

June 2016-Quaid Genetics Web

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Today I'm going to talk to you about some of the ethical issues that arise in the different types of genetic testing. Now, many of you have probably heard of the Human Genome Project. It was a 13-year effort to map and sequence the entire human genome. It was funded by the National Institutes of Health and the Department of Energy, and if you're anything like me -- when I heard this, I wondered what on earth was the Department of Energy doing getting involved with the Human Genome Project.

Well, it turns out the Department of Energy has a long-standing interest in genetics and genetic mutations since we dropped the atomic bomb on Japan. And they saw a way of putting some money into this effort, as a way of keeping their scientists and their labs open. So this began formally in 1990 with funding of about \$135 million, and was increased to about \$3 billion in public funding by the year 2000. In February of 2001, a working draft of the human genome was published simultaneously in both Science and Nature magazines.

The project goals were to identify all the approximate 25,000 genes in human DNA. Now, that number -- I've given versions of this talk several times, and that number, of the number of genes, keeps going down. It was 30,000, then it was 25,000, maybe it's a little closer to 20,000 at about this point in time. So we're continuously refining our knowledge of the human genome.

Another goal was to determine the sequences of the three billion chemical base pairs that make up human DNA, store this information in databases, and improve tools for data analysis. Now, one of the things that was really interesting about the Human Genome Project, and the area of the project with which I'm most familiar, is Ethical, Legal and Social Implications Program, effectually known as ELSI. It was funded on the concept that a new technology, such as gene identification, is likely to engender problems that could be minimized if anticipated and dealt with promptly. Now the interesting thing about this, is it was the first time that the ethical issues of a large scientific enterprise were studied along with the enterprise itself. This program's also known as Full-Employment for Philosophers.

So what is a genetic test? A genetic test is the analysis of human DNA, RNA, chromosomes, proteins and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes, for clinical purposes. Now, what are these clinical purposes? They can include predicting the risk of disease, identifying carriers, and establishing prenatal and clinical diagnoses or processes.

First up is, predicting the risk of disease. I am also the Director of the Predictive Testing Program, so this is the area of genetic testing with which I'm most familiar. I deal primarily with late onset [unintelligible] disorders like Huntington's disease and early onset Alzheimer's disease. So these predictive tests are tests that are performed on healthy or apparently healthy individuals, with the goal of identifying their risk for developing disease in the future. And these tests are of two types: there's pre-symptomatic testing and susceptibility testing.

Pre-symptomatic testing involves looking for genetic mutations that have high penetrance,

usually autosomal dominant. Now penetrance is a word we use in genetics which basically is an estimate of if you carry genetic mutation that causes a particular disease, how likely are you to actually develop that disease? So, in these kinds of tests, we're looking for disorders that, for the most part, if you have the genetic mutation associated with the disorder, you will develop the disease in the future, so full penetrance.

These tests need to be highly specific and sensitive, which means there are few false negatives or false positives. Examples, as I mentioned, include genetic testing for Huntington's disease and early onset Alzheimer's disease. Now, probably the most famous person that died of complications of Huntington's disease was the folk singer Woody Guthrie, who was the author of "This Land Is Your Land."

So, what we can do is basically identify healthy individuals, who we now know are very likely, virtually 100 percent, to develop devastating and debilitating diseases at some point in the future, which at this time have no treatment or cure -- which is one of the reasons why you want to make sure there are few false negatives and few false positives. We have developed testing protocols for this type of pre-symptomatic testing. These test protocols usually involve a neurological examination to establish a base line; pre-test counseling to construct an elaborate pedigree, to get some sense of whether or not the person is making this decision to be tested freely, of their own will; what kind of support system they have; what life changes might be riding on this decision; to get some sense of who the person is, and why they're making this decision.

We usually get informed consent, written informed consent, for this type of testing. Results are usually given in person, and we make available several types of follow-up. They may include additional medical exams, they may include support groups, they may include individual or family therapy, depending on the needs of the individual.

