

GENETIC AND PUBLIC POLICY CENTER

“DNA AND DEPRESSION: TESTS, TRUST, AND TREATMENT”

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KATHY HUDSON: Good afternoon. Welcome and thank you all for coming. My name is Kathy Hudson. I'm the director of Genetics and Public Policy Center at Johns Hopkins University. I want to start with a thank you to the cosponsors for today's seminar in our Genetics Perspectives on Policy series: first, the Bazelon Center for Mental Health Law – Bob Bernstein from the center is a panelist today. I'd also like to thank the Centers for Disease Control, and Linda Bradley from the CDC's Office of Genomics and Disease Prevention is here somewhere. Over there. Thank you, Linda. And I'd also like to thank The Pew Charitable Trusts, who have supported this series and much of the work done by the Genetics and Public Policy Center since our founding.

So today's seminar is titled, "DNA and Depression: Tests, Trust, and Treatment." We've known for many years, certainly way before we started sequencing the Human Genome, that there was a genetic component to many mental illnesses. But like with most common, complex diseases, there aren't individual genes that can tell you that you will or will not definitely get a particular mental illness. Instead, it's a number of genes interacting with one another and interacting with complex environmental factors and lifestyle factors.

New genetic tools and technologies are allowing scientists to identify the genes that are involved in the development of mental illness, and also the genes that are involved in how an individual responds to drugs that are used to treat mental illnesses. So these discoveries are leading to a new understanding of mental health and disease, the development of new genetic tests to aid in diagnosis, the identification of targets for the development of new medicines, and the identification of genes involved in how we respond to drugs, either adverse reactions or in helping to get the right dose as quickly as possible.

Today, we're going to focus on the pipeline from basic science discovery through the translation to public health benefit and where there may be cracks in that pipeline that we can solve with public policy changes. In addition, we're going to talk about the social context for these new developments and the need for safe and beneficial uses of genetic tests in mental health.

I'm particularly pleased today that we're going to have our very own Joan Scott, who is standing in for Jeff Botkin who couldn't get out of Utah, who is going to be talking about a new report from CDC's Evaluation of Genetic Applications and Prevention in Practice. They published a report this weekend talking about the use of genetic testing and helping physicians and patients identify the appropriate treatment with SSRIs, and Joan will be talking about that today.

I'm going to introduce the four panelists and they will each speak for about 10 minutes, and then we'll open up the floor for a panel discussion and for questions and comments from you all. We are videotaping today and so, during the question and answer

period, I'd ask you all to identify yourself and your organization. And I'd like to ask you all now if you'd please turn off anything that makes noise, beeps, sings.

So our four panelists – first is Francis McMahon, who is the chief of the genetic basis of mood and anxiety disorders unit at the National Institute of Mental Health at NIH. He received his M.D. from Johns Hopkins University School of Medicine, where he also did his internship and residency in psychiatry and a post-doc in psychiatric genetics before joining the faculty at Hopkins. He subsequently was an associate professor of psychiatry at the University of Chicago, where he served as the medical director – he also served as the medical director of the electroconvulsive therapy clinic. He serves as a scientific advisor on numerous scientific and patient-advocacy organizations and he was the senior author on a paper, published in October, describing two genetic variants that appear to increase the risk of suicidal thoughts in those taking particular antidepressants.

Our second speaker is Kim Bechthold, who is the founder and CEO of a genetic testing company NeuroMark. She's an international businesswoman and entrepreneur, which she's been doing for many years with experience in business development, finance, and technology transfer in the sciences, biomedicine, energy and engineering. She's formerly the founder and president of GenMark, a biomedical business development company. And Kim's company is now offering investigational testing based on Dr. McMahon's test, which you'll hear about. So we'll sort of move from bench to bedside as we move down the table here.

Our third speaker is Joan Scott, who is standing in for Jeff Botkin today. Joan is the deputy director of the Genetics and Public Policy Center. She's a certified genetic counselor with over 25 years of experience in the clinic, in the biotechnology industry, and, more recently, with us in genetics policy. Before coming to the center, Joan ran the biorepository at Gene Logic, which is a genomics company. She ran the genetic counseling training program at the University of Colorado Health Science Center. And importantly, she is a part of the EGAPP working group whose recommendations I referred to earlier. And she'll talk about those recommendations about genetic testing for SSRI prescribing.

And last but not least is Bob Bernstein, who is the executive director of Bazelon Center for Mental Health Law in Washington, which is the nation's leading legal advocacy organization representing people with mental disabilities. He's a recognized expert on public mental health services. Previously he was the architect and, for 19 years, the director of a Detroit program to serve older adults with persistent mental illnesses. He has a doctorate in psychology from Wayne State University and is an experienced clinician, having worked primarily with young people.

So those are our four panelists today and we'll start off with Dr. McMahon.

FRANCIS MCMAHON: Thanks, Kathy. Kathy asked me to keep my remarks very brief today, so I'm just going to give you a brief overview of some of the work we've been doing on a particular aspect of genetic testing which is in the realm of

pharmacogenomics. Of course, genetic testing has been around in medicine for many years, whether it be tests for Tay-Sachs disease or cystic fibrosis or Huntington's disease. But only in recent years have we begun to think about ways that we could use that same kind of technology to use genetic tests to tailor treatment to an individual's genetic makeup in order to improve both outcomes and side effects that might come from medications. And that's the idea behind the realm of pharmacogenetics or pharmacogenomics, which I'll be talking a little about today.

The idea of pharmacogenetics is really to move into the realm of personalized medicine using genetic technology, both to provide guidance for treatment decisions by matching medications with patients most likely to benefit from them, as well as identifying patients at highest risk for adverse events or side effects from the medication they're given.

Another long-term goal of pharmacogenetics is actually to identify novel drug targets, new medications that could be designed by reasoning back from the genetic information. Up to now, most of our medications that are available have been found largely through serendipity, particularly in psychiatry, and they have an impact what we call downstream in the biochemical pathways leading to mental illnesses – often effective at relieving symptoms, but not doing much for the root cause of the illness. One of the long-term goals of pharmacogenetic approaches is actually to come up with medications that might target upstream effects in the biochemical pathways that could have preventive or curative effects for mental illness, although this, at this point, remains a fairly distant goal.

We began to focus in recent years on studying the outcome of antidepressant treatments. Antidepressants work for about half of people for whom they're prescribed, and it's been difficult to figure out whether a particular patient falls into the responsive or the non-responsive half. We've known for many years that there are lots of non-genetic factors that affect the likelihood of someone responding to an antidepressant, such as their marital status, their race and ethnicity, the type of depression they suffer from, and their socioeconomic status.

