**An International Analysis:
Enhancing the Regulation of Genetic Tests Through Responsive Regulations
Q&A**

DR. FERREIRA-GONZALEZ: Thank you. Thank you very much. That was a very interesting presentation and very comprehensive.

We are going to open it up for questions, and I guess I will take the prerogative, being the chair of the session, to ask you a question.

When you show some of the current oversight for laboratory-developed testing, you show a role for the FDA but I didn't see anything about the CLIA or the role of CMS, which does have currently oversight over laboratory-developed testing. I was just wondering if you can comment on that particular issue.

MR. HOGARTH: Yes, that's right. There is a gap in my analysis as well as a gap in the regulations. So I think this is really a crucial issue, and it is a crucial issue for us in Europe as well. We really need to think about this question that has been thrown up in the last year of the ways in which there are overlaps between the two systems of regulation.

If you start to have FDA involved in laboratory-developed tests, how do you deal with the issues of quality assurance and analytic validity, where clearly CLIA already has a role. That is a very important issue that has to be addressed because what we absolutely don't want is to subject anyone to unnecessary duplication of regulatory requirements.

I think that equally applies perhaps in some cases, or you could argue it would apply to companies who are already subjecting their tests to pre-market review by NY State. I think there really needs to be careful consideration of how you deal with what could become a serious kind of a matter of duplication of effort by regulators, which is a waste of the taxpayers' money, and effort by companies when they could be better spent developing useful innovations for patients and doctors.

DR. MELZER: Could I just add to that a little bit?

DR. FERREIRA-GONZALEZ: Go ahead.

DR. MELZER: I think, especially in Europe, the emphasis on self-certification and review has been mainly on the analytic level. For most purposes, the analytic validity is really very good. The problem for clinicians is the clinical evidence. I think that is why our analysis is focused mostly on the clinical evidence. So clinicians in Europe are getting tests marked with a CE mark that certifies compliance with European directives but it actually means nothing for clinical evidence. That is also very misleading, to have tests that are given a mark of approval on an analytic basis but their clinical validity might be completely absent or claims might be completely misleading.

DR. FERREIRA-GONZALEZ: Francis.

DR. COLLINS: I want to thank you both for a very clear elucidation of the issues and some thought-provoking recommendations. That was really quite a thoughtful presentation.

With regard to the principle that you are putting forward I think as one of your main themes, namely the disclosure of the evidence that underlies the clinical validity and utility of tests in a fashion that is possible for both patients and providers to be able to get access to that, that does seem to be a general theme that many people are beginning to embrace quite strongly. I guess it is the idea that sunshine is the best disinfectant if you are trying to make sure that this is done in a credible way.

With regard to the specifics of how to do that, I wonder if you could reflect, based upon what you have seen of various models, about the value of having such a registry be purely voluntary versus having it be mandatory in some form or another. Is there a comment you would like to make about those alternatives?

DR. MELZER: Stuart is averting his eyes.

[Laughter.]

DR. MELZER: Reflecting on the European position, the European position requires test-makers to assemble information supporting their claims in a dossier that can be inspected by the regulatory agencies if concerns are raised for tests at the lowest level of vigilance. So there is some specification of what should be in the dossier.

There is a major problem in Europe in that currently this is regarded as commercially sensitive and not made public. Certainly, all our stakeholders in Europe are saying this is absolutely unacceptable. We have the situation where people are marketing tests and refusing to say which snips they are actually testing, what evidence it is based on, and how the results are generated.

But of course, if you look up many of the companies that are marketing in the U.S., you cannot find on their websites which snips they are testing or what the evidence is based on. So there seems to us and the stakeholders we talked to a way forward which involves, say, the central regulator of this country, the FDA, specifying the headings under which information needs to be structured and made available on the Web. I'm talking about clinical information.

You might think of that, for example, as identifying which groups of patients and what the purpose of the test is, saying exactly which snips are going to be covered, what the scientific basis is, and so on. Then the idea would be that that would be made available on the Web.

There is no sign that that is happening voluntarily. Many companies are being very secretive and there is a tendency to perhaps compete on including as many diseases as possible, starting this new wave of genome-wide pseudoanalysis, and so on.

I think many of our stakeholders felt that we need to get to a position where companies don't compete on clinical evidence, on the number of snips they put in, they compete on other things. It would be as crazy as the airlines competing on safety. They don't compete on safety. They all collaborate on safety. We need to get to a point where the clinical evidence part is available. There is no sign that that is happening naturally in Europe yet.

I think there is another thing that worries clinicians, which is it is all happening now. I noted in your report that you are talking about a five-year window of voluntary registration. The worst abuses are going to happen in the next five years. Coming back in five years will leave clinicians with very little to look at on the Web while this revolution starts.

We have had patients, for example, who have taken very poorly supported tests for prostate cancer who are now considering having their prostates out. So it is pretty serious for clinicians. They are being asked to advise patients, and there is nothing on the Web and no sign of the success of the voluntary kind of ethos of disclosure.

MR. HOGARTH: One of the issues about going for a voluntary system would be why wouldn't you make it mandatory? What are your concerns. Is it that you think it is suddenly going to impose too much of a burden and that people won't be able to provide this information quickly, and so forth.

If your concern is that, one alternative approach is to make it mandatory but have a risk-based prioritization of who you expect to comply with it first, if that is your concern.

