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Elizabeth J. Thompson M.S., R.N.

ETHICAL, LEGAL AND SOCIAL IMPLICATIONS OF THE HUMAN GENOME PROJECT

*Elizabeth J. Thomson, M.S., R.N.**

I would like to take this opportunity to thank you all for inviting me to join you. I want to especially thank Bruce Cooper and Deb Ryerson for their patience in trying to reach me by telephone.

My presentation today is designed to present information about the ethical, legal and social implications arising as the Human Genome Project moves forward, and I am going to start out with my first slide.

The human genome initiative is a worldwide research effort with the goal of analyzing the structure and chemical makeup of human DNA and determining the location of the estimated 100,000 genes in the human genome. Those 50 to 100,000 genes it is believed, are made up of three billion pairs.

The U.S. Human Genome Project (HGP) is an international effort, directed jointly in the United States by the National Institutes of Health and the Department of Energy. The goal of the HGP is that this project will be completed certainly within our lifetime and sometime around the year 2005.

The information generated by the Human Genome Project is expected to provide the source book for biomedical science in the Twenty First Century. It will have a profound impact and expedite progress in a variety of biological fields.

Within a few years, information about DNA sequences will undoubtedly be a major tool in most areas of basic and applied biological research. The Human Genome Project is also expected to immensely benefit medical science. It will improve the understanding of human development and also human diseases in which genes play a role, and hopefully will eventually lead to treatments of many of the thousands of genetic disorders that currently affect humankind.

The scientific goals of the HGP are, first of all, mapping and sequencing the entire human genome. By mapping we are talking about identifying the location of each of those some 100,000 genes; and sequencing, that is determining the makeup for the entire gene sequence.

The second goal is to make and sequence a number of model organisms. Those include at least the mouse, drosophila, and *C. Elegans*. These model organisms were chosen for a variety of reasons. Certainly one of the main reasons they were chosen was that they, may, provide a model for the study of some human genetic disorders.

The third goal of the HGP is the development of computerized data collection, storage and handling. There are literally hundreds of researchers around the world that are working on the HGP, these researchers are charged with releasing their data as early as possible and working together so that the data is available to share with other scientists. The tools need to be developed to collect, manage and store the data that is now being generated.

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*Diploma, St. Luke's Hospital School of Nursing, 1971; B.S., Coe College, 1975; M.S., University of Iowa, 1983.

The fourth goal of the HGP is related to the ethical, legal and social issues related to the HGP. It is in that branch that I am currently working.

The fifth goal is to provide research, training, and to develop a cadre of researchers who are trained in the area of genome and genetic sciences. The sixth goal is technology development and transfer.

Early in the planning stages of the U.S. Human Genome Project, it became clear that mapping and sequencing the human genome would have profound implications for the diagnosis and treatment of human genetic diseases. Although it was believed that initially the Human Genome Project and its products would produce information that would lead to the detection and diagnosis of genetic disorders. The longer range goal was to go beyond detection, to provide improved understanding, treatment, prevention, and hopefully a cure for these disorders.

The interim phase, however, the phase in which detection is possible and treatment is unavailable, was identified as the period in which a number of deleterious consequences may occur.

As a result, the Ethical, Legal and Social Implications (ELSI) program was established as an integral part of the U.S. Human Genome Project. This program was identified as a necessary and critical component of this project.

The ELSI initiative was viewed as a novel approach, that is, a project designed so that the ethical, legal and social issues are being studied at the same time that the basic biological research was being carried out. It was agreed from the beginning that about five percent of the total U.S. budget would be set aside and devoted to studying these issues.

Before I go on and talk about some of the developing applications for these technologies, I would like to briefly touch on the goals of the ELSI program as set forth some four years ago.

The original goals of the ELSI program were, first to anticipate and address the implications for individuals in society of mapping and sequencing the human genome; second, to examine the ethical, legal and social consequences of human genome mapping and sequencing; third, to stimulate public discussion of these issues; and , fourth, to develop policy options that would assure that the information is used for the benefit of individuals and society.

My understanding from my basic science colleagues is that we, in fact, are ahead of schedule in mapping, locating the genes and that we are not ahead of schedule in terms of sequencing the genes. I, of course, believe that when the genes are all mapped and sequenced, we will still have a great deal of work yet to be done in the areas of ethical, legal and social implications.

Now, how are some of these technologies actually being applied in human populations? I have identified six areas in which some of these technologies are now being utilized.

First of all, the technologies are being used in the form of "carrier" identification. One example of "carrier" testing is testing for individuals who have a single cystic fibrosis (CF) mutation. The ELSI program has spent a substantial percentage of its budget for the last three years studying issues surrounding testing and counseling for CF mutations.