And one of the big questions has been to what degree genetic variation contributes to that individual variation and whether, if that could be identified, we could harness it to design better treatments and identify who is likely to respond to particular antidepressants.

Our work has focused on a particular study known as the STAR*D, the Sequence Treatments to Alternatives to Relieve Depression study, which is by far the largest study of antidepressant treatment that's been carried out to date, enrolling about 4,000 people, almost 2,000 of whom were willing to give DNA for future genetic studies. Everyone in the trial had major depression, what we call clinical depression, of the non-psychotic variety, meaning the kind that most typically would be treated in an outpatient setting. Patients were treated both in specialty care by psychiatrists and psychologists, as well as by family doctors and internists, who actually treat most of the major depression occurring in the community nowadays.

Almost all co-morbidities were allowed, since we know that major depression tends not to occur as an isolated illness, and the goal of the STAR*D was to have as representative a sample as possible. Research outcomes were measured by a variety of instruments over time and they were separated from the clinical practice, so that the relationship between the doctor and the patient occurred separately from the measurement of the research outcomes. Everyone was treated through several different levels of treatment up to 12 weeks per level until they got well, and then they went into follow-up care. And the follow-up went on for about one year.

This is a graphic that shows the overall design. The work we've done so far has focused on so-called level one, where everyone received treatment with the antidepressant citalopram, which is a selective serotonin reuptake inhibitor, in the same family as Prozac. We've done some work looking at predicting who is likely to respond to the citalopram during level one and this summarizes the work that's gone on over the last several years.

We found markers in several different genes, shown as HTR2A, GRIK4, and BCL2, which have modest effects on who is likely to have a response to antidepressant treatment. You can see that, overall, about 32 percent of people had a definite non-response to the first round of citalopram treatment. And when we look at individuals who carry a marker in a serotonin-receptor gene, HTR2A, that number drops to about 28 percent – very modest, but a statistically significant drop.

We look at individuals who carry a marker in the gene GRIK4; it drops a bit further, a little bit further for individuals who carried this marker in this gene BCL2. And then, when we look at various combinations, we can start to get differences in response rates that reach as high as about 28 percent, so that people are about 25 percent less likely to fail to respond to the antidepressant if they carry favorable alleles either for HTR2A and BCL2 or BCL2 and GRIK4. And this compares to people who carry none of the favorable alleles. So this is a result that, from a statistical standpoint, is of interest, but it's too small to really affect clinical decision-making and treatment.

To get more into the clinical realm, we decided to look at a particular adverse event that's been linked to antidepressant treatment in recent years, known as treatment-emergent suicidal ideation. This is a phenomenon that occurs in about 2 percent, particularly of young people, who receive selective serotonin reuptake inhibitors. They develop suicidal thinking while receiving the drug even though they didn't have it at the time that they first came into treatment. It's likely that the suicidal thinking does not actually lead to suicidal behavior, per se, but concern about it led to a black-box warning on all antidepressants that was issued by the Food and Drug Administration a couple of years ago.

The biological basis of this phenomenon isn't clear, since we know that suicidal thinking itself can occur just in the context of depression. So we wondered whether we could use the STAR*D study to try and identify individuals who might be at particular risk for this kind of adverse event. We found, when we looked at the data, that treatment-emergent suicidal ideation was present in about 6 percent of all cases in about the 2,000 who were treated in the STAR*D. Only two people actually attempted suicide, however.

So we asked the question whether these cases, what we call TESI, differed genetically from treated participants who denied suicidal ideation throughout treatment. And this is what we found. We published last month that two markers, both in receptors for the brain chemical glutamate, predicted with reasonably high specificity, but rather low sensitivity, individuals who would report suicidal thinking on a questionnaire that was administered throughout treatment.

Subsequent work using a larger list of genetic markers spanning the entire genome identified two additional markers that were associated with an increased risk. They approximately doubled the risk of suicidal thinking in individuals who were receiving citalopram, providing higher sensitivity, but a lower specificity for this phenomenon, because they are quite common markers in this sample.

We had no placebo group in the STAR*D study, so we can't say what fraction of individuals who reported suicidal thinking would have developed it anyway as a result of their depression. And we also can't tell what fraction of responders are actually placebo responders, that is, folks whose depression responded anyways, even without the antidepressant treatment. And of course, all of these findings need replication and independent samples. It's very important for genetic studies to look for replication and independent samples, both to be sure that the genetic associations are valid, and also to get more accurate measures of the size of the effect of the genetic marker on the outcome.

So I'd like to leave you with just a couple of summary points. What we really need in the realm of pharmacogenetics are markers that will predict which patients will respond to a given treatment versus alternative treatments that may be available. We need to be able to identify patients who will suffer intolerable or dangerous side effects, or those who would do best with specialized care. And I would propose that, as a standard for this, we really would like to see markers that will increase treatment response by two- to threefold, far larger than what we've identified so far, and give at least a 95 percent negative predictive value – in other words, sensitivity for severe side effects, so that we can be confident that individuals who don't carry those markers would be unlikely to suffer the side effects.

We also need ways to provide this information at the point of service, when patients come in for treatment, so that patients and the doctors can consider the information in real time, at the time that treatment decisions are made.

So some open questions – are clinically useful effect sizes as attainable, even with multiple markers? What we've shown so far are rather small effect sizes, particularly for treatment response, and it's not clear how the effect sizes will increase when multiple markers are considered. How can genetic information be combined with non-genetic information? And how can we help doctors and patients think in the actual way that that sort of information requires? And will the primary value of pharmacogenetics lie in the identification of new treatment targets, what I call the iron lung problem. Our goal here is not simply to come up with better ways to apply the existing treatments, but also to come

up with better, more effective treatments in the future. And that's all I have today.
(Applause.)

KIM BECHTHOLD: Good afternoon. I'm Kim Bechthold and in the audience today is the president of our company, Dr. Peter Tolia. Dr. Tolia is a professor of pediatrics at the University of Medicine and Dentistry in New Jersey. He's the executive director of the Institute for Genomic Medicine at that university, and he'll be here to answer your questions, especially your scientific questions, later.

As you know, neuropsychiatric disorders are huge, 1.5 billion projected in the world. And the World Health Organization has also projected that, by the year 2020, depression will eclipse heart disease in incidence in the world. And depression in the United States right now is running at about 20 million. Neuropsychiatric pharmacogenetic test growth is projected by Kalorama, and the red line is the neuropsychiatric testing, and the green is HIV, and the yellow is cancer. So we're looking for major growth in what is a major medical field, absolutely huge.

