Human Genomics Research

new challenges for research ethics

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The 1975 Asilomar Conference dealt with two different kinds of threat: a threat to human safety and, implicitly, a threat to the independence of scientists. The moratorium it called on some kinds of research with recombinant DNA made it possible for the safety of such research to be more thoroughly investigated. It also made it possible for biologists to present themselves as worthy of public trust. Both results were important to the future of research in molecular biology.

Today, a branch of science whose tools descend, in large part, from that recombinant DNA research faces a similar double threat. Research into human genetics has stretched current regulations of human subjects research beyond the breaking point. In the context of this kind of research, those regulations, while they largely protect the *safety* of human subjects, no longer protect their *interests*. And, as a result, research conducted under those regulations risks violating the public's trust and thus imperiling future studies in human genetics.

Problems in human subjects protections arise in two different contexts. One set of special problems concerns research conducted with "groups" of people, groups that have a pre-existing cultural significance. The second set concerns a broader type of research that seeks associations between genetic variations and human health in large populations through the development of vast databases of phenotypic and genotypic information. Each type of research, as currently regulated, risks leaving its human subjects feeling cheated and embittered.

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RESEARCH WITH CULTURALLY-DEFINED GROUPS

The issue of "group" or "community" concerns in genetics research stems from one common approach to human genetics research. Researchers identify a somewhat discrete human population that has a higher than average incidence of a disease or condition thought to be linked to genetic variation. The higher incidence in the population might make the genetic links easier to find—as may the likely greater similarities in the group's environment, broadly defined. Thus are born studies of schizophrenia among the Old Order Amish, non-insulin dependent diabetes mellitus among the Pima, or asthma on Tristan da Cuhna. Similarly, those interested in using patterns of genetic variation as evidence of the history of populations will examine genetic markers from individuals from different ethnic or cultural groups. These two kinds of group-based research lead to publications about "diabetes among the Pima" or the "ancestry of the Han." And therein lies the problem.

Genetics research on groups that are, or are perceived as being, closely genetically connected has implications for all members of those groups, whether or not they decided—or even were asked—to take part in the research. Sometimes, those implications might be positive, such as when a good medical intervention is found to aid the health of the group. Other times, the results may be negative, leading to stigmatization of or discrimination against the group involved—or to a change in the group's culture through contradiction of the group's own historical knowledge. Most of the time, the research will have little effect, one way or the other. But, whatever the effects, they will land on many group members who did not give their informed consent after weighing the foreseeable benefits and risks.

This issue was first confronted directly in the context of the Human Genome Diversity Project. The North American Regional Committee of that Project opted in its Model Ethical Protocol for the Collection of DNA to require, when feasible, the consent of the "group" to such group research (North American Regional Committee 1997; Greely 1997a; Greely 1997b). The resulting discussion of how to protect the interests of groups or communities in research has now spawned a substantial and growing literature (Weijer et al. 1999), some of it in favor of some kind of group consultation or consent (Foster et al. 1997; Foster et al. 1998; Foster et al. 1999; Sharp 2000; Freeman, 1998) and some of it in opposition (National Research Council 1997; Juengst 1998a; Juengst 1998b; Reilly 1998; Reilly and Page 1998).

There are, certainly, some serious problems in implementing group consent ideas. The problems of defining the group membership and then determining who can legitimately give consent on its behalf are often difficult. There are ways to deal with these difficulties (North American Regional Committee 1997; Sharp and Foster 2000), but in some cases they may be intractable. The existing regulation of human subjects research in the United States does not require any such process (National Bioethics Advisory Commission 1999), but the reasons

for trying, even imperfectly, are compelling. Ethically, the post-war consensus—from Nuremberg to Helsinki to the Common Rule—is that, to the greatest extent possible, people should not be exposed to the risks of human subjects research without their informed consent. When an entire group is so exposed, it would seem to follow that, where possible, the entire group should give its informed consent. Pragmatically, a population that finds, to its dismay, that aspects of its genetic heritage have been published without its knowledge or consent may be extremely unwilling to participate in research again. This may be particularly true when the research leads not just to publications, but to patents and products. The risk of embittering the population is great and should be avoided through whatever form of consultation or consent is practicable under the circumstances. The regulation of human subjects research must be changed to take these group concerns into account.

GENOTYPE/PHENOTYPE RESOURCES

A newer style of research poses broader problems for the reigning method of human subjects regulation. Particularly when common (and usually genetically complex) diseases are involved, researchers increasingly are exploring "associational studies." These studies correlate detailed phenotypic data on large populations with detailed genotypes of the same subjects, looking for associations between health variables and genetic markers. The tool to do this kind of research is a vast "genotype/phenotype resource," a database containing medical and genetic information on hundreds of thousands, even millions, of individuals. Unlike people in families with a high burden of genetic disease, the subjects of these resources will not necessarily have any personal connection to the studied disease; they will be, largely, a sample of the general population.