For a long time, it was thought that if you examined an individual's genes and they were normal, they were going to look like everybody else's genes that were normal. Some

time back we learned that, that wasn't the case. In fact, we learned that normal genes looked different in different people. The same sort of thing is true in genes that aren't functioning. Genes that aren't working properly, altered genes, have also been found to have different mutations even though they cause a clinically similar disease; we suspected that altered genes would look the same as well.

The cystic fibrosis story has been a really interesting one. The CF gene was actually discovered in 1989. It was found to be 250,000 DNA letters in length. CF is one of the most common recessive genetic disorders in the United States affecting, well, a mutation is present in about one in twenty-five Caucasians. Right around 1989-1990, if you look at the medical literature, you'll see a number of policy statements about CF testing; one by the American Society of Human Genetics in conjunction with an NIH workshop; one by the American College of Obstetrics and Gynecology; and one by the American Medical Association.

If you look at those early statements, everybody thought that we have come to a point where we identified a mutation for a disorder that affected a substantial number of people in our population. Many people thought from gene discovery we would be moving fairly quickly toward "carrier" identification programs, so that people would be able to find out if they were that one in twenty-five people who carried the gene, and thus have the opportunity to make reproductive decisions based on having access to that information.

Since its discovery, the CF story has gotten more complicated. Presently, there are somewhere around 350 different mutations that have been identified that are associated with cystic fibrosis.

So even with those 350 different mutations identified. We still can only account for somewhere between ninety and perhaps ninety-three percent of people who have what we have known to be cystic fibrosis.

So we still have people who clinically have cystic fibrosis who apparently have genetic changes that we not yet been identified. It's certainly likely that there will be other mutations found in that gene, but, in fact, there may be other genes that result in a disease that we've in the past clinically called cystic fibrosis.

In 1991, we actually started funding a series of eight studies to look at issues surrounding testing and counseling for CF mutations. At that time, there were a lot of unanswered questions. How could these CF testing services be delivered in an organized and meaningful way, in a way that people could become informed, consent to testing if desired and understand the meaning of their results?

Genetic testing is complex. The results are not easy to understand. Taking a blood sample or scraping a few cells from the inside of your mouth is the easy part. Doing the test, interpreting the results, and helping people to understand the results are the hard parts.

As a result of some of our studies, we have evidence for just how difficult that can be. We have it in our power to educate people about CF testing. When we provide videotape or pamphlet or a combination of educational interventions, we can improve understanding about these tests. However, educating people about complex genetic testing results is difficult.

For example, remember that I told you that the CF test still does not detect all carriers for CF. So one of the issues was whether people would understand what it meant when

they had a negative test, a negative CF test. Would they understand that they still had the possibility of carrying a CF mutation.

One of our studies showed very clearly that in those individuals who had less than a high school education (which is a substantial part of our population) zero percent, not one person understood the meaning to a negative test. In spite of repeated efforts to educate people about the meaning of the results of this test, those people never did understand what it meant.

So that is I think one example of how difficult providing information regarding complex genetic tests can be. So it is possible to do CF testing. Some of the things that will need to be decided in the future is whether it should be done, and if it should done, how such services should be provided.

Genetic tests are complex. They are difficult to understand. Obtaining informed consent, and I emphasize the word "informed" consent, is difficult. And helping people to decide what to do with the information, once they have it, is also not easy and takes time.

A second area in which genetic technologies are being applied is in the area of prenatal screening and diagnosis. The number of methods of prenatal diagnoses available has increased over past decades. The prenatal test that most people have heard quite a lot about is amniocentesis. During amniocentesis a needle is inserted into the uterus and some amniotic fluid is removed and studied for chromosome abnormalities, biochemical abnormalities or molecular genetic changes.

A somewhat newer method, is chorionic villi sampling, where a small tube is placed into the uterus either through the abdomen or the vagina and some chorionic tissue (the outer lining of the chorionic or the amniotic sac) is removed so they can be studied for chromosomal or molecular genetic changes.

It is not possible to use that tissue to look for a biochemical change which is associated with neural tube defects, but there are a variety of disorders for which that test might be offered.

Another test that many women are now having is maternal serum AFP (MS AFP) screening. Although many people don't consider it a "genetic test", it sometimes leads to further prenatal genetic testing, because if you get an abnormal result, it may mean that you need amniocentesis or chorionic villi sampling for follow-up studies.

Some studies have indicated that many women who have prenatal testing are not well informed about the reasons for the testing. Let me give you an example. You may or may not be aware, but the state of California actually has a law that says the every pregnant woman must be offered MS AFP testing.