The promise of personalized medicine in our field, in neuropsychiatry, is really quite extraordinary. Dr. McMahon mentioned several of them, and besides preventing adverse response, personalizing treatment and diagnosing, we can also, with genetics, determine the efficacy of the drug as the patient is being treated. That's a new first and a very exciting one a little ways off.

Prevention is the other area of true excitement for pharmacogenomics and personalized medicine. We can shift to wellness medicine from medicine that treats illness. And we can do that with genetics. We can use information and education because patients actually understand the genetics and it can be explained fairly easily. We can reduce the cost of medicine; we can regain for the individual personal productivity. And, I think, really excitingly, we can reduce the stigma of mental illness, the alienation and the loss of dignity of the individual.

So our company has a program in this new opportunity. Our program is, first of all, a course for the clinician to do just what McMahon said, and that's to provide strong clinical utility in the tests that we develop, to work to find and make possible very solid reimbursement for those tests. And then we take on a new task which is different for a laboratory-test development company, and that task is to educate the patient and the family. We've just found a study that shows that patients and consumers actually really trust genetic tests. There are no laboratory tests in neuropsychiatry, but they do trust their genetics.

And so we have to respect that they are going to trust what we tell them. We have to know the science is good; the science is strong. And we also have to be sure that we've interpreted the science for them so that they're not misled, so that bad things don't happen. So we have a very exciting and a very challenging task. We need to work very hard at privacy. It's a huge and a very, very important issue. And we need to reduce the stigma of these diseases by working in partnership with the patient-advocacy organizations, with

groups like Revolution Health that are available to the health-seeking consumer, and advise and let the consumer know what's available for them and what they can ask from their doctor.

So we're working in four areas. We're personalizing medicine for depression by in-licensing Dr. McMahon's work and that of his colleagues, developing a test for suicidal ideation with antidepressant use, citalopram. We know that it's difficult to differentiate between major depressive disorder and bipolar disorder, and that it's critical for the doctor to do so because the medication path is different for the two disorders.

And then we're working to personalize drug treatment as Dr. McMahon mentioned as well. We're not there yet; it's going to take a little while. And we're working the area of prevention in an exciting new area of gene by environment discoveries.

As has been described, the black-box warning apparently created a rise in suicide rates in the year 2004. The CDC announced this in September. We don't have the data from 2005 so this isn't definitive, but the rise was extreme in certain categories and I think was fairly unexpected.

Ten to 14-year-old girls committing suicide, the rate increased 75 percent. Fourteen to 19-year-old girls, the rate increased 38 percent. Fourteen to 19-year-old boys, the rate increase was 8 percent overall, 14 percent increase. And the reason this is so phenomenal is that in the past 15 years, suicide rates in the United States have declined 28 percent. In the United States, we have 32,000 suicides per year. And what most people don't know is that suicides outnumber homicides by a margin of three to two.

This is a website that I found last night and I was amazed. It goes on for page after page after page of citing antidepressant issues with violence and school shootings and on and on. One of the papers that Dr. McMahon mentioned that came out this year cited the publicity surrounding the use of SSRIs as one of the possible reasons for doctors not prescribing as many of the drugs as normal and for the suicide rates to increase.

The ones that we remember most, and I think will stick out in our minds, of course, are that Eric Harris, the young shooter in the Columbine school slayings in 1999, who was taking Luvox. And Jeff Weise, the young American Indian boy in Red Lake, Minnesota, who took nine lives and his grandparents, was taking Prozac. We heard about this; I'm sure most of you had. And in 2000, a Wyoming father who took his own life, his daughter, his granddaughter – and GlaxoSmithKline, in that instance, settled with that family for \$6.4 million.

So we believe that the work that Dr. McMahon and his colleagues have done is the basis for a history-making test. And we call it the Marc-C test. C is for citalopram. And the test, with the early data from Dr. McMahon's studies, and others, show a 98.3 percent sensitivity and a 99.2 specificity. The most important part – because that's just a little bit misleading – the most important part is that we currently can predict the risk of suicidal ideation from 1 percent to 59 percent. I'll talk about that in just a minute.

There are 4.2 million new prescriptions written per year for citalopram. The class, Celexa, is the primary drug; that's off-patent now. And we have the test – as it stands, the four markers are validated in our CLIA-contract laboratory in Dayton, Ohio. Physician reimbursement hotline has been established and we've identified the CPT codes for the physician to code to seek reimbursement. And we have a patient financial-assistance program that we're ready to launch when the test is ready for the market.

This is some commentary from opinion leaders. By and large, I think the one that I would direct you to is Dr. Gershon's, who is an editor of the American Journal of Psychiatry, stating, "It would be a major clinical and biological advance if a dangerous clinical event were associated with specific genetic variations." And the confirmatory studies, of course, are the key now that the original research has been done. And one confirmatory study has been completed and the data are now being analyzed. And this was completed by Dr. Elizabeth Bender and her associates at the Max Plank Institute. Four hundred more patients are going to be added, and we're told that the results so far are very, very encouraging.

And then our company is going to be launching a second – or actually, a third – study this year of 2,000 patients in the United States. And we're projecting that that will be completed by 2009. At that time, we would move for FDA approval of a test kit. And we project that that would be ready by the second quarter of 2009. Interestingly, under current U.S. regulations, a test can be performed out of CLIA-certified laboratory without FDA approval. And we're preparing for discussions with the FDA to see if the early data from the Max Planck Institute will constitute in their minds sufficient data for a commercial test, or whether they feel that we should wait for the second confirmatory study before the test is launched for our clinicians.

This is the part that we wanted to show you. This is risk prediction for the doctor. Secretary Leavitt's Health and Human Services study on pharmacogenomics named one of the barriers to this new field of medicine as being the doctor's inability to understand the tests and not wanting to take the time figure them out. Of course, who has the time if you're a physician? So our scientists and consultants had developed this chart. And you'll see the males are – it's a little bit shorter because one of the markers there, the GRIA3, is on an X-linked chromosome, so they have fewer. But if we take a female who is homozygous for the interleukin 28RA at AA, and she is homozygous for the PAPLN, and she is homozygous for the GRIA3 and the GRIK2, her risk is 36 percent of developing suicidal ideation on treatment with Citalopram.

Now, the doctor has information he has never had before. He also uses his own clinical judgment in determining – is this patient going to return for follow-up treatment? Is she conversant? Does he know her? So he can now use this particular risk to make his clinical judgment as to whether to use this drug, change to a different drug, or institute psychotherapy and a number of other things. But let's take a look if we have a different patient.

This is a 16-year-old patient, let's say, and she is homozygous for the first two markers, but way over in the right-hand category. She is homozygous for the GG of the GRIA3 and homozygous for the CC of the GRIK2. She is at a 59 percent risk, according to these early studies. So the doctor now knows that it's not really in that patient's best interest to use that drug, and he may institute a number of other policies.