Some of the ethical issues we encounter in pre-symptomatic testing -- the first would be, are we better off knowing our fate? Are we better off knowing that at some point in the future, we are going to die of a disease that, at this time, cannot be treated and cannot be cured? And especially disease that we've seen affect members of our family, usually one of our parents, usually one of our grandparents, aunts and uncles perhaps, or cousins.

And since there's no treatment or cure, it's very important that we respect personal autonomy. Informed consent, as I mentioned, is an important part of the process. And we also have to respect people's right not to know. Part of the counseling process is to enable people, if they have second -- if they're second-guessing their decision, to opt out of testing at that time. They can come back later, they can refuse to get testing, they can change their mind.

Also, because of our concerns about autonomy, we're very reluctant to test children. In the case of Huntington's disease, one of the things that we know over time, is that the number of adults who were seeking testing, at-risk adults, is usually about 10-13 percent, which is fairly low. So if fully autonomous adults are not rushing off to be tested, we believe it's very important to preserve the autonomy of children who are at-risk, to decide for him or herself, when they reach the age of majority, whether or not they want to be tested.

It also means that we're very reluctant to test anyone at the request of a third party, be that a lawyer, a judge, the police, a spouse in the middle of a divorce. That issue has certainly come up. Our concern also is the psychological cost for those tested. We certainly, in the essence of, "Do No Harm," would not want to create difficulties in the time that people have left while they're healthy. So we're very concerned about depression and difficulty, psychological difficulties if people test positive.

We also have some reluctance to pursue pre-natal testing for late onset disorders. Pre-natal testing is possible, but most of the onset in these disorders that I primarily deal with are perhaps in the late 40s, early 50s. So that's many years of healthy life before people do become affected. Now, susceptibility testing involves looking for genetic mutations that confer a high risk for developing disease, but not necessarily a yes or no 100 percent answer. These disorders are usually multi-factorial, being a mix of genetic and environmental effects. They have variable sensitivity and specificity. Examples that include testing for apolipoprotein E4 alleles for Alzheimer's disease, and the BRCA1 or BRCA2 for breast cancer.

Test results of this type do not mean the disease will inevitably occur or remain absent. They replace an individual's prior risk based on population data or family history with risk based on genotype. Some of the ethical issues in susceptibility testing, education and counseling for those at risk. These results, since they're not black and white, you get a level of risk, and as a species we are not very good at dealing with risk. Test interpretation can be very complex. And many of these diseases, primarily cancers, there is a potential for increased monitoring and possible treatment. So there is something that may, that can be done.

But the question that comes up is what counts as useful information? If I look at my family history, and know that my mother had breast cancer early age, my grandmother had breast cancer early age, my maternal aunts had breast cancer early age, I could probably figure out that my risk for getting breast cancer at some point is pretty high. Does it help me that much to put an exact number on it? Maybe yes, maybe no. That's the individual's decision.

One of the things that we do see is what we call the Angelina Jolie affect. When Angelina Jolie went public with her genetic test results about BRCA1, BRCA2 and subsequent double mastectomy, interest in genetic testing for breast cancer spiked considerably. And I think many physicians see that the fears that a television show, for example, that features a specific genetic disorder -- there's often a spike in requests for testing across the country at that point.

Now, carrier identification identifies individuals who do not themselves have a particular disease, but who are at risk for having a child with a particular disease. These are usually disorders -- carrier testing involves individuals known to be at high risk because of family history. For example, testing a woman whose sister had a son with cystic fibrosis, which means she has the possibility of being a carrier. Carrier screening involves testing all individuals with no family history. For example, testing all Caucasian women of child-bearing age for cystic fibrosis.

And these are some examples of carrier screening: the prevalence of Tay-Sachs disease in the Ashkenazi Jewish population is approximately one in 27; for sickle cell anemia in the African

American population, it's approximately one in 13; and cystic fibrosis in the Caucasian population is approximately one in 25. Some of the ethical issues in carrier screening and testing, since this involves reproduction primarily, is respect for individuals' and couples' beliefs and values concerning test-taking for assisting reproductive decisions. Mutations for certain diseases may have a higher prevalence in certain ethnic populations, raising the issue of stigmatization in that particular population. And we've seen this historically, certainly with sickle cell screening back in the 60s.