In one study, it showed that one in three women in one population, had the test done because they thought the state mandated it. This is one example which highlights the problems associated with obtaining adequate informed consent.

A third application of genetic technologies is the area of both preconception and preimplantation genetic diagnosis. Genetic diagnosis has been accomplished in "pre-embryos" in a number of cases. This type of diagnosis occurs in which a fertilized egg after in vitro fertilization an embryo is allowed to divide several times so that there are eight or ten or twelve cells present. One of the cells can then be removed and studied for genetic abnormalities. If the genetic disorder for which the testing was being carried out is

not present, the embryo is then implanted into the uterus, and if it is present, the embryo is not implanted.

Although this currently is a technically feasible application of these technologies, it is not being used very much, but is certainly a technology that people ought to be aware of and be thinking about and be openly discussing.

Another area that these technologies are being applied is in the area of confirming suspected diagnoses. There are a number of genetic disorders that for years there weren't tests available to say yes, you have it or no, you don't have it.

In conjunction with my colleagues, we examined a person and tried to determine by looking at them, by making some observations, by having some consultations, we tried to determine whether an individual had Marfan syndrome or didn't have Marfan syndrome; whether the person had neurofibromatosis or didn't have neurofibromatosis, and we did that based on the clinical picture, that is, what kinds of signs and symptoms the person had and whether there were enough clinical findings to make a diagnosis.

Increasingly the genes for these disorders are being discovered and they are going to be available to help us to sort out who has a disorder and who in the family doesn't have the disorder.

Another application of this technology is in the area of presymptomatic or in some cases asymptomatic testing. These are people who are at risk to develop a particular genetic disease, such as Huntington disease.

Years ago when people would come in for counseling, and they had a parent with Huntington disease, we were left with saying, "you have a 50/50 risk to have inherited that gene." The gene for Huntington disease actually was mapped about ten years ago on chromosome 4.

It wasn't until this past year, however, that actually the gene and its mutation were identified. We now know that people with Huntington disease have a repeated sequence of DNA, I mean many times repeated. The sequence is a normal sequence. It's just that people who don't have Huntington disease have fewer than 54 of those repeated sequences and people who have the Huntington disease mutation have many more of those repeated sequences.

Sixth is the increasing ability to identify people who have genetic predispositions to develop disease. And those include gene discoveries such as alpha 1 antitrypsin deficiency. That results from an enzyme deficiency which leads to severe lung and liver disease, especially if you're exposed to smoke, alcohol or other irritants and toxics.

There's a p53 gene which is, as I understand it, a tumor suppressor gene that predisposes, if you have a mutation in that gene, you're more likely to develop some forms of cancer.

And most recently, there are genes that are being discovered for very common forms of cancer. There was the mapping of a gene on chromosome 17 (BRCA 1) which predisposes women in certain families to have breast cancer. This gene had not yet been identified, but should be in the near future.

It is estimated to be present in about one in two hundred women. As you know, one in eight to nine women, in the United States gets breast cancer.

So this is likely to be only one of many genes that predisposes women to develop breast cancer. There is a major effort underway to find that gene sequence so that hopefully

we can begin to understand the change that causes that disease in women.

Recent months have brought reported discoveries in the area of colon cancer. A gene for familial polyposis colon cancer was discovered. In December a gene for a hereditary non-polyposis colon cancer was discovered, and in March a second gene for hereditary non-polyposis colon cancer was discovered.

These are genes for which tests are going to become available for people in the relatively near future. These genes are also estimated to be present in somewhere around one in two hundred people. Now, these are estimates, because these studies have so far been carried out in which there is a family history of colon or breast cancer.

No one has yet done studies in the general population to know how frequent these mutations are, or what percent of people who have the mutation will also get colon cancer.

I envision genetic testing and genetic services moving out of genetic specialty clinics and potentially moving in fairly soon to primary care settings. And it's going to be a local doctor saying, "well, this lab has a test for colon cancer, rather than doing your colonoscopy this year, why don't we do this test instead." Or certainly I can envision there may be providers who will say, "since, one of the breast cancer genes has been discovered, why don't we think about doing that test and then we'll see if you need a mammogram."

Now, I'm envisioning such things happening in the future, and I'm worried about it. I'm worried that we have a generation of primary care providers who don't necessarily have a very strong background in genetics; who may have difficulty explaining the testing that's available; and may have difficulty sitting down with the family to let them know what the test results mean, and knowing what to do with that information.

