THE HUMAN GENOME PROJECT AS SOCIAL POLICY: IMPLICATIONS FOR CLINICAL MEDICINE*

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PLANS FOR THE HUMAN GENOME PROJECT to spend 3% to 5% of its budget on ethics, law, and social policy have been widely heralded. I have argued in the past that this amount doesn't show much respect for ethics, law, and public policy. On the other hand, its more than any other institute or center at NIH spends on these aspects, and one should perhaps take this as a sign of the times. Maybe more good things are coming in this direction. Our program today is obviously devoting a lot more than 3% to 5% of its time to law, ethics, and social policy—about half of it. The next four speakers will discuss these subjects, so this is hardly the forum to complain about the position of these issues in the hierarchy of science. The next four speakers will be addressing the human genome as social policy. My perspective will be clinical: the genome project's impact on clinical medicine. I am a lawyer, not a physician, but I have spent the last 20 years in the field of legal medicine and bioethics, with a special interest in clinical genetics and human experimentation. My colleague, Sherman Elias, and I also hosted NIH's first extramural workshop on law, ethics, and social policy related to the Human Genome Project; it was funded by the Genome Center and held in Bethesda this January. So I have given these issues some thought.

Before I summarize the major issues in clinical genetics, let me make a small comment about budget issues. It is true that $200 million a year is not a great deal compared to the entire NIH budget or compared to the gross national product. Nonetheless, as you may know, Congress recently held a debate about how much money we should spend to try to decrease the infant mortality rate in the United States from its third world characteristics in many

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of our large cities (including New York and Boston) to a much more reasonable number. The Bush administration (not one to give out much domestic money) has recommended $54 million for that project to target 10 cities. They were going to take that from existing programs and move it over. Congress was able to come up with $25 million in new money. That is 10% of one year of the genome project. Had we voted genome project versus infant mortality, infant mortality would win. But, as many people have pointed out, that is not the way we do budgeting in the United States. Probably the most important ethical issue is, where do we spend our money now? Can we really continue to develop new medical techniques that we know most people are not going to get access to, that are only going to benefit the richer people in our society, at a time when we don't give basic medical care to a large segment of our population? That is the premiere ethical issue in health care today. It will not arise in the genome project, but it should at least be mentioned at the outset of any serious discussion of ethical and social policy issues.

In the United States much of our budgeting is driven by hype and by advertising. In fact, most policy in the United States is driven by hype and advertising. This includes decisions to go to war and the way we look at war. We won the war with Iraq, and it is over even though the devastation continues in Iraq. It is not something we're interested in any more, although we do continue to use war images in contemporary advertising in the United States. Physicians are not immune from this; physicians used to advertise smoking and promote smoking in the United States. Currently smoking is being promoted by advertising based on military images.

In the human genome project, hype has been the order of the day. Today, however, most of the speakers have tried to pull back and say that Watson and Lander and other people who have talked about the "book of man" and the "holy grail" of biology, as well as the cornucopia of products that are going to come from the genome project, have overstated the case. We shouldn't look for a new harvest of genetically engineered species and we shouldn't necessarily believe, as James Watson has said, that "We used to think our fate was in our stars but now we know our fate is in our genes." We shouldn't look at the genome project as producing a new Garden of Eden where human beings are much better off than they are now. If I were to propose the first principle of medical ethics as applied to the human genome project it would be: Never believe your own advertising.

So let us look at the ethical issues in human genetics, what may be termed the "dark side" of the human genome project. At the January genome workshop Robert Procter was the only one of the 24 invited speakers who men-

tioned military applications of the human genome project, and his suggestion was greeted with horror. No one at that workshop wanted to talk about that. They thought it was out of bounds and that it should not be mentioned, even though the Department of Energy is heavily involved in the project. I do not think that it is out of bounds. I think this may be one of the most critical issues in the human genome project because, as we have just seen in Desert Storm, ethical principles can quickly be ignored in the name of national expediency.

The Nuremberg Code is perhaps our primary set of principles in bioethics. The primary principle in the Nuremberg Code is no human experimentation without informed consent. No government in the world since 1947 has said publicly that they would do research or use experimental drugs on competent adults without their consent. Yet one of the first things the United States military did in Desert Shield was seek and obtain from the FDA a waiver to use experimental drugs and vaccines on our troops in the Gulf without their consent. The justification was that consent was "not feasible" in this potential combat situation. One of the investigational agents used under this waiver was botulism vaccine. In the aftermath, there is no evidence (maybe there is some that we do not know about, but the Pentagon and the CIA have supplied no evidence) that Saddam Hussein even had botulism to use as a weapon and, if so, whether or not the vaccine would have had any effect on that and, finally, what effect that vaccine has had on our soldiers. So, even though we talk a good line about ethics, we should realize that expediency easily trumps ethics. Even if we develop some wonderful principles about the genome it is unlikely that they will be followed if we believe it expedient not to follow them.