There are few choices available to those identified as carriers. You can refrain from child-bearing, you can pursue donor eggs or donor sperm, or you can pursue -- and this is an option that is becoming more popular -- pre-implantation genetic diagnosis. And what that would be is that we would hyper-stimulate a woman's ovaries, and harvest a number of eggs, as opposed to the one that she usually drops a month. We would fertilize those in a petri dish. We would wait until the embryo grew to about the eight-cell stage, and then we would actually be able to take one of those cells and test it for the presence or absence of the genetic mutation that we're looking for, such as cystic fibrosis, or sickle cell, or whatever. Then we would only implant back in the woman those embryos that did not carry those particular mutations. There's an obligation to offer education and counseling, because these are complicated situations. The difference between being a carrier and having -- being affected when you have two copies of a mutation -- can be a little bit more challenging, in terms of education and counseling.

Prenatal genetic testing is testing of a fetus prior to birth in order to identify genetic mutations that may cause disease. The aim is to enable parents to have children they otherwise would not have been willing to have because of the fear of birth defects or genetic disease. For example, a common prenatal test, approximately 2.5 million women are screened each year to see if their fetuses are high-risk for Down syndrome or neural tube defects.

Some of the ethical issues in prenatal testing is respect for individuals' and couples' beliefs in values is crucial. The ideology of non-directiveness is compromised by the fact that you are offering a test for a specific disorder. What I mean by this is in genetic counseling, we have an ethos of non-directiveness, which is we -- our job is to give you the genetic information. What use you make of that information is going to be up to you and your partner based on that your religious values are, your social values, what your family structure is like, your financial situation, and a host of other things that are personal to you.

But the fact that you're actually offering a particular test means that, at some point in time, a value judgment has already been made that you might not want to have a child with that particular condition. So, the ideology that we carry for non-directiveness is compromised by the fact that you're actually offering this test. There can be potential for increased pressure on couples not to have children who so-called "deviate" from normal. There's the possibility of decreased tolerance and fewer resources for those with disabilities because you can say, in essence, these parents had a choice.

There's also the possible termination of a fetus based on ambiguous information -- and I, for example, got a call from a friend yesterday, whose niece had had a particular mutation identified, and her report actually said, "A micro-array result of uncertain, likely pathogenetic clinical

significance.” And when it talked about what the prognosis might be, it said, “Generally mild, but can include intellectual and/or learning disabilities, delayed psycho-motor development, growth retardation, and hypotonia.” So, it could be nothing, it could be fairly serious, and you have to make a decision.

So that's, I think, the ambiguous information. And can't go without New Yorker cartoons. “The good news is that you'll have a healthy baby girl. The bad news is that she is a congenital liar.” So there's your ambiguous information. As the mother of two teenage girls, I have to think twice about that.

So newborn screening is screening newborns shortly after birth to identify genetic conditions. The aim is to identify conditions that are treatable in order to begin treatment as soon as possible to prevent serious mental or physical handicaps. There are criteria that've been set up for expected newborn screening programs: that there's a treatment available; that early treatment can reduce or eliminate permanent damage; that the disorder would not be revealed in a newborn without a test; that there is a rapid and economical laboratory test is available, and that is highly sensitive and reasonably specific; that the condition is frequent and serious enough to justify the expense of screening; and that there is a societal infrastructure in place to inform the newborn's parents and their physicians of the results, confirm the results, begin treatment, and offer counseling. So there's a lot of pieces that need to be in place for expected newborn screening.

There is some indication that those criteria may be changing somewhat, but traditionally the major justification for all newborn screening programs was for the benefit of the child. In 2005, guidelines from the American College of Medical Genetics expanded that justification to include a benefit to the family, as well as a benefit to the public, such as contributions to the advancement of science. This expanded justification could be used to include virtually any test. Now, that's somewhat concerning, because in most states, newborn screening is mandatory, and parental permission is rarely sought.