So moving on, the development of the bipolar test for differentiation from depression. The need here is of course that – the story that we all remember, Chris Pittman at 12 years of age, who was prescribed Zoloft and shot his grandparents, and now is serving a 30-year life sentence – those things can be avoided with the new genetics, response to antidepressant drugs.

And then we have an area of prevention, using personal genomics, and here is the experience of life, combined with a person's genetics, to determine one's risk for depression when under stress. And we can predict depression, we can predict post-traumatic stress disorder, heart disease, anti-social behavior disorder, psychosis, risk for migraine headache, simply using this new field of gene-by-environment research.

This comes from the clinical brain disorders branch and shows a totally different connection between two areas of the brain that are mood regulating in persons with different genetics.

Preventative medicine absolutely requires privacy. We have got to see GINA, the Genetic Information Nondiscrimination Act, must be passed. Patients are passing on being genetically tested, and they are not entering clinical studies. Some companies, such as IBM, are announcing that genetic data is off limits. Reimbursement, the change is coming, thank heavens. There needs to be incentives for wellness. Medicare currently does not pay for educational tests. And we'll see much of this coming in the future.

So in essence, the need is great, the opportunity is absolutely amazing, and we're doing our very best to bring these tests to those people who really need it most.

(Applause.)

JOAN SCOTT: Thank you, Kathy. I will be playing the role of Jeff Botkin today, who is stuck in Utah someplace. And today I'm going to talk about the recent recommendations that came out of the EGAPP working group on the use of CYP450 testing in individuals with depression who are being started on treatment with SSRIs. And I'll explain more about what EGAPP is in a second. But let me just set the stage as to why the EGAPP working group started this evidence review.

As you have just heard, depression is a major public health issue in the United States. The lifetime prevalence is 16 percent, which is a pretty sobering number, and it's a major cause of disability in the United States.

The first category of choice in the treatment of depression are this category of drugs called SSRIs. They are the first drugs of choice because of their tolerability and safety as compared to other categories of anti-depressants. But the problem, as you've just heard, is it can be very challenging for clinicians, in individuals with depression, to find the right balance of what is the right drug, what is the right dose, and it can take a while to go through that entire process. It can take two to four weeks before you know whether or not a particular drug is going to work, and if it doesn't, then clinicians and patients often go through several cycles of trying different medications, different doses, et cetera.

In addition, there is a certain percentage that don't respond at all to this category of drugs, and then some that need to stop treatment because of adverse reactions. So it would be nice to have a method or a test to be able to do on individuals who have depression, who are starting treatment, to determine which is the best drug, what is the right dose, to narrow that therapeutic window to start getting responses fairly quickly and avoid adverse reactions.

And that is where genetic testing for CYP450 could potentially play a role. Now CYP450 is a whole category of genes that altogether metabolize probably 90 percent of the drugs that are on the market today. There are two specifically that are involved in the metabolism of the SSRIs, and they come in different variations. So we all have different versions of these genes, and there are versions that can produce enzymes that have higher levels of activities so that when you take the drug, it clears it out of the system more quickly. There are versions of that gene that have lower activity so that when you are given that drug, it may not get metabolized as quickly.

And this is sort of a schemata to show you how that could work. For most of us, if we're given a standard dose of one of these SSRIs, we probably have one of the the variances that are more prevalent in the population, and we metabolize the drug in sort of the intermediate route. However, individuals who are called poor metabolizers, who have variations of that gene that produce enzymes that have lower activity – when they are given the standard dose, they may not metabolize that drug as quickly, and so if you measure the circulating levels of the drugs in their blood, they have elevated levels of the drug. And those individuals, theoretically, could be then at risk for adverse reactions because of the elevated drugs in the circulating blood.

On the other hand, though, are those individuals who are called ultrarapid metabolizers, who have variances of the gene that have increased activity. Those individuals, when you give them the standard dose, may be metabolizing the drug so quickly it gets – whoosh! – out the door, and theoretically, those individuals may not be getting a therapeutic response because the drug isn't hanging around in the system.

So the concept is, then, if you have an individual with depression, and you do genetic testing to figure out which of the variances they carry, you may be able to better predict which drug to start them on, which dose, and narrow that therapeutic window and prevent adverse reactions.

The test is available clinically through many different laboratories, and some of the laboratories develop their own versions of the test. There is also an FDA-approved kit that a laboratory can use to offer the test. The test can also be received directly by consumers without needing to go through a healthcare provider, through the Internet.

So that is what the concept is, that is what the theory is, and that is what the potential benefit is of testing for CYP450 genes, but does it really do that? That is what the EGAPP working group set out to evaluate, by doing a systematic and thorough review of, what does the data show to suggest that doing CYP450 testing ahead of time will affect clinical outcomes?

And let me just say a few words about the EGAPP working group. EGAPP is an initiative that was sponsored through the CDC that has been working for a couple of years now. It is an independent non-federal working group that specifically has developed methods and processes to rigorously evaluate genetic tests coming out so we can look at the evidence of, do they work or do they not.

And the need for EGAPP, or an entity like EGAPP where we are systematically reviewing the information, is necessary because there are a proliferation of tests that are coming out. It can be a very short turnaround time from the time when a genetic discovery is made to when a test can begin to be offered clinically. And clinicians need guidance: Who should be tested? When should they be tested? How should they be tested? What do you do with the information when you get testing? And that information should be based on rigorous review of the literature.

And so the goal of EGAPP was to develop a process, a sustainable rigorous process to evaluate what is the data that we know about these genetic tests, to really answer the question, does testing really improve clinical outcomes.

The one particular review that I'll talk about today on the CYP450 testing was conducting through the Duke Evidence-based Practice Center. In addition, the EGAPP working group did a review on literature that wasn't included on the initial AHRQ review. Those reviews are sent out for peer-review process. And then based on the quality, the quantity, and the consistency of the data, and the review of the data, then the working group develops recommendations based on that.

So what do we look at? Well, first of all, we look at does the test work, because that is very important. And then we also look at, is the genetic variant that we are testing really associated with a clinical outcome of interest? And those outcomes, of course, can differ depending on which particular test you're looking at.

For the CYP450 review that we just did, the outcomes that we were looking at were, was that previous graph that I showed you correct? If you do genotyping on individuals, do the variations of the genes that they have really correlate with what their circulating levels of the drug are? And then, even more importantly, does the genetic variance that a person have predict how well or not they will respond to a particular SSRI?

And then the ultimate question, of course, is knowing this information, even if there is good clinical validity, does it really make a difference to have this information in the clinic? Does it really improve clinical outcomes by doing this test?

