An International Analysis:
Enhancing the Regulation of Genetic Tests Through Responsive Regulations
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DR. MELZER: Thank you very much. It is a great honor to be invited to talk here. It is obviously a bit daunting in such illustrious company.

What we would like to cover very briefly is a little bit about the scientific context, which of course you have heard quite a lot and you have some fantastic leaders in the field, but I think this is going to be very important for the regulatory internationally.

Then I'm going to hand it over to Stuart, who is going to talk about the early commercialization of some of this new generation of common disease markers, some of the policy problems, which are global -- this market is taking off in Europe as well as the U.S., and many of the companies cross international boundaries -- some of the policy problems and some of the policy proposals.

What we are talking about is the result of a policy research project funded by the Wellcome Trust in the U.K., and it focused really on a very simple question: how do we ensure that doctors, patients, and healthcare systems can make informed decisions about the use of the new genetic tests.

So we are interested in the three phases of evidence generation. In talking to stakeholders both in the U.S. and Europe, we heard a lot about problems of incentives and the difficulty of financing clinical studies for the generation of clinical evidence.

The next step of course is the evaluation of the evidence by regulators or the public health and medical community and patient groups. Crucial, also, is the sharing of evidence. This issue of secrecy about the evidence, what exactly is in the genetic tests that people are selling, has been a really pressing problem in Europe.

What the project involved was individual interviews and workshops, focus groups both in Europe and the U.S., contacts with people in Canada and Australia, and I would like to thank the FDA for much advice and attending our workshops here in Washington.

Just to be clear, the Wellcome Trust is an independent research philanthropy with no connections with the drug companies anymore. The project was totally independent, and both of us have no conflicts of interest. We have no patents or anything. Our funding has come partly from the NIH and from U.K. research grants.

We are all familiar with genetic testing in the past, the family-based, often high-penetrance disorders where the clinical significance of a marker is fairly clear. But as you were discussing this morning, we are moving into a much different scenario in which there is a statistical association between claimed markers, in which the marker is rather more common in the cases than the controls. Sometimes the marker is only present in a small proportion of the cases. Sometimes some of the controls have the markers as well. So we are talking about predisposing effects in this project.

Again, you are probably all very aware of the enormous explosion in results, especially from the genome-wide studies. So the Wellcome Trust Case Control Consortium, for example, published 28 independent signals for eight conditions. We have seen some wonderful breakthroughs in age-related macular degeneration. In asthma we have seen really quite a big effect for mutation not

from the genome-wide studies but from similar work, and even such syndromes as restless leg syndrome and type II diabetes.

I work with a group in Exeter that does half of the Wellcome Trust case control analysis for type II diabetes, so I'm going to talk about that and use that as an example.

This is the sort of result that one gets from looking at 2,000 cases and 3,000 controls having genotyped some 500,000 markers across the genome. Along the Y axis is the strength of the statistical association, and along the X-axis is the position. What one ends up with is a massive statistical association, and so far we have only really worked through the ones that really stand out, the really big effect one. I think we are up to about 12 that are now robustly proven.

The important message, I think, for policy-makers and regulators is that there are probably many, many more in the bottom of those fountains that are going to prove to be robustly associated and of course many, many more that were just coincidence.

I was one of the many authors on the FTO gene finding that was reported that came out of the diabetes analysis. It was reported in the media as the obesity gene, the fat gene.

This polymorphism homozygote risk status adds about 3 kilograms of fat mass. The effect is there by age 6. It lasts into old age. There is no sign that is a kind of susceptibility to increasing weight gain, which a lot of people have claimed, or somehow susceptibility to continuing to gain weight. It has been portrayed in this extraordinary way in the media as the obesity gene.

On the lighter side, I guess I should translate the best approach, I think, from our media in the U.K. "'Does your butt look big in these jeans? Absolutely,' say scientists." But of course, these are the messages that the public are getting. At the end of the day, it is a 3 kilogram difference. Very small.

To emphasize that point some more, if you look at type II diabetes snips, the first one to be found, actually a little bit far from linkage studies, was the TCF7L2 polymorphism, which is associated in the homozygote state with about 60 to 70 percent increase, a 35 percent increase if you have one.

Many of the new ones are relatively modest. They are wonderful scientific breakthroughs that will lead to wonderful ideas about new interventions, but in terms of risks to individuals, they are down at the 15 percent, 10 percent increase in risk levels. There is a whole set of them, so we are going to have to regulate whole sets of these genes.

Now, older people are an interesting group to look at because if Cause F diabetes is going to develop, type II diabetes is going to develop, it should have developed by age 65. I looked at just the prevalence of this top genotype, TCF7L2, in people age 65 and over against whether they had diabetes or the intermediate stage, impaired fasting glucose, or no diabetes.

As you see, in the risk group there is a very clear association with this marker. Far more of the TT risk group have got it. But most people with the risk status don't have diabetes or the subclinical prodrome, and many people with the so-called protective allele do have diabetes. So I think this really puts into context that these are wonderful scientific breakthroughs opening up new biochemical pathways, but really, it is very early for clinical use. Of course, people are already marketing this test as a diabetes marker.

We played around, along with a lot of other groups, with combining the allele scores across I think there are 12 markers now that are proven. If you add up the number of risk alleles that people are carrying, you do start getting pretty big odds, so pretty big differences in risk at the extremes. Many people, however, are in the middle. The top 12 markers seem to explain about 5 percent of the variation in type II diabetes risk.

So with 12 markers, we are only explaining 5 percent, and for most purposes, people would be much better off just having their fasting glucose tested.

Another interesting aspect, which I guess you may have heard already, is that many of the things that have been marketed and that people have been working on have failed to replicate in these big, decisive studies. So for example, there was a paper in the New England Journal showing that of the top 85 markers for myocardial infarction, none of them really showed up. If they are true, there must be an extremely small effect.

But what is also very interesting with the top myocardial infarction marker is the pretty big effect: doubling of risk for early myocardial infarction, so really standing out.

What is really interesting is it sits pretty close to a cancer locus, the P16P15 locus. Mutations in this site are involved in malignant melanoma, and we really have no idea what other effect that snip is having. Although not the same snip, the same locus came up as the second-biggest marker for diabetes. So it suggests that we are just beginning to scrape the surface of the biology. It may also have some effects on cancer.

When people get these tests, we have no idea what the overall predictive value for health outcomes as a whole could be. Again, this test is already on the market.

So, conclusions of that rapid context. A rapidly increasing list of markers, a few with large effect, large enough, some of them, to tempt people to use them in paternity testing or pre-implantation testing. For example, the macular degeneration ones and maybe even the myocardial infarction ones. So there are quite possibly high risk applications but also a lot of small effects. Most of the tests we see and have to regulate are going to be sets of markers.

I haven't mentioned this. Most of these studies are from Caucasians. Very little evidence on minority groups at the moment. The predictive value of these markers may be different. Lots of unknowns on the biology.

I will hand it over now to Stuart, who will talk about the market.