Genotype/phenotype resources will be difficult and expensive to assemble. Because of the expense, it seems likely that their use will not be limited to specific conditions or disease. In the most public effort at creating a genotype/ phenotype resource, deCODE Genetics, a private firm, is making a controversial attempt to construct such a resource using the entire 275,000 person population of Iceland (Greely 2000; decode; Mannvernd). deCODE's Icelandic resource is only the first and the most public such effort. The creation of similar resources is being planned for populations in places such as Estonia, Newfoundland, the United Kingdom, and Framingham, Massachusetts (Frank 1999; Greenwood 2000; Hagmann 2000; Kolata 2000b).

This approach to genetics research, which faster and cheaper genotyping and computer tools are making increasingly feasible, raises new questions for the regulation of human subjects research in at least four ways: consent, control, return of information, and commercialization (Greely 1998; Greely 1999). Those questions are now beginning to affect Icelanders; they may, without our knowledge, already be affecting many other people. For example, under at least some inter-

pretations of current American regulations, any American's medical information and genetic samples might be the subject of such an existing effort as long as they are not "personally identifiable." Ask yourself, when reading the discussion below, how *you* would feel about being a research subject under these circumstances. The question may not be hypothetical.

CONSENT

Medical research on human subjects generally proceeds only with the informed consent of those subjects. Obtaining this consent can be difficult, time-consuming, and expensive. And particularly where the research and its implications are very technical, whether the consent is meaningful often can be questioned. But since at least the end of World War II and the Nuremberg trials of Nazi researchers, medical research has generally stressed the importance of explaining the risks and benefits of the research to potential subjects, and proceeding only with their affirmative permission. This concept is enshrined in the Helsinki Declaration of the World Medical Association and in the laws or regulations of many nations, including the United States.

In December 1998, the Icelandic parliament passed the Law on a Health Sector Database, which allows a private licensee (deCODE) to create a database including the medical records of all Icelanders—one big step toward deCODE's genotype/phenotype resource—without requiring this affirmative informed consent (Law on a Health Sector Database 1998). Instead, under this statute Icelanders' consent will be presumed unless they file a special form with the government. Minor or incompetent Icelanders will be covered unless their parents or guardians object on their behalf; the medical records of dead Icelanders will go into the database. And in May 2000, the Icelandic parliament extended this kind of presumed consent from medical records to human blood and tissues. In its "Biobanks Law," Iceland allows the use of clinical medical samples for non-anonymous research use as long as the clinic had written information on this presumed consent "available" and the patient did not object (Act on Biobanks 2000).

The Icelandic procedure lacks both elements of informed consent: the explanation to the prospective subject of the specific risks and benefits of the research and that person's affirmative agreement to proceed. At the same time, the Icelandic plan does not require any physically dangerous intervention with the patient—just the research use of her medical records and, ultimately, of her DNA. Defenders of deCODE's plan see it as similar to the kind of epidemiological research that is commonly done without informed consent when the data involved has been stripped of personally identifying information. And, if the medical records cannot, in fact, be identified with individuals (a question in dispute in Iceland), any potential *tangible* harm to the research subject is hard to identify (Greely 2000). But that is not the only kind of harm. It is, I believe, a harm if people who did not agree to be research subjects are unhappy to learn that their

medical records—and their genomes—have been used for research, research of which they might, or might not, approve.[1] If so, one should not dispense with affirmative informed consent without compelling reasons.

CONTROL

The issue of control is separate from, though tied to, the issue of consent. It involves who can get access to a subject's information and for what purposes. In the traditional model of human subjects research, a researcher solicits the participation of a subject for a specific research project, to be done by that researcher and her colleagues. With genotype/phenotype resources, the information might be used for research on any imaginable medical or genetic question and will likely be available for use by a wide range of researchers. Subjects might be willing to participate in studies of the genetics of diabetes, but may be unhappy about their information being used in studies of the genetics of alcoholism, mental illness, sexual preference, or intelligence. Similarly, subjects might trust a particular researcher with their information and materials, but may feel no trust toward other researchers, far removed in space (and perhaps in time), whom they have never met.

The costs of creating genotype/phenotype resources for associational genetics research may make it impractical to create resources that are used for a single kind of research or by a single research lab. The researchers' financial constraints, though, do not resolve the question of the subjects' interests or expectations. When multiple uses or users are to be involved, what kinds of control should individual subjects be able to be impose? Or what warnings should they receive, in advance, as part of their informed consent, about the possible lack of controls on the use of their information and materials?