Again, we don't know if people— I mean the estimate is if you have BRCA 1 gene, there's about an eight-five percent chance in your lifetime that you're going to get breast cancer if you're a woman. Now, if you don't have the BRCA 1 gene, what's the chance that you're going to get breast cancer? Well, there's still a good chance you're going to get breast cancer for another reason, not the BRCA 1 gene. So, of course, there's the concern that people who don't have this gene won't feel that they have to have mammograms or won't feel they have to do self breast examination and so forth. So these are issues that all have to be sorted out before we're able to make recommendations about follow-up care for people.

Now, I'll just touch briefly on some of the developing genetic technologies in terms of the therapeutic applications. For a long time we've had the possibility of gene product replacement, in the form growth hormone, in the form of factor 8 for people with hemophilia and so forth. So gene product replacement therapy has been around for a long time.

More recently there has been the development of some types of somatic cell gene therapy.

Somatic cell gene therapy is body cell gene therapy, and that means developing some sort of gene therapy that you put into an individual's body. This has been accomplished in the treatment of an severe immune deficiency syndrome called the ADA deficiency. That was the condition that the bubble boy had in case you ever saw that movie.

The other type of gene therapy that has the potential to be developed is in the area of germ line gene therapy. And that will be extremely controversial, because in germ line gene therapy, genes are altered in an egg or a sperm cell that's going to form a child.

If germ line gene therapy occurs, that changes the genetic makeup of all the future generations of that offspring. So that will present many ethical issues. Some people have called for a moratorium in the area of germ line gene therapy, because of concerns about altering the process of evolution.

I've already raised a number of issues, but now I want to focus on some of the major ethical, legal and social implications that are arising as a result of the Human Genome Project.

First, a major issue, informed consent. The concept of informed consent means that individuals agreeing to genetic testing or genetics research understand why the test or why the research is being carried out. They understand the risks, and benefits of testing, and what the possible outcomes of testing are.

Some of the studies we've funded demonstrate that this whole issue of informed consent is a difficult one. We've also reached a point of having to deal with new concepts. You see, in the past oftentimes informed consent was designed because people needed to know whether there was a risk to be harmed (usually physically) from a procedure or a test.

We're now talking about informed consent when having information or knowledge is the risk. That's not a concept that most people have thought much about. Because the test is a simple blood test, the physical risks associated with having a genetic test are minimal, extremely minimal, and commonly that's how they've been treated in the past. However, once people have information, there are potential risks that can be associated with having that information.

A second set of issues are in the area of psychosocial issues. Individuals undergoing genetic testing may experience anxiety or other negative psychological outcomes. For example, women undergoing prenatal screening and diagnosis may experience anxiety at the time of testing.

Commonly the anxiety is relived when the normal test results come back. However, there are some results that come back that are not interpretable or people don't know exactly what to make of the results of that test.

I think there is a limited amount of information that can be given to women when the results of the tests are indeterminate. So although the test has the potential to make you feel relieved, once you have normal results, if you get one of those indeterminate results, there still is potentially some low-level anxiety or in some cases high-level anxiety if further tests suggest that there is something significantly wrong.

In the cases of Huntington disease, cystic fibrosis, and breast cancer, some early studies done in this area, have shown something kind of surprising. That is, people who find they don't have the gene, sometimes have some very difficult time coping with this new information.

The word "survivor guilt" keeps coming up. A family in which sisters are all at a fifty percent risk to have the breast cancer gene, some of them get it and some of them don't. And some of the women who we thought would be relived and happy about not having the gene, all of a sudden find they feel guilty for not having inherited the gene. Some individuals need to reorder their lives in order to move forward.

That's been particularly noted some of the Huntington disease families where everybody assumed people who found they didn't have the Huntington mutation would be happy and

thrilled. In fact, what's happened in some cases is that it has led to significant psychologic upset. For example, imagine the young man who decided, in his mind, that he's got Huntington disease. He thinks, "I'm going to live for today." He didn't go to college, didn't make any commitments in relationships, had no long-term plans for the future, expecting he were going to be dead by forty or fifty.

Well, now all of a sudden at age thirty or thirty-five he's told "Guess what, you're probably going to live a lot longer than that, what are you going to do with your life?" You can imagine how that may cause some difficulties. If you weren't anticipating living to be seventy or eighty the prospect of that may seem daunting.

In the U.S. there have been a number of reported cases of social stigmatization and discrimination as a result of genetic testing. And this is most certainly, at least in part, because of our current health care system and our insurance industry.

For example, there have been a number of instances reported in which insurance coverage has been denied due to the diagnosis or even suspected diagnosis of a genetic disorder, whether or not the person is actually experiencing any health problems associated with this risk or this disorder.