I shall review three areas in clinical genetics where the genome project will have an impact. But the first and most important point I want to make is that it is not the human genome project that produced these problems. The genome project may make them more immediate and critical by providing us more products that can be used in clinical medicine, but it did not create these basic problems.

It may in fact be true, as Norton Zinder has argued, that the genome project is not skewing molecular biology research. It is not true, however, that the genome project is not skewing bioethics research. At 3% of the budget, funding could be $90 million over 15 years. This is more money than has ever been spent on bioethics in the United States. And even the annual budget right now is more money than is being spent on all the other bioethical issues put together. So if you want to talk about distortion of activities, one likely distortion is in the area of bioethics. On the other hand, the genome project

raises almost all of the fundamental issues in bioethics. So in one sense bioethicists could take advantage of the money that is available (just as many researchers did with cancer) and say, "What we're really doing is genome research. We thought we were working on the doctor/patient relationship, or on informed consent, or on autonomy, or confidentiality, but really we were working on the human genome project." Similarly, the three areas that I shall review are areas of traditional, bioethical, and health law concern: Our view of health and disease, ethical and legal problems in screening and counseling for genetic disease, and ethical and legal issues in human experimentation involved in somatic cell and germline gene therapy.

The general notion of health and disease and the role of genetics is worth commenting on because of the metaphor that is used by the human genome project: mapping on a Vesalian Model. The analogy is that when Vesalius mapped the anatomy of the human body, his "map" helped us to understand human beings better and that mapping the genome will likewise help us to understand humans better. But one point Vesalius made strikingly clear is that he saw human beings as full-figured bodies in command of the world. His was a human being as an entire person, never to be seen as a reductionist view of humanity. We hear the term reductionism in the human genome project all of the time, the idea that somehow we can reduce humans down to their genes, and that would really mean that humans are a package of genes. It is very interesting that the illustrator of the cover of an issue of *Science* devoted to the human genome project could not buy this. He put Vesalius' man in front of the genomic bar graph to emphasize that a nonreductionist view of humans is necessary. Human beings are more than merely a collection of their genes, and it is dangerous to see them as such, because when we see them as a mere collection of genes we start thinking that we can do things to human beings that we would not otherwise do.

This is a major policy question: How do we view genetics versus the environment? We have had one occasion for the editor of *Science* to write that he thought the human genome project would help to solve homelessness and another that it could decrease our crime problem. It is very seductive to legislators and Congress to think that here is a cheap fix to homelessness and crime. We do not have to build houses or try to provide alternative economic opportunities to our youth; we can just work on the genome project and say that we are trying to solve homelessness and crime. So the first central issue is whether or not a concentration on genetics will lead our society to undervalue the influence of the environment and to overvalue the influence of genetics.

The second issue gets us more directly into clinical genetics, the issue of

genetic screening and counseling. This usually takes place at different points in the life cycle: prenatal counseling and screening, neonatal counseling and screening, and the adult counseling and screening. In terms of screening the neonate we can move backward from amniocentesis to chorionic villus sampling, to early first trimester diagnosis, and to preimplantation embryo diagnosis (and perhaps treatment in the future).

The cystic fibrosis area of the gene was not found by the human genome project. Nonetheless it helps us to focus the issues as to when prenatal genetic screening should be offered, who it should be offered to, who should pay for it, and what decisions should be made as a result of it. The human genome project has been asked to fund the pilot project on cystic fibrosis screening and apparently will fund at least a part of it. Rightfully so, because it does set up a paradigm for trying to answer the social policy issues about the medical standard of care: When should we make a genetic screening test available? And what information should prospective screenees be given? Cystic fibrosis is especially problematic since the only intervention for a fetus right now is abortion. But there is a possibility of a cure for cystic fibrosis in the next decade or two. How should this possibility influence a woman's decision about whether to abort a child with cystic fibrosis? Is a treatable condition still a disease for which abortion is a reasonable intervention?