So for the CYP450 test, the overarching question that we were looking at is, what is the evidence that doing genetic testing on individuals with depression prior to initiating treatment with SSRIs can affect patient outcomes? And here is what we found. First of all, the analytic validity was good, so that is good. However, the data associated with clinical validity found that there was no consistent association between an individual's association's genotype and their clinical response, both how well they responded, and additionally whether or not they would have adverse reactions.

Now, part of the problem in looking at these studies is that there are few of them. The number of studies that have been done is relatively small. They are small patient populations, and so some of the quality of the data is problematic. And one piece of data that I'll show you here is looking at, does the genotype really correlate with the blood levels of the SSRI. And as opposed to that previous slide that I showed you, that showed that there were three different groups depending on which genetic variants that you have, when you actually look at the studies, there is considerable inconsistency and overlap, and what the actual blood levels are depending on what your genotype is. And then there were no studies at all that actually tried to address the overarching question, which is, does testing really affect patient outcomes?

So based on looking at all of that information and evaluating, again, the quantity, the quality, and the consistency of the information out there, the EGAPP working group ended up with the statement that there was really insufficient evidence to either recommend for or against the routine clinical use of CYP450 testing for SSRI treatment.

Now, when you have insufficient data, there can still be very important clinical contextual issues that could influence a clinician's decision about whether to test or not. So we looked at some of those contextual issues, like the cost of the test, and the fact that there are really no good clinical guidelines about what to do with that information, and that testing may in fact lead to mistreatment or delayed treatment or inappropriate treatment. So for that reason, the EGAPP working group discourages the use of CYP450 testing at this time until there are additional clinical trials.

Now, does that mean that we should eliminate all CYP450 testing and say, hmm, let's go home; there is no benefit whatsoever? And the answer is no. I think what we have done is we've outlined what is the evidence that we have to date, and where are the gaps and the information that needs to be filled in. And at the end of the EGAPP recommendation, which is in the pamphlet that you received today and can be obtained through the EGAPP working group, there are a number of areas where it's outlined of where additional research should be encouraged, because it very well may be that there are subsets of patients that would benefit from testing, and that CYP450, though, plays a piece in a very complex puzzle about how we treat depression.

Thank you very much.

(Applause.)

ROBERT BERNSTEIN: Good afternoon. I'm Bob Bernstein from the Bazelon Center for Mental Health Law. And I'm here to give you sort of a different view of this whole enterprise. I'm giving it to you from the perspective of civil rights and how this kind of science may land on the ground for people who have mental illness. So I was very respectful of the alliteration that the conference organizers put together, but I added to it a bit. "DNA and Depression: Test, Trust, Treatment," and I added, "and a Touch of Trepidation." I didn't say terror, but I think there is – (laughter) – a good deal of unease in the mental health community about what all of this means.

In order to understand it, we need to understand that there are two very different worlds of mental illness. There is the middle-class world – and I think you know which is which from looking up there – and there is the world of people with serious mental illness who drift into public systems. Clinically they may start out not that all different. But if you're an individual without good commercial insurance, without access to the best mental health services, you may find yourself on a downward spiral that moves you to the group that is very reliant on public mental health services. And depression itself is sort of an interesting diagnosis to consider because those symptoms straddle both populations.

Now, there are some crosscutting issues, and some of them have been alluded to earlier. First and foremost mental health consumers, let alone the people who treat them, don't know very much about the new neural science at all. They hear buzzes about it, but well, those of you who have been at a seder will know that there is the son who doesn't know enough to ask a question, who requires a certain amount of information to even know what it is you should be asking about.

Second, there are questions about how valid is this whole enterprise, and I'm going to get into the history of what people have experienced a little bit later. Privacy is certainly an issue, not only my privacy but does my genetic information reveal information about my family members who may not want that out there? Stigma could go either way. Is it good news to know that I have a genetic marker for depression so in a sense it ain't my fault, or does that lead to the next thing? Am I indelibly labeled as somebody who is at risk of depression, and what does that mean in terms of my stature within society?

Some people question, given this era where access to care is getting harder and harder to achieve, whether genetic markers are going to become a factor in terms of eligibility for benefits. Will I only get treatment for depression if I have markers which ultimately show that I have the real thing? And that leads to something that people in both worlds are concerned with, but even more so, people in public mental health. Is this going to further depersonalize mental health care and reduce services to the use of a pill. And for many people, that's a very bad thing.

Finally, given all of these unknowns, how do I give informed consent to participate in treatment that involves my genetic history? Now, marginalized people receive marginalized health care, and this is a whole discussion in itself, but I think it's important to know that the public mental health and the private systems are separate and very unequal systems.

Many people in public mental health are experiencing the hollow promises of community mental health that in the 1970s was envisioned as not simply becoming a mechanism for distributing pills, but a whole comprehensive system of services that would look at all kinds of factors affecting mental illness, including poverty and racism and access to opportunity, and what we have is nothing near that right now.

For many people, including people with major depression who are in the public mental health system, therapy, unlike what Woody Allen may access, consists of a 15-minute session with a psychiatrist maybe every six or eight weeks, and that is what is called therapy. The outcomes are very poor. Many people experience cycles of re-hospitalization. And when things don't go well, there is the shadow of coercion, that if I don't go along with an inadequate treatment plan that really hasn't met my needs, the courts may step in. And all of this sort of has contributed to a message of hopelessness.

Now, as I said, in some sense, the courts have become enablers of inadequate mental health. And some of the scenarios, not those that were mentioned earlier, but some of the scenarios associated with mental illness and violent behavior really have set the stage for the courts to become much more involved in health care. And that is another question; what is that all going to mean in the future?

Now, everybody will benefit from better tailoring of the sort that has been discussed earlier. The treatment for depression and other mental illnesses is often much more random than the public tends to believe. And particularly in the public sector where there is an interest in cost-cutting, we've had to battle initiatives such as fail-first policies, which require a physician to first use the cheapest drug and see if that works, and if the individual fails on that, then they can go successively to other drugs.

The idea that genetic testing might validate more precise tailoring is a very positive thing. For people with serious mental illness who often don't go for services willingly, the bad experiences with drugs really have contributed to dropout rates among people for follow-up services. So this is a very good thing. But this says it all really, where is the beef going to be? How is this going to land on the ground for people who receive mental-health services?

Looking at the Institute of Medicine – and there are other sources that have very similar conclusions – despite what we currently know about effective care for mental or substance-abuse conditions, numerous studies have documented the discrepancy between care that is known to be effective and care that is actually delivered. And often the gap is, how cheaply can we get away with serving people who are regarded as a social burden.