In at least one case, employment was denied to a perfectly healthy individual who had been previously identified to be a carrier for the autosomal recessive disorder called Gaucher disease. The reason that was actually stated on the employment form for his denial from employment was that "he was a carrier of sickle cell."

I don't know if you know Gaucher disease and sickle cell disease, but they're quite different disorders and, in fact, in both cases, carriers do not have health problems.

In another case, a couple, both of whom were known to be carriers of cystic fibrosis, became pregnant. They elected to have prenatal testing. And the reason they knew they were both carriers was they'd had a previously affected child with CF. They knew they had a one in four risk to have another affected child.

They had prenatal testing and found that the fetus that they were carrying was affected with CF. After much deliberation, they decided to continue the pregnancy. They were notified by their insurance company that if they continued the pregnancy, their child would not be covered by health insurance and, in fact, they threatened to cancel all of their health insurance.

It took some negotiation and discussion with the insurance company to get them to understand that was an inappropriate response for them, that, in fact, people do have reproductive choices and those choices should not be dictated by an insurance company.

This couple took on the insurance company, and as we all know there are some couples that might not choose to do that. As I understand it, this couple continued the pregnancy and were able to keep their health insurance coverage.

Another issue that we are dealing with now in the area of genetic studies and genetic testing is the area of family issues. Recently it has become clear that there are some DNA family study issues that are distinct from other research and testing issues that may occur.

For example, there may be subtle or not so subtle coercion by family members to participate in a genetic research study or to participate in genetic testing, that is, some member of the family really wants the family to enroll in this study or some member of the family really wants to be tested for a particular disorder, and they go out and recruit

everybody to come in to the family get-together. so that the test are all done at the reunion.

For example, in one of our CF studies, it was reported the matriarch had gathered all of her children and grandchildren together, to have them all tested for CF. She not only brought them to the reunion, but she even paid for the tests to be done. so, there is the concern that there may be the possibility of coercion by family members.

On the other hand, there's the opposite end of the spectrum. In some situations certain parts of the family won't talk about possible testing. There isn't even the possibility of dialogue about whether or not the family should participate in testing or in a research project.

When you have people in a family who really don't want to participate, it is a difficult situation, particularly when they're important (from a genetics standpoint) to the study of the family. In some cases, a person can explicitly refuse to be tested or explicitly refuse to participate in the research, and if we study everybody around that person, we can sometimes deduce what that person's genetic makeup is. So that does bring up an issue of, again, the issue of consent.

There also are issues surrounding genetic testing of children or other individuals who have diminished autonomy (who are unable to consent for themselves) such as those with mental retardation or metal illness.

The Department of Health and Human Services regulations allow research imposing more than minimal risk to be conducted with children only when there is promise of direct benefit to the research subjects.

In situations where there is little to be done as a result of a positive genetic test, the risks of labeling, stigmatization and uninsurability suggest that genetic studies should not involve children. Thus, in the case, for example, of Huntington disease, a decision has been made to exclude individuals who are under the age of eighteen. Now, that's a difficult decision to make, because, of course, we all know there are 20-year-old's who perhaps should not be tested and we all know there are 16-year-old's who psychologically could potentially benefit from such testing.

So setting a cut-off like that has its own issues to think to consider. Increasingly, however, the case for excluding children and incapacitated adults form testing is not so clear-cut. Participants in a recent workshop on p53 gene testing argued that with genetic markers for cancer risk, the potential benefits of early warning of cancer risk and of a negative testing result (allowing some children to avoid sometimes otherwise invasive testing) outweigh the risks associated with testing.

The standard of care if you have familial polyposis colon cancer running in your family is that sometime around age nine or ten you start having colonoscopies, on an annual basis to watch for developing polyps.

So in this case a cogent argument can be made for testing of children who are at risk for familial polyposis gene, so that at least half of the children don't have to go through annual colonoscopies, if it is not necessary.

Questions have arisen such as under what circumstances can one person serve to grant permission to involve another person in genetic testing or research. Is it ethical to study children, when the possibility of obtaining informed consent is unlikely and the results of testing may potentially cause anxiety, stigmatization and discrimination.

One relatively common and particularly distressing finding in large family studies is the documentation of what's called misidentified or misattributed paternity. This means that the genetic markers identified in the offspring do not match and could not have come from the stated father of the child.

In such situations, the question arises regarding how to explain the results to the family. Sometimes it is extremely difficult to keep this information from a family, and, of course, there are many people who feel it shouldn't be kept from the family.

Do you explain the findings to the biologic mother only? Does the stated father have a right to know that he's not the biological father? Does the child have a right to know his true parentage? Does the mother have an overriding right to privacy? This issue has many unanswered questions and ones which may result in much attention and debate.

