that patients knew in advance not to expect the results and that disclosure would entail a controversial and potentially stigmatizing conclusion (as will be explored in the following discussion) make individual release inappropriate. As such, individual disclosure is not warranted. However, there could be an ethical duty to publish the general results of the study, or disseminate information about the progress of the research in a responsible way that reflects what has actually been proven. The failure to publish, in fact, has been characterized by many as "scientific misconduct."4

Q3. Are the ethnicity-related exploratory results relevant for publication of the study? How should they be communicated?

The type of information revealed through pharmacogenomic testing can have both positive and negative effects. For example, it may help to identify people with sensitivities to certain drugs, but, at the same time, uninformed use of such information can cause the stigmatization of individuals. As such, an important concern in all genetic studies is ensuring that sample groups are accurately described, without perpetuating the idea that the results apply uniformly to an entire group or segment of the population. Too narrow a categorization may lead to the invasion of privacy of small population groups, while too broad a categorization can lead to the erroneous equating of genetics with the social construct of race.6

While there may be genetic differences between ethnically defined population groups, there are also genetic differences within them. There are also many similarities between ethnicities. As such, over-generalization and singling out can lead to inefficient diagnostics when ethnicity alone is associated with a particular drug reaction. It has been cautioned that the perpetuation of the use of these categories "may unintentionally blunt the precision of genetic technologies and pose new threats to socially identifiable populations."7 Pharmacogenomics gives us the opportunity correct this. The promise of individualized medicine is that it can take into account the specifics of a patient, rather than generalizations based on the categories within which the patient can be classified. However, at this exploratory stage, the results of general population studies should be reported cautiously, with a mind to preventing the problems highlighted above.

In any case, race should not be perpetuated as a category of distinction in scientific analysis. As many studies have recognized, it is not socially constructed “ethnicity or race,” but rather geographical origin that may be responsible for genetic similarities among population groups. Most notable in this group of studies is the International HapMap Project, the goal of which is to develop a haplotype map of the human genome and determine distinctions in haplotype frequencies between populations.6 These studies show that the general indicators of “African” or “Japanese” are not helpful. As such, in order for the results in the presented case to be relevant and publishable, more information would be needed about the sample groups such as: where were their ancestors born? Are the participants of African descent? Of which country and which tribe? Are they of Caribbean descent? Of which islands? Do the people who reacted negatively live in similar locations or similar environments? Are they from the same socio-economic background or are they exposed to similar lifestyle factors? If no trend emerges from the answers to these questions then the categorization is irrelevant and potentially discriminatory.

However, if there was a trend in the answers to these questions upon a wider application of this study, more specific indicators that better encompass the affected group should be used when publishing the results. Good guidance can be found in the HapMap Citations guidelines.7 According to these guidelines:
It is permissible to use a short-form to describe a population subgroup, but that group must be described in detail before being reduced to a short name.

Researchers should explain the criteria for membership of a certain group (e.g., to be Japanese, four grandparents must be of Japanese descent).

While it is possible that a drug may be more effective in a particular population group, research has established that race alone is a dangerous category by which to identify people. Classifying an entire group as "poor responders" may result in an over-broad segment of the population being perceived as too expensive to treat and denied access to the most effective treatments. It can also have negative implications on the ability of members of the group to obtain insurance.

The Secretary’s Advisory Committee on Genetics, Health, and Society of the National Institutes of Health has released a document titled "Realizing the Potential of Pharmacogenomics: Opportunities and Challenges." This document suggests that when a researcher believes he/she has found a correlation between a population group and a drug, further research into genetic and biological factors should be conducted to see if these account for the differences. The document also suggests performing the research in other population groups to see if a similar response can be identified, which would lead to the conclusion that racial factors are not the cause of the reaction. Finally, upon the discovery of a correlation between race and drug response, additional research into biological, social, behavioural and environmental markers should be undertaken to see if these may account for the variation in response.

References

3. Halushka v. University of Saskatchewan et al. 53 DLR (2d) 436 (Sask. CA) 1965.

Further Reading

Resources

For additional and updated laws and policies, consult: www.humgen.umontreal.ca

Secondary Articles


For answers to FAQs (frequently asked questions) about pharmacogenetics, and information about the ethical, legal and social issues it raises, consult: www.humgen.umontreal.ca.

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