Now, in mental health, system failure has become business-as-usual in many ways, and this has contributed to an atmosphere of low expectations. People who come in for public mental health are often given the message that you're going to have a mental illness for life, you're going to have an unstable living situation, and prepare yourself for it.

And I thought I'd share with you some information that I think speaks volumes. This is from the federal government, the Center for Mental Health Services, which is a part of SAMHSA, and I can't imagine it's any better now. Within 30 days of discharge from a state hospital, 9 percent of people will be readmitted, 14.6 percent will be readmitted to some psychiatric hospital, which may be a private hospital as well, and within 180 days, over 20 percent of people will be readmitted for care.

Now, in any other area of medicine, these outcomes would be jaw-droppingly shocking. But this is what has been tolerated in mental health. And I'm sharing this with you because notwithstanding the hope of science, there is also the cynicism and the underfunding that exists on the ground for many people. And it's going to be very interesting to see how those reconcile themselves.

In 2002, there was a very honest appraisal of the nation's mental health service delivery system by the president's New Freedom Commission on Mental Health, which stated very succinctly that America's mental health system is in shambles. And, again, we're talking about some very good science, some very promising science that is going to be delivered to a system that really is ill-equipped to even deal with the most basic of care for people with mental health needs. There has been quite a lot of discussion promoted by the federal government, promoted by SAMSA, recognizing that the system is in such bad shape. The federal government is saying we're beyond reform; we need to transform ourselves into something new.

And just to tell you how bad things are, one of the ambitions of transformation is to ensure that people have a single treatment plan. And you think that is pretty basic, but you know, if we can accomplish that for people, that would be something good.

Another ambition that is less tangible is this: There has been a real push to move services in the direction of being more person-centered, more tied to recovery, less tied to a pill, and more looking at how services can enable people with mental illness to move from the margins of society to the mainstream. So here from 30,000 feet is really the issue as I see it. How will this intense focus coming from science that focuses pretty narrowly on symptoms and response to medication, how is that – and will it risk further blurring the attention to the individual who has the symptoms? I don't know where this is all going to go. I do know that our history doesn't bode well for where this might end up. So those are my remarks. Thank you very much.

(Applause.)

HUDSON: I'll start off with a couple of questions, and then we'll open it up to all of you. Joan, I have a question for you. You talked about the period of time that it can

take for a physician and patient to work out the right dose to an antidepressant. You mentioned two to four weeks. And I'm wondering if a genetic test is done and that sample is sent off before initiating treatment, what is the turnaround time for laboratories to actually get a result back, and if there were sufficient evidence to recommend testing, would it even be realistic for physicians, given the turnaround time for testing? Or do you need tests that can be performed by physicians at the point of care?

SCOTT: The turnaround time for genetic tests can vary greatly. And I honestly cannot tell you how long it takes to get a CYP450 test back. It shouldn't take all that long. Now, that doesn't mean that it does take all that long. But you still should be able to get results back within a week or so, which you – two weeks?

Now, where you're sort of going there though is, a clinician really needs to make a decision fairly quickly, and it would be useful to have a test that they can do right then to determine, I'm going to give you your prescription and you go home. And so, yeah, there is going to be a delay when you're sending off a test and getting it back.

HUDSON: Kim?

BECHTHOLD: I think Francis might want to speak about the time that it takes for medications to be tested and the changes in medication that he found in the STAR*D trial. But I wanted to say that for the Mark-C test, our turnaround time is 48 hours. And because the doctor needs those results very quickly – in Dr. McMahon's study, I believe it was 97 percent of patients exhibited suicidal ideation prior to the 28th day. So for this particular adverse response, there isn't time. And in the future, that test can be done in the physician office. Also, a patient coming in for treatment – after he's signed all the various forms – the DNA sample can arrive at the laboratory and the test results can be there before the doctor sees the patient.

MCMAHON: I'd just add that I think this is going to be a short-term practical problem, because the technology is advancing so rapidly. Many people have predicted that the complete genetic sequence will be part of everyone's medical record within the next five years or so. So then, it really will be an issue of your physician looking up information that is already present in the chart. But I think that until that's possible, it's going to be very important to have the information back to the physician and patient as soon as possible; not only because of adverse events, but because you really don't want to waste time starting drugs that ultimately may not work.

The STAR*D trials showed that in order to give an anti-depressant a proper trial, you really need a full six weeks. And so once you commit a patient to a particular treatment, you're really in for what can be a very long haul if someone is feeling very ill and struggling with depression. So the sooner we can get that information back, the better. But I think the technology may solve this problem for us pretty soon.

HUDSON: I'll make this question sort of generic. You talked, Bob, very compellingly about the risk of depression and other mental illnesses and the various

socioeconomic and environmental factors. And I don't know if those were supposed to be proportionate, but socioeconomic status had a big wave there. And so I'm wondering, what are the relative risks here of the genetic contributors that we're beginning to identify and are likely to identify? And what do we know about the inability to identify them in terms of how important they might be, and the attention and focus versus the attention on some of these environmental and social factors that contribute to mental illness? And I guess that's for Francis and Bob to respond to.

MCMAHON: Well, they're both important for sure. The account we have at the moment for genetic factors adds up to an effect that is much smaller than the non-genetic factors. In the STAR*D, socioeconomic status was a huge predictor of who did well. And that's not so easy to fix, but it was a huge predictor, much better than any of the markers we found so far.

BERNSTEIN: Well, what I'm wondering actually is this, that I think it's safe to say – and I don't have data at my fingertips about this – but I think it's safe to say that people of lower SES tend to get into treatment later on than people who have ready access through commercial insurance. And there is sort of a double-edged sword here that you're suggesting. That's that, if in fact my genetic markers are already in my records somewhere, the good news is, perhaps some sort of screening with a small "s" can allow some earlier intervention for people who are known to be at risk of depression. On the other hand, as I said earlier, what does that mean? Do I have a label that is indelibly assigned to me? So I think it really is going to be a matter of, what do we as a society do with the science? And what choices do we want to make? And how can we use it most strategically to help people?

MCMAHON: Yeah, I would agree. I think we need to make a distinction between the kinds of testing that might be used to make good treatment choices when someone comes in with an illness, and testing that might be used to predict an illness. Some of the prevalence numbers we heard today: One in five people are going to have a depression sometime in their lives. So in a practical sense, we're all at risk. And I think then that the issue really becomes, once we do fall ill, how do we get the most effective treatment quickly? And the socioeconomic barriers to that in this country are huge.

Interestingly, in the STAR*D, of course, everybody had equal access to treatment, and even still, socioeconomic status was an important independent predictor. So there are other ways that struggling to make ends meet can affect depression adversely, even when you're getting the same care as somebody who is of higher SES.