And finally, is the issue of confidentiality. In some family studies, it is difficult, because, again, as I mentioned, in some cases you can deduce the results of other family members' results based on studying people around them. In some cases, you have to have information about other family members in order to provide an accurate interpretation of an individual's results.

So confidentiality among family members is a very complex issue. Although we'd like to think that families all get along with one another and this shouldn't be information that would be harmful, we all know that's not always the case. As a result, confidentiality is an issue that really has to be wrestled with before starting a big family study. One of the legal issues include issues that deserves attention is the ownership of samples. One somewhat unique feature of obtaining DNA samples is that they can be banked indefinitely. Using these banked samples, it's possible to ascertain genetic information which was not originally sought through the testing. It's possible to develop new testing technologies and, in fact, even possible for somebody to profit from the new technologies and, in fact, even possible for somebody to profit from the new technologies that are developed.

Pedigree information and DNA samples collected in the course of a particular gene hunting project can be used again to support subsequent projects. Traditionally, tissues and blood samples donated for research have been considered to be available for further study by researchers and some consent forms for linkage studies make this assumption explicit for their subjects. Some further uses of these DNA collections, such as their use for creating physical maps of chromosomes, are anonymous and analogous to a pathologist's investigations of any donated tissue. However, in genetic studies, some of the research promises to uncover new genetic facts about individuals and may require the collection of additional phenotypic or family information from medical records, and it's basically felt that this type of gaining further access to records and doing tests that are really unrelated to the test that was originally done probably do require a reconsent by the subject.

Thus, many questions surrounding genetics research and genetic testing have arisen, such as to whom does the stored DNA sample belong, should new testing technologies be applied to stored DNA samples for which permission has not been granted? What agreements are necessary to use stored DNA material for new studies or for clinical diagnoses? What should happen to the information that is obtained from these technologies? Who should be able to profit from the new technologies developed, and what are the obligations of researchers to go back to people if clinically relevant information becomes

available?

To summarize, there are a variety of ethical, legal and social implications that are arising in response to the technologies developing through the Human Genome Project. I think that although the Ethical, Legal and Social Implications Branch is not in a position to mandate policy, I would like to say that I believe we are in a position to contribute to the body of knowledge, the underlying body of knowledge that will help policy makers to develop sound policy.

Just like we need good sound basic biologic research in order to move forward to do research in the area of human genetic diseases, we need good sound psychosocial, sociocultural, and , theoretical research, so that we have that framework by which sound policies can be developed. I believe that we are beginning to develop that underlying body of sound knowledge.

I do believe we are having an impact on some of the discussions regarding policy. We certainly have been involved in the discussions regarding informed consent in genetic studies and in genetics research and in genetic testing. It is time to revisit some of those issues. What we've "always done in the past" may not be appropriate anymore, and we are urging that the policies that were once in effect be re-examined to assure that they are still appropriate with now the new capabilities and power that we have through some of these tests developing technologies.

Member of the Audience: At the end of your outline you have something called gaps in knowledge and abilities. That's terribly tempting. Could you tell us more?

Ms. Thomson: I think we are at a point where we've learned a tremendous amount in the last few years, but we have a long ways to go. The science, however, is progressing rapidly. We're at a point of knowing too much and yet not knowing enough.

We are at a point where genetic tests are not perfect. That is, they don't have one hundred percent sensitivity and one hundred percent specificity. Some of the genetic tests are very good and certainly are close to that level, but many genetic tests are not near that level.

Some of the tests are imperfect and some of the providers of the tests don't fully understand the tests. We're in a place where, in fact, we sometimes can make a prediction about an individual, but do not yet have good interventions to reduce risks. For example, you have the BRCA1 gene at this time we think you have about an eighty-five percent risk to develop breast cancer sometime in your lifetime.

What do you do with that information right now? Does that mean that you have a prophylactic mastectomy and oophorectomy? That's what some women are currently opting for.

In some of the early studies that have been done in families where the BRCA1 gene is present in the family. The women are ones who have lived with breast cancer. some of their mothers have died, their sisters are dying, their aunts and cousins are dying, maybe their grandmother died of breast cancer. I guess it's not surprising that some of those women would opt for removing their breasts and ovaries so they don't get breast or ovarian cancer. Now think if you're a woman in the general population with no family history of

breast cancer and you have a genetic test for BRCAI.

Let's say you're the one in two hundred in the general population that has that gene. What do you think women who don't have that family history will opt for? In fact, we don't even know what should be recommended. We really have no idea what those women will do.