RETURN OF INFORMATION

Return of information is another controversial area and perhaps the most difficult. What if a researcher, analyzing a subject's medical records or DNA, discovers something that would be of interest to that subject? The discovery might involve the subject's personal past—such as paternity questions—or it might concern the subject's medical future—such as a high risk of a specific disease. If the information is about the medical future, there might be a useful medical intervention, even one that could be lifesaving. On the other hand, researchers often will be probing the edges of medical knowledge, where giving subjects

[1]In the case of Iceland, one might argue that those who did not bother to fill out and mail an "opt-out" form (albeit without the individual discussion of risks and benefits that is part of informed consent) cannot complain, but that still leaves those whose guardians did not fill the form and those who did fill out the form—and then died.

information about new or still speculative disease associations could do great harm. Researchers also often will not be set up to provide clinical genetic testing. Their research labs may not work to the regulated standards of clinical laboratories; they may not be able to provide their subjects with access to skilled genetic counselors. What obligations, if any, do researchers have to return information to their subjects in such cases?

In the United States, researchers are generally given the choice of telling their research subjects, as part of the informed consent process, that they will, will not, or might if they choose return information to them. Often they choose to tell subjects that they will not return any information. This option is the most convenient, logistically and legally, for the researchers' institutions. It may not be the most comfortable for individual researchers if they find out something of medical importance to a research subject. What would research subjects—and their families—think? Imagine if a research subject, or his grieving family, learns that a research team had information that might have prevented a fatal illness but did not reveal it. Bitterness—and litigation—seems not only possible but likely.

COMMERCIALIZATION

Finally, commercialization raises concerns. In the past, research into genetics and disease has often, though not always, involved academic researchers studying people from families with a high rate of the disease. Research subjects could presume that academic researchers were motivated largely by the pursuit of knowledge and the alleviation of human suffering; the research subjects were motivated not just by altruism but by the hope of lifting a curse from their own families. This stereotype is, of course, an exaggeration. Researchers have always been motivated in part by the drive for academic tenure, the next grant, and the Nobel prize; research subjects may have been tempted in part by small payments or benefits given them as part of the research—or by desperation in the face of untreatable disease. And connections between academic research and pharmaceutical firms are by no means new.

However inaccurate the old stereotype, the genotype/phenotype resources completely explode it. The resources will often be created, as in Iceland, by commercial firms; they will inevitably be used for commercial ends. The research subjects will be a cross-section of the population, with no special interest in any particular disease to motivate them to participate in the project. These differences certainly do not, in themselves, make this kind of research wrong. If research is to result in effective drugs, medical devices, or other treatments, commerce will almost inevitably be involved. And many people would likely be willing to take part in research in the general hope of alleviating human suffering. But the differences may change the calculations, at least for some potential subjects. Some might ask why, if a company is planning to make billions of dollars from the research, they should participate for free (Kolata 2000a). Others may

not reach that conclusion but may still want to know whether commercial interests are involved.

Fair treatment of prospective research subjects should require, at the least, discussion of whether the research involves, directly or indirectly, commercial interests. Individuals should be able to take that information into account in making their decision whether to participate. One could also argue that commercial benefits should be shared, in some manner, with the group of people who took part in the research—and thereby made the commercial benefits possible. That might not be through a (probably minuscule) cash royalty to each participant; it could be through benefits that affect the subjects as a group—such as improvements in their hospital or health care system or community facilities. The combination of the more intimate connections of commercial interests to the research and the more distant personal connections of the research subjects to the research requires rethinking both the process and the substance of the relationship between researchers and research subjects.

Imagine that you discover that, without your knowledge or consent, your HMO—or hospital or physician group or government health care system—has allowed your medical records and DNA samples to be used in research by many different researchers on many different topics. Some of the research topics you think are important; others you know nothing about; some appall you. Furthermore, you learn that four years ago, the researchers could tell that you were at high risk for the colon cancer that was diagnosed last month, and furthermore, that the research using information and materials from your group has enabled a pharmaceutical company to come up with a treatment for diabetes that it estimates will bring over $10 billion in profits over its patent life. Ask yourself how these revelations would make you feel about participating in, or politically supporting, medical research. The abuse of African-American research subjects in the notorious Tuskegee study still has consequences for black participation in and support of medical research (Jones 1993). These new ethical issues in the fair treatment of the human subjects of genetic research, though much less serious than the deadly consequences of Tuskegee, *are* important—both to prospective research subjects, which now means all of us, and, in long run, to the health of human subjects research itself.

CONCLUSION

In 1975, researchers—and outsiders—feared that recombinant DNA technology could unleash great safety hazards on the world. And researchers worried that the fear of such hazards, even if the dangers turned out to be insubstantial, could lead to political restrictions on their use of recombinant DNA. Asilomar 1975 was the result—a result that not only produces justified pride in those who were there but that advanced the interests of both science and society. Twenty-five years later, less concrete and perhaps less dramatic risks beset human genetics research,

risks to the interests and rights of human subjects. Through an Asilomar process or otherwise, we need to act to limit those risks—for the sake of the science as well as for the sake of human subjects.

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