HUDSON: I'm going to open the floor in a couple of minutes to questions, so get your questions ready. Kim, in your talk, you presented some really stunning and troubling statistics about suicide rates, and suicide rates increasing. And we talked about this over lunch, and I think it's important to be really clear with people about – so the speculation is that it was the decreased prescribing of anti-depressants that led to the increase in suicide rates. But can you talk a little bit – maybe both of you talk a little bit about the correlation between suicidal thoughts and suicide?

MCMAHON: Well, we focused in our study on suicidal thinking, because that had been the cause of so much concern about prescribing antidepressants. There really is, as far as I am aware, no good data suggesting that antidepressants actually increase suicidal deaths. In fact, the overwhelming data is that death by suicide is prevented by antidepressants, and that by far the greatest risk factor for completed suicide is depression.

So this is a distinct phenomenon that seems to be related in some ways – in a subjective sense, at least – to suicidal thinking and suicidal behavior. But suicidal behavior itself is quite rare. And in the STAR*D, only two people attempted suicide, as I mentioned. Interestingly, one of the people who did, whose DNA we had, carried both of these high-risk markers, so that ultimately what we'd like is a way that we could use testing to identify people who would be at risk even though they may not be able to tell us that they're having that thinking. But I think this is a distinct phenomenon. It's driving a lot of concern. It was underlying the ultimate decision to put the black box warning on. But it doesn't really seem to predict suicidal behavior in any powerful way.

BECHTHOLD: And I think as far as taking a little bit different tactic, I don't think we know from the studies yet whether the reduction in prescribing was the cause of the rise in suicide rates. There are just a lot of factors, I think, to consider. The important thing is, we have three times as many suicides as homicides – three to two – in terms of suicides versus homicides in the United States.

No matter how you cut it, that's too much; it's a treatable illness. We have good drugs. What we can do now with personalized medicine is to make those drugs safer and create more confidence in both the physician prescribing, and in the mother and father taking in the young teenager, and in the young adult who is considering therapy. So the challenge really is to make them safer – and then I completely agree with Bob, there are many, many other challenges here. But we have excellent drugs. We need to get people into treatment.

BERNSTEIN: I want to add on a bit to that as well. I mean, clearly suicide and homicide are just tragedies, and they're awful. But they're both low frequency. When you look at the numbers of people who were treated for depression – I forget what the millions was – but it was millions and millions and millions. And there are 32,000 suicides, so it's a tiny, tiny fraction. So a percentage increase may look large because the denominator is pretty small to begin with, so you have to be careful about how you look at those statistics.

Whether this has anything at all to do with prescribing practices, I don't know, because we're living in a time when there is a war going on; there are people coming home with PTSD; and they affect family functioning. There are all kinds of potential explanations that have to do with time of measurement, and I think it's certainly something we need to look very carefully at. But again, a message that I'm not sure gets out as clearly to the public as among scientists is that genetics doesn't foreclose the possibility that environmental factors have a huge impact as well. And I think that's the risk that people are going to latch onto this as the answer instead of part of the answer.

HUDSON: Great, so now we'll open up the floor for your questions. There are two microphones here, so if you walk up to a microphone, we'll take you as you appear there. And if you'd say your name and your affiliation.

Q: My name is Andrea Kalfglou. I'm from the University of Maryland, Baltimore County. And your thoughts about the military just brought up a question for me. And that is that we talk about how we don't want genetic discrimination. However, the number that I've heard is that 6,000 American servicemen and women have committed suicide since coming back from the Gulf, which is more than have actually died in combat. If we were able to do genetic testing for predisposition of PTSD, is that something that we in fact might want to do in order to prevent these deaths?

BERNSTEIN: What's scary about that is do we want to test to find the best soldier? And I think the beauty of your question is, it really gives us pause about what does all this mean? Where might this lead us? And I don't know what to say beyond that, but that's just a very interesting observation I think that you made.

BECHTHOLD: I'd like to add that we're in touch with a group of psychologists at Ft. Bliss Army Post. They transition 20,000 servicemen going to and from Iraq every month. And the issue now appears to be that there are a good number of suicides that occur after deployment in Iraq. And so the post-traumatic stress disorder may be a factor, and the doctors there are concerned, because we have a genetic marker that identifies those individuals who are likely to have a higher risk for depression as a result of stress. And of course, wartime and serving on the front lines is stressful, exceedingly. So the double-edged sword, which you –

Q: (Off mike, inaudible.)

BECHTHOLD: Very likely not, and do we want to eliminate a career Army officer from serving in Iraq because he has a particular genetic predisposition, or do we want to take a smarter approach, and when he returns home and he's suffering from post-traumatic stress disorder, do we look at his genetics and use those to help him receive treatment and help his family understand him, and not judge whatever is going on with him as though he is similar to everyone else, because genetically he very well may be quite different.

BERNSTEIN: You've got me thinking, and I don't know if that's a good thing or a bad thing. But you reminded me, there was a study done – I think it was during World War II – to see who would be most suitable to be a pilot in the Air Force. And they found that some people – I don't have this exactly right but this is the essence of it – some people really became very dizzy and seemed not to be very good pilots. And there was another group of people who didn't become dizzy at all. Turned out, these were the worst pilots in the world, because they didn't know if they were flying upside-down or not.

And the question that you're bringing up is this: Let's admit that PTSD is a horrible, painful thing. But it may mean that these are people who have their eyes open to

what war is all about and how awful it is. And in screening those people out, are we perhaps going this science fiction direction of looking for some ruthless people who will just be machines for us? So that's a very good question, as I say.

Do you have the answer?

SCOTT: No, I don't have the answer. But I guess I would just go back to what is the evidence? You identify genetic associations that are associated with this, that, and the other thing. And we, as a society, want to do things. We want to do things, because that's the way we are. And I think we have to really critically look at – and these are such complex issues that we're talking about. So what does one piece of this very big complex puzzle tell us and how do we use that information? And I guess that's where I would come back speaking to what Bob said. Our system just doesn't handle things well now as it is.

HUDSON: Question over here?

Q: Thank you. Khaled Bouri from George Washington University. My question is to Ms. Scott. Does the FDA have an EGAPP-like group that can rigorously oversee the hundreds of genetic tests that are in the pipeline? And if not, is EGAPP coordinating any results with the FDA?

SCOTT: Right now the FDA does not look at – and jump in here if I'm misspeaking – does not look at genetic tests that are laboratory-developed. They will look at the evidence around tests that are being submitted to them as a kit. And they certainly do look at the analytic validity of that kit, and they will look at what studies have been done in the way of demonstrating clinical validity. But with exception of one small category of laboratory-developed tests, they have not taken on doing reviews of every laboratory-developed test that's out there. You want to add to that?