In 2008, there was some push-back from this. In 2008, the President's Council on Bioethics reiterates that screening should follow the classic criteria, and that would be for the benefit of the child. In 2013, the American Academy of Pediatrics' policy statement reaffirms that screening decisions should be based on the child's best interest.

Some ethical issues in newborn screening: voluntary versus mandatory testing. The value decision was made a long time ago that, because the purpose of screening was to identify disorders that could be treated to prevent permanent damage, that on balance, we would do mandatory testing for the most part. But since you're doing mandatory testing, there's a lack of informed parental consent. You're not asking permission; you're just getting the heel stick. Therefore, there's a lack of education and counseling of parents, prior to coming up with a result.

Also what's happening, as the genetic technology expands and gets cheaper, there is what we call technology creep. Tests are often added to a panel without discussing the benefit to the child, because it's only a couple pennies, and it can be serious, and why not add it. There is necessity for treatment and follow-up to prevent damage, and there's increasing pressure to use residual samples for population-based research, raising issues of informed consent for research. So we're

not even getting consent for the actual clinical use, but now the question of whether we should be getting consent for research use as a sample. At least two states, Texas and Wisconsin, have been sued for using newborn blood spots in research for which they did not have permission.

There tends to be parental anxiety about false positive results. Usually if you get a positive result from a newborn screening test, you would do a confirmatory testing. But for many parents, if you've been told that there's something wrong with your child, even if confirmatory testing finds out that your child is fine, there may be residual anxiety about whether your child actually is healthy or not.

There may be harm to parent-child relationships by a parent misunderstanding the meaning of the child's carrier status. For something like testing for cystic fibrosis, the child may be a carrier, but may never be affected, and parents may not understand that difference between being a carrier and being affected with a disorder. There's also the possibility that children will be subjected to needless monitoring, and potentially risky medical interventions or monitoring, based on this misunderstanding.

So there's always the phrase, "There are two types of people in the world." There are genetic libertarians who feel that patients have a right to a full and complete accounting of all possible risks conveyed by both established and novel variants found through genetic testing, or even variants of unknown significance and disease genes. And then there are genetic empiricists who believe that there is insufficient evidence about the penetrance of most pathogenic variants in the general population to warrant the showing of incidental findings, and that it is irresponsible to create the psychological burdens of being a patient waiting, or to expose patients to unnecessary surveillance or diagnostic testing. So certainly in genetics, there is a tension between the empiricists and libertarians about how much information -- as we're finding, we're doing more and more screenings for more and more things, and finding variants that aren't normal, but we don't really know what they mean. There's a tension between how much to give patients, and even research participants for that matter, and how much to hold onto that information and wait until we actually know what it means, which is a moving target.

So then there's some general ethical issues related to genetic testing, and these include lack of knowledge, direct marketing of tests to consumers, and fear of discrimination. As for consumers, a recent poll indicated that only 26 percent of a population-based sample knew what DNA was. As far as physicians go, a 2012 study in the *Cancer Journal* reviewed dozens of cases in which doctors ordered wrong or unnecessary genetic tests, misinterpreted the results of correct tests, or failed to refer patients to a genetic counselor despite a strong family history of a genetic condition.

In a study funded by the National Human Genome Research Institute, 74 percent of more than 200 internists said their knowledge of genetics was very to somewhat poor, that 34 percent admitted to going ahead and ordering genetic tests anyway. So this lack of knowledge on the part of both consumers and health care professionals, is somewhat worrisome in the face of the sheer volume of genetic tests that are coming down the pipes ever-faster.

In terms of direct marketing, in July of 2001, Myriad Genetics based in Salt Lake City, Utah,

announced that it was preparing to market genetic tests directly to consumers. These were primarily genetic tests to identify risks for certain familiar cancers, breast and ovarian primarily, which are really only appropriate for a relatively small number of individuals, but for which Myriad held the patent. This decision was made primarily because the sales of these tests were not up to the original sales projection. And many of you may remember that there was a period of time on television, that there were commercials for BRCA1 and BRCA2 testing. "Go ask your doctor." And these were really tests that were not appropriate for the vast majority of women.