So we're at a point of being able to make predictions, but, we're not sure what our recommendations should be. And the concerns, of course, are that the use of these technologies may be driven by factors other than evidence that they should be used.

Commonly, policies are made extemporaneously. Somebody decides that a policy should be implemented. In the case of MSAFP screening, a committee of the American College of Obstetrics and Gynecology, recommended that all OB/GYN folks offer MS AFP testing or risk being sued for not offering it.

So sometimes policies develop because somebody makes a recommendation or because of market forces. Sometimes policies are made because of fear of liability. There are a variety of reasons why policies might develop, some reasons are better than others.

And what we in ELSI are hoping, is that clinical policies will begin to be developed more often on the basis of clinical evidence by having the underlying body of knowledge, so that policies will make sense and be based on sound evidence that they are good policies.

Members of the Audience: The last thing you said just about answered my question. ELSI is not a policy making body. You mentioned that in this one case of these people had the fortitude, this one couple, to take on the insurance company.

Who in this country at this time is attempting to take on the insurance companies, who have gone on public record recently on the *48 Hours* television show, a spokesman for the insurance industry said, yes, we demand access to all genetic information. Who has taken them on, anybody?

Ms. Thomson: We, the ELSI community, and the insurance community. We actually supported an insurance task force which released a report in 1993 called "Genetic Information and Health Insurance." I brought several copies with me, but they are also available through my office.

The uninsurability of people who have preexisting conditions is a substantial problem. I believe with the power of genetic technologies, the issue of preexisting conditions may become even a bigger problem. It is possible that more people will become uninsurable. We know that everyone has a certain number of genes that aren't entirely normal. If they happen to be ones that predispose to disease, it could result in the person becoming uninsurable. This could potentially bring the issue to a crisis point where more and more people are not able to get health insurance. Yes.

Member of the Audience: When a person comes in to see his or her primary care physician today and they might be interested in having genetic testing done for BRCA 1 or some other type of test, what type of risk factors are physicians looking for in particular patients to decide whether or not to go ahead with the test and whether or not it's advisable for this particular patient?

Ms. Thomson: At the present time, BRCA 1 testing is only available in a small number of centers and on a research basis.

In order for somebody to be considered for testing at this point, you really have to be in a family where BRCA 1 is potentially being inherited in a dominant form, that is, parents, children, grandchildren, usually someone is affected in each of the generations.

Right now the BRCA1 gene has not been sequenced. So that such a study can only be undertaken by doing linkage analysis through a family study, that is, following the roadmarks that are segregating or being inherited with the gene. But in the future, once the gene and its mutations have been identified, and you can do direct testing, and actually look directly at whether a person has it or not.

Right now I don't know who will decide what women will get the test and what women won't get the test. It's probably going to be fairly expensive, at least at first.

So probably one of the features will be whether or not there's a way to pay for the test. I think payment will end up being one of the features that determines which women get the test and which women don't.

Members of the Audience: From what I've heard today, it seems likely that in, say, fifty years or so we're going to know the sequence in the human genome or know what the genes are and we may be able to even treat the majority of genetic diseases before they take their full effect. It's possible we may even have uncovered the secrets to the aging process. The genetic stages can be perhaps programmed, in essence, that type of thing.

Is the Human Genome Research Project and NIH looking at all of the changes in demographic factors that might result from that, the change in the age structure of our population and how that will affect social institutions, just bare population size?

Ms. Thomson: The Human Genome Project is not presently directly involved in such studies. There are other components of the NIH and other agencies that do studies about such sociodemographic information, but we are not involved in that at the present time.

Members of the Audience: You mentioned discrimination based on identification of certain markers. And then I'm not sure I heard you accurately, but I believe you said also discrimination based on suspected identification of certain markers. Can you just elaborate on that?

Ms. Thomson: For example, if you have a family history of breast cancer, an insurance company will use that information to determine the rate that they will charge you for premiums.

So it doesn't necessarily mean that you have to have genetic markers that indicate you're at increased risk. This could occur because you have a family history of heart attacks, high blood pressure, breast cancer, or colon cancer.

Members of the Audience: So you're talking about discrimination based on a possible predisposition to a disease?

Ms. Thomson: Right. I mean it's one thing to know you have one of the colon cancer genes, and it's another to know that you're at risk or to suspect that you are, and in either case it could result in insurance discrimination.

Member of the Audience: How would predisposition to diseases, for examples Huntington's or Alzheimer's, affect getting applications for disability benefits or social security or life insurance?

Ms. Thomson: Well, any time someone knows that they have the Huntington disease gene mutation, we known with a high degree of certainty that they will become disabled relatively young in the scheme of life. The average onset of Huntington disease is in the thirties or forties and the average age of death is in the fifties or sixties. Thus there can be ten or fifteen years of disability.