BECHTHOLD: I should just add quickly that we're advised by counsel that the FDA has the legal right to review a laboratory-developed test when they determine that there is a public risk or there is a public issue involved. So while tests are generally laboratory-produced in this country, the FDA does have the right to step in and make certain that the public is protected.

HUDSON: It caught my attention when you were speaking, Kim, that you are in conversations with FDA, and it sounds like at least considering going down the FDA-approved kit route. And it is true that FDA says they have authority to regulate all laboratory-developed tests, and they're using so-called enforcement discretion, and only looking at a small slice of those many, many tests that are out there. But it was interesting to me that you indicated that you were going to go that route. And I'm wondering, from a business plan perspective, what were the costs that presumably encouraged you to do subsequent research and trials to be able to have enough evidence to submit to FDA, whereas that wouldn't be necessary for a lab-developed test?

BECHTHOLD: The decision is really not what we need to do for the FDA; the decision is what do we need to do for the clinician, what do we need to do for the scientific community, for them to embrace a test such as this? The cost is, of course, substantial for a young company.

The time issue is more of a concern for all of us, and that's because we're talking about suicidal ideation; we're talking about a serious adverse event. So the faster we can get everyone comfortable – the FDA, the scientific community – that these markers can be relied upon; they're clinically useful; then that's really what we're after. The additional time for FDA approval of a test kit is only about a year, gathering information six months or so in the approval process. So it's worth it to us; but again, we're relying upon the FDA to tell us what they see as necessary, what they see as important. And we understand that they rely upon the scientific community largely. So it's worth the time.

HUDSON: Well, and I think that you make an important point. And maybe Joan can reinforce this: Let's say that EGAPP comes out with a very strong recommendation that a particular test is ready for primetime and every physician should be using it. The time from that recommendation and even adoption by primary care medical societies – the time lag for adoption is very slow. And I think it's one of the big challenges we have in personalized medicine, is how do we make that translation process much quicker so it's in the hands and in the minds of physicians when they're seeing their patients?

BECHTHOLD: We think that a very interesting thing that is happening in this country right now is the consumers' interest in medical issues and the consumer online searching for information. So in years past, it was totally up to the physician for adoption. And we may find now that parents and young adults are very, very interested in what they find online, and so we have a major program that we're going to be instituting to reach those people who have a concern, who are going to pick up their mouse and see what's going on in the field of depression.

Q: Gale Javitt with the Genetics & Public Policy Center. That actually was a perfect segue for my question. Having followed Neuromark and the tests that you're working on for some time, I've seen apparent changes in your business model, and it appeared that at least some of your tests at some point were going to be offered directly to consumers, like the stress gene test that you talked about. I was wondering, will the Mark-C test be offered directly to consumers, and if you've changed from that approach to one where you're going through clinicians, what were the reasons that you made that change?

BECHTHOLD: Thank you. We don't see the Mark-C test being offered directly to consumers. And our original pre-market experience with the stress test told us that without legislation, without GINA, without legislation to protect the individual, that even preventative medicine was simply not going to get off the ground. So we did an early study to see what the consumer, what the doctors would do. We shifted our focus at our company then to developing clinical tests simply because of all of these issues – many of the issues that Bob brought up. So no, the Mark-C test will go through the physician; we don't see a change in that.

HUDSON: Okay, I am looking at my watch, and we have I think four people in line, or maybe three. So we're going to take these questions over here and then we'll probably wrap up. Joe?

Q: Thank you. Joe McInerney, I run an organization in Baltimore that is focused on educating healthcare professionals about genetics. And we've heard a lot of discussion about the importance of educating patients and families. But I would like to hear anybody on the panel answer two questions. What would you like the gatekeepers that are prescribing physicians in particular to know about these kinds of tests so they can use them effectively and explain them to their patients before they order the tests? And second, how would you like to see that educational content delivered to the providers? Who should do it?

MCMAHON: Well, I'll take a stab at that. I think the first part of the answer is that physicians need to get moving because consumers are able to get genetic information themselves now. We're no longer the gatekeepers. There are these companies that people can access through the Internet, and for a few hundred dollars, they can get information back on a half million markers.

Q: But we're still the gatekeepers for the drugs.

MCMAHON: The gatekeepers for the drugs, yes. But we don't have a monopoly on the information anymore. So I haven't had it happen yet, but I don't think it's too far off before I'm going to have a patient come into my office and say, okay, I already know what all my markers are and I'm depressed. Now give me the best drug.

And so it's critically important that we improve genetics education in medical school, in residencies, and psychiatry residencies as well as every other one. People who go through a residency in oncology now will learn a lot of genetics. Someone who goes through a residency in psychiatry will learn very little. So it's important to start very early. Physicians need to be able to intelligently consume the literature, keep up with it so they can interpret information that increasingly shows up in the popular press at about the same time it shows in the medical journals. There isn't a simple answer, but it's going to take some hard work, and physicians no longer have a monopoly on this kind of information.

BERNSTEIN: Just a quick answer. There is some work being done on health literacy in mental health that entails the consumer getting online in the physician's office and filling out information about what the symptoms are, what the goals are, and it leads the consumer to screens that show various treatment options and what the risks are and what the benefits are so that there can be some informed discussion with the physician when the consumer hits the physician's office. And I'd really like to see this kind of information incorporated in that as it becomes available so that everybody comes to the table a little bit informed about what we're discussing here, what the limits are, what the potentials are.

Q: Ed Abrahams, Personalized Medicine Coalition. I had a short two-part question regarding the EGAPP study that just came out. Given the paucity of data, I guess its conclusion was not really a big surprise. So my questions are, how can we generate more evidence around these diagnostic tests, particularly how drugs are metabolized? And the second part of my question is, as a genetic counselor, would you advise a patient who presented for depression to learn how he or she metabolizes drugs?

SCOTT: For the first, it would have to have funding available to support some of these studies that are out there. And I know that the CDC has recently put out an RFA for studies that will help fill in some of the gaps in the knowledge that we have. So I think there is an opportunity there for studies that need to be done to fill in that information.

As a genetic counselor, would I recommend is to have the tests done at this particular point in time? Again, it's a very complex issue around what's the particular setting and the clinical setting for that individual. At this point in time, I don't see that the evidence suggests that having that information will really help determine how to treat that individual, but again, there's usually a very complex contextual issue that you have to make that decision around with the clinician and with the family.

HUDSON: Okay, with that, I'd like to ask you to join me in thanking our panelists today. Thanks for coming.

(Applause.)

(END)