Should prenatal cystic fibrosis screening be available to every woman in the United States, as has been suggested by many? The cost is not trivial. Assuming half of the pregnant women in the United States got this test at a cost of $100, it would cost $200 million a year—the entire genome budget. So it is not the money that is spent on building the human genome's infrastructure that should have us thinking, but the money that will be spent on each and every test that comes out of the human genome project. Again, the question is should we be putting our money in developing tests that only relatively well-to-do individuals can take advantage of?

The ultimate issue, of course, is who we screen, when we screen them, what we screen for, and who makes the decision about what to do with the information that is gained by screening? It is all very well to say (and absolutely right) that only the pregnant woman should make the prenatal decision, and that only she should have access to the information (unless she agrees to have it shared with other people). On the other hand, it would be very difficult, if not impossible, to keep this type of information secret. The Office of Technology Assessment said this about genetic screening, "Human mating that proceeds without the use of genetic data about the risks of transmitting diseases will produce greater mortality and medical costs than if carriers

of potential deleterious genes are alerted to their status and encouraged to mate with non-carriers or to use artificial insemination or other reproductive strategies.''

I think we miss the point by talking about a ''brave new world'' where government imposes genetic screening and testing by law on its population. For our country, it will not need to be imposed at all. It will be advertised, and subsequently demanded by people as their right. It will not have to be imposed. People are already demanding screening and counseling as their right, and it will quickly be seen as something that individuals have a right to. In terms of neonatal screening, our history with phenylketonuria and other screening tests is that we tend to make it mandatory nevertheless. We do not permit couples to decide whether or not to have their newborns screened. Rather if any treatment or intervention can be used to help the child, the screening decision is made by the government.

James Watson has used what I think is not a useful example in an interview with the *Journal of the American Medical Association*. He said that he wished that he could have been genetically screened when he was a baby so that his parents would have known that he was susceptible to skin cancer because they could have kept him out of the sun. That raises a whole host of issues. Do we screen all neonates at birth for susceptibilities to cancer? If so, are parents then obligated to keep children like James Watson out of the sun? Do we need a ''beach patrol'' to check to see that parents had applied the proper amount of suntan lotion to their child? Do we need a genetic identification card that can get you into the beach in the first place? Just last week we had a case in Seattle where two waiters were fired for trying to badger a pregnant woman into not taking a drink of alcohol on the basis that this might injure her fetus. Must we have a genetic identification card to take into the bar as well to see whether or not you have an alcoholism predisposing gene if we ever find that there is such a gene? These are major social policy issues that have not even been properly framed for discussion yet. But we know some things. We have a very broad view of child neglect and child abuse in this country, and it is not very farfetched to think that just as parents must now put their children in seat belts, they will also have to keep them from being exposed to environmental hazards that might trigger a gene that they carry, one that predisposes them to cancer, for example.

As for adults, we can ask whether we're going to screen adults for presymptomatic diseases the same way we might screen children. Adults always think they should be able to make their own decisions about whether or not they are exposed to certain carcinogens or teratogens or mutagens. And

Johnson Controls, a decision by the United States Supreme Court just last week, certainly makes it clear that as a matter of law in the United States, it is the pregnant woman, not the employer, who should decide whether or not she continues to work in a potentially hazardous environment. How long can we really maintain that position? How long are we likely to continue to say that individuals get to make their own choices when those choices seem to us to be wrong, just as the choice of the pregnant woman seemed to be wrong to the waiters in Seattle?

For clinicians at our January workshop, the major issue was not so much the global issue of how we view genetics and genes in terms of our humanness, but when is it legally required for them to offer genetic screening tests to a patient. This is understandable because they worry that they might be sued for not offering such a test should the child be born with a genetic disease or defect. And here both the Ethical, Legal and Social Policy Working Group and our workshop agreed that perhaps the most pressing legal and ethical problem in clinical genetics today is just that question: When should a new genetic test be offered as a matter of standard care to a patient? It is a very difficult question.

In the past 10 years we have seen a number of tests introduced into clinical practice on the basis of one law suit. Other tests have been introduced because of the over-reaction of a professional organization that thought that its members might get sued if they didn't offer maternal serum alphafetoprotein screening, for example, to all pregnant women. I would not say that we are in chaos right now, but we are in a situation where there is no clear answer to this question, and without very heavy duty professional association guidelines with major public input, that individual courts will still continue to set the standard of care based on individual law suits by default.