This is a screen shot of 23andMe, a company that was offering direct genetic testing to consumers. In 2013, the FDA issued a directive to 23andMe to stop offering their health-related genetic tests. And one of my concerns is given the fact that many consumers don't understand genetic information -- a lot of these direct marketing tests, for example for cystic fibrosis, they're only testing for the most common cystic fibrosis mutation, Delta 508, but there are over 900 cystic fibrosis mutations. So someone might get a test back that says "No you do not have the mutation for cystic fibrosis," and yet they may still be at risk, and not pursue further genetic testing, because they don't understand the context. And that's true where, for breast cancer, they're only looking at three mutations that are common in the Ashkanazi Jewish population, but there are many, many, many more mutations that are out there.

So discrimination, the concerns with discrimination were insurance, and employment, and law enforcement. In this slide, "Unfortunately you have what we call no insurance," which was a big, big concern of many people that I dealt with, primarily in the autosomal dominant late onset kind of testing situation. The Genetic Information Nondiscrimination Act, or GINA, was signed into law on May 21 2008, and protects consumers from discrimination by health insurers and employers on the basis of genetic information. The health insurance regulation took effect in May 2009, and the employment regulation in November 2009. Does not apply to those in the military, interestingly enough.

And Affordable Care Act prohibits insurers from discriminating against persons with preexisting conditions. So there are, where there weren't before, at least some legal protections for people with genetic conditions. I think it remains to be seen how much protection is actually afforded people.

Concerns people have about discrimination in employment, "Very nice resume, leave a sample of your DNA with my secretary." Between 2000 and 2014, the cost to employers of providing medical and dental insurance increased 10-15 percent per year. By 2013, health insurance benefits comprised approximately 11.7 percent of employee wages and benefits. Employers have major incentives to have a healthy workforce, and we find out more and more about how a person's genetics relate to the possibility or risk of them developing serious diseases in the future, it's easy to see that employers would have an interest in knowing the genetics of their workforce.

And then there's law enforcement. The greatest advance in forensic science in the past decade has been the application of DNA analysis. The ability of DNA analysis to exclude suspects with virtually 100 percent certainty may be the single largest cause for a major shift in attitudes

towards the death penalty in this country. In cases where they were -- in projects like the Innocence Project, were able to go back and actually analyze DNA samples that were evidence in cases of rape or murder, they often exonerated people that had been on Death Row for many, many years.

But again, Function Creep. In 1930, the Social Security number was invented to be used only as an aid to access the new retirement program, and it is now pretty much a universal identifier. DNA banks that were established by the military in the early '90s were to identify the remains of soldiers -- with the idea that there would never again be a tomb of an unknown soldier -- have been accessed in criminal cases that have occurred on or around military bases. So again, if you have a data bank, people are going to want to use that bank.

In less than a decade, sample collections for forensic databases have gone from convicted sex offenders, to all violent offenders, to all persons convicted, to juvenile offenders in 28 states, to all persons arrested. In this case, the judge says "Please accept the apologies of this court. You're free to go now. And by the way, here's your DNA back." Except they don't give it back. They enter it in the database, where in all likelihood, it will remain.

So in summary, the completion of the Human Genome Project in 2003 will provide a wealth of genetic information and an ever-increasing array of genetic tests, I'm sure many of which were covered in your previous webinars. The results of testing can help individuals make important decisions about their own health, and about reproductive decisions in the face of genetic risk. There's a lack of education about genetics in general, and the proper use of genetic testing on the private consumers as well as health care providers. The use of genetic test results by third parties -- insurers, employers, law enforcement -- may be cause for concern. And it remains to be seen whether recent laws passed to prevent discrimination in employment and health care actually do so.

So this is my contact information. I would be happy to take any questions that you may have.

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