So it's not surprising that companies selling disability insurance would say, I am not going to insure this person because we know he or she is going to be disabled for fifteen years before they die.

It's the same for life insurance. If you by life insurance at age twelve, you're expected to live a long time. If you buy life insurance at the age of forty, you're still expected to live quite a long time; but if you by life insurance at age forty and you have Huntington disease, you're not expected to live a very long time.

So, related to life insurance and disability insurance, discrimination is not uncommon, especially when you know someone's at risk for a disabling or condition leading to death early.

Members of the Audience: If you knew you were at risk, that you were going to get a specific disease, would it be unadvisable to get genetic testing?

Ms. Thomson: That's a good question. We know that many people are not tested for that very reason. The people who, in fact could benefit by getting adequate health care. Some will choose not to be tested because they don't want to confirm what they suspect. We have seen many families with Marfan syndrome, where people didn't want to be tested, because they knew that they or their children once they left their health policy might not be able to get insurance in the future.

So I'm not saying it's advisable not to be tested. I'm saying that many people decide not to be tested, for that very reason, in our current system.

Member of the Audience: Do you have any reasons as to why you left out economic implications from the ELSI? It seems to me that in all this testing, economics would play a major part, especially to those that don't have the money to get tested.

Ms. Thomson: Economics does play an important role in the development and diffusion of genetic technologies. In all honesty, I'm not an economic expert. I will tell you that we have funded one study to examine the economic impact of doing population based CF testing.

Their preliminary data suggest that it costs approximately $400,000 to detect one fetus with CF. And in weighing as to whether or not the benefits of testing outweigh the cost is no small task.

Member of the Audience: But with ethical and legal and social implications, to me it seems that they're all intertwined and you can't talk about social implications without really addressing the economics. It will give you all a better idea of how genetic testing will really affect the population.

Ms. Thomson: We do have one other activity going on and that is to examine the potential economic impact of testing for cancer genes.

As you know, health care costs associated with cancer is high. Much of the treatment is expensive. It may save your life, but it is expensive. So there right now is a study going on to look at the economic impact of early detection with the possible prevention interventions, to see its relation to costs associated with cancer and its treatment.

And, of course, in weighing the costs, there's something that you really can't weigh into the cost, and that is the price of saving a life. Sometimes it is more expensive to save people's lives.

Mr. Cooper: It's wonderful to be a lawyer when you see a field like this. Intellectually, there's nothing more challenging than being a lawyer today, because we're at the point where the lawyers have the responsibility of dealing with science, with ethics, with public policy, and trying to help the courts and the legislature to do something with the challenges arising from these biotechnological discoveries.

It's a wonderful challenge and responsibility and I hope that lawyers, particularly the young lawyers, appreciate the opportunity they have to do something in a field as important and as timely as this.

One consequence of the knowledge produced by the Human Genome Project and genetic research is that within ten years people will be able to have a good idea of the nature and the approximate time of their deaths, their own deaths. Now, what good will this knowledge do?

In the long run, scientists hope to use this new knowledge to cure genetic disorders, but there will be an unknown period of time, decades perhaps, between the point at when we can understand flaws in the genetic code which cause disease and at the point when we can do something about them.

It's during that period that society has one of its greatest challenges and the law has one of its greatest challenges. Finding one's genetic profile for a while may be like hearing your own death sentence. That's something that we all have to think about.

Parents will have access to the same knowledge about their unborn children. Such genetic profiles may create reasons, valid or not, but reasons in a parent's mind to terminate a pregnancy, a serious matter. What if genetic testing would show that a child will have a tendency to be overweight. Is that a reason for terminating a pregnancy? It may be in some people's minds.

So we're going to have to deal with problems of that kind. Insurance companies will

want to know who carries defective bits of code and people who know they have gotten defects will want to buy a lot of insurance.

Are the insurance companies going to be able to get this information freely? Should the insurance companies for life insurance and/or health insurance be permitted to get this information freely? Would employers like to know that if they're taking on an employee with significant Blue Cross-Blue Shield expenditure, maybe they don't want to take that employee on. Does an employer have a right to have that information?

The military wants to know this informtion. Voters may want to know this about their potential candidates, although there are plenty of defects around now, we probably don't need any more. People may want to know the same thing about their potential mates. Would a young person who wants children insist that his prospective mate be tested and he be tested to make sure that their children have the best chance of being healthy.

These are things that we're going to have to wrestle with now. Hopefully we're going to wrestle with these issues now before it's too late.