It is now possible to counsel and to screen people for only a handful of specific genetic diseases. But once we get dozens or hundreds of genetic conditions that people can be screened for it will then become impossible, literally, to get informed consent for each one and to do meaningful counseling for each one prior to screening. The question will then be whether one can develop some kind of "generic" genetic screening and counseling. For example, would we tell a person, "We're going to screen you for 150 or 200 diseases. We do not think you have any of them, but if you do, then we shall come back if we find any and then we shall talk to you again." Something like this seems likely. Again, we haven't really started to think very much about this predictable future scenario. Screening and counseling issues are still very

primitive on all three major points when they are now done, prenatal, neonatal, and adult.

Finally, let me just say a few words about therapy, since we all say that the ultimate goal of all this research is to develop new human health and disease insights that could, hopefully, lead to treatment. We hate to think that we are just developing new reasons to abort fetuses, or that we are just developing new ways to tell people that they are diseased, but they can't do anything about it or new ways to tell people that someday they are likely to get a disease, but there's nothing that can be done to prevent it. We like to think, and I think this is the belief of most scientists, that someday we shall be able to treat some of these genetic diseases.

The long debate about somatic cell gene experimentation and therapy in the United States is more or less resolved. The model that is being used is, I think appropriately so, the general model of treating any illness. Treating an illness at the somatic cell level is seen as substantially the same as giving a drug, or at least like transplantation. On the other hand, there is no doubt that this new method is still highly experimental, only having been used, I think, on four humans so far. Nonetheless, it is being widely advertised and touted. In a long article in the *New York Times* magazine yesterday, French Anderson made a remarkable statement. He said that he is just proceeding by trial and error, and we shall know in six or eight years whether it was ethical to start somatic cell therapy now. That, of course, is wrong. It is ethical to start now based on prior work, based on what we know of the potential risks and benefits and the subject's informed consent. Human experimentation cannot ethically or legally proceed on the basis simply of possible success. That is not the way we judge the ethics of experimentation, and Dr. Anderson knows this (he may have been quoted out of context). The key is again to resolve the ethical and legal issues *in advance*. An experiment is ethical or not at the time that it is performed, not in retrospect.

Even though somatic cell experimentation is well accepted in the bioethical community, germ-line gene experimentation remains very, very contentious, and for reasons that are not entirely clear. Usually people refer to the Nazis, who obviously didn't do germ-line gene experiments and never thought about it. But there are some issues here. Germ-line gene therapy is likely only to be done on embryos, and here the primary justification is efficiency. We would like to do germ-line gene therapy to remove a deleterious gene for both the carriers and their children. On the other hand, unless we treat embryos as children, the much more efficient thing to do is simply to discard embryos

that are genetically diseased. It is essentially pointless to try to correct a defect in an embryo. Secondly, if one really did believe embryos were children, one would be hard pressed to justify this type of gross human experimentation on this "child" without its consent. So there is not much of an argument for doing germ-line gene therapy on embryos to correct diseases.

On the other hand, even though people like to make the argument that we are not going to enhance characteristics, that is the only thing that makes any sense to do with the embryos. To make a bigger mouse, a smarter kid, a bigger kid, or whatever. We say that we're not going to do that because we can draw the line between disease and enhancement. I would like someone to show me that line. That line is probably impossible to draw if we go into the area of germ-line gene therapy. It thus seems to me that the major danger we run is the possibility of creating not an underclass, but an overclass. The rich will not only be richer than you and I, they will be the ones who will be able to take advantage of germ-line gene therapy to engineer their kids in ways we haven't thought of yet.

In conclusion and summary, let me say that my guess is that, as with Apollo, in which the main product turned out to be the photograph of the earth and the beginning of environmental awareness on this planet, we may not yet know what the main product of the human genome project will be. On the other hand, I think that it is worthwhile to look at the ethical, social policy issues here and try to decide what we want Americans and American families to look like in the next century, all the while remembering that we are in America, that we are likely to follow American values. Sometimes we have a hard time remembering what they are, but justice and equality have always been major American values which we haven't so much shared in the health care field. In addition, autonomy and respect for individual choice (self-determination), although it is under tremendous attack by the new genetics, must, I think, remain the cornerstones of clinical genetic medicine. The challenge is real, and dedicated funding for ethical, legal, and social issues, as well as meaningful public debate is a necessary, though not sufficient, component of the human genome project in America.

NOTE

For a much more detailed discussion of these issues, as well as supporting citations to the medical, legal, and ethical literature, see Annas, G.J. and Elias, S., editors: *Gene Mapping: Using Law and Ethics as Guides*. New York, Oxford University Press, 1992.