I would suggest that it really is not unreasonable to expect someone who has developed and is offering a clinical test to be able to summarize in an evidence dossier the analytic and clinical validity of the test, its likely clinical utility, the indications for its use, and so forth. If someone cannot provide that information, then what on earth are they doing providing the test.

DR. FERREIRA-GONZALEZ: Mara and Steve.

MS. ASPINALL: Thank you so much for your thoughtful report. I have a question about when you looked at the molecular model and you looked at the IVD model. It seemed that you focus on a small number of companies, relatively new companies, that have spent a huge amount of money on the clinical validation, clinical trials, and the science. Have you done comparable analysis on the dozens of existing molecular tests that exist today that are not part of this relatively new generation of different types of tests, or comparable types of tests with different kinds of business models?

MR. HOGARTH: Yes. I think you are absolutely right. Obviously, Mara, there are lots of companies who are developing and commercializing molecular diagnostics, including your own company, Genzyme, who don't follow the business model that I outlined.

But nevertheless, I do think it is a very, very significant development. I think the oversight debate has for too long neglected having an adequate discussion of what emerging business model means or its significances. So I think it is a really important thing to bring to people's attention.

One of the things that we have been thinking about is the fact that historically we have had two big debates going on, one about oversight, one about regulation of genetic tests, and another one about gene patenting and IP and biomarkers. They have been completely separate, generally. In some senses, on the one hand, you are beating companies over the head saying you must provide more clinical data, and on the other hand, you are saying one of the incentives that might allow you to invest more money in clinical studies we think you should have.

We need to think about how those two debates connect up. I think that is a very important idea for this Committee because, of course, you are actually looking at gene patents at the moment as well as developing your Oversight Report. I don't think there are any easy answers there. Absolutely not. Apart from anything else, this is an emergent business model and we don't even know if it is going to work. But nevertheless, it is something I think we need to think about.

MS. ASPINALL: I would agree. I agree very much on the importance, both short-term and long-term, of this new emergence there. But, have you looked at the existing ones that are not in that model and the impact of regulation on the currently existing tests, many of which don't have any IP covering them? Have you looked at the impact of regulation on those?

MR. HOGARTH: All the companies that we spoke to when we were doing our research, including your own -- I'm very grateful to Bob Yoher [ph] for participating in one of our workshops and speaking to me at length on a number of occasions for probably far longer than he was really happy to.

A lot of the companies that we spoke to don't follow that business model, so we are very much hearing their views as well as the views of other companies.

DR. FERREIRA-GONZALEZ: That is a very good point. Steve.

DR. TEUTSCH: Thank you. This has been very helpful. You talked about getting back to the issue of where in this process you provide oversight and to what level of intensity. I wonder if you could talk a little bit more about the reimbursement level.

If reimbursement were not to occur, if the information that you just indicated should be there, potentially on a mandatory basis, were necessary for reimbursement, then I wonder if you could reflect on whether a voluntary system would be all right. Then, do we have examples where the payers have actually required that so that we know there would be some level of greater scrutiny at that level?

MR. HOGARTH: Probably the most important thing to point out about the whole role of reimbursement as a gatekeeper is that it doesn't function in the area of direct consumer testing. We don't have a health technology assessment for direct-to-consumer tests.

The degree to which some of the companies that have entered the space on a direct-to-consumer basis are doing so because they don't think they would stand a cat in hell's chance of getting approval through a rigorous HTA process I leave for you to speculate on. But I do think that is one of the issues that we need to think about.

I do think the Amplichip is an excellent example of where FDA said, okay, you have told us what you know and what you don't know about the strengths and weaknesses of this test. On that basis, as long as you are careful in your claims for the test and your labeling, then we will allow you onto the market. Reimbursement then took on the role of having a rigorous assessment of the clinical utility of the test.

I don't know if I'm answering your question.

DR. TEUTSCH: No, you are. That's fine. I think EGAP is trying to tackle at least the direct-to-consumer products as well, at least to see if they can. So there is nothing intrinsic in an HGA process that limits it to reimbursement tests.

DR. MELZER: Could I offer a couple of comments? The situation in Europe is rather different because of their nationalized health services, which have a much easier role in reimbursement. But there is a bit of a catch-22, which is some of these tests really do offer real clinical advantages and there is nobody there in the gap between discovery and getting all the clinical cost benefit data to the point where reimbursers might shell out.

Many of these tests will have some components that are under patent and many of the other markers not under patent. So we are going to have a real lack of incentive to do the cost benefit and cost utility studies. I know you flagged this up in your report as an area for public-private partnership, but it would be pretty awful if the reimbursers were so strict that some of the fruits of this wonderful discovery don't come through to patients.

DR. FERREIRA-GONZALEZ: Marc.

DR. WILLIAMS: I have a couple of comments, one related to what you just talked about. I think it is an issue that has been raised in other contexts about pay for evaluation. You release something out into the marketplace and let the evaluation take place in the context of a post-market and then make a decision as to whether or not there is utility to support the claims. That has been promoted in some ways.

I think there are a number of us that are concerned about, once something gets out there, trying to reel it back in can be a real challenge when clinical practice actually changes, although given the rate of change of clinical practice perhaps that is not a concern. But I would be interested in a reflection on that.

The second comment relates to some of the international aspects that I think, as one of the people that has been working on this report, we didn't have perhaps as broad a view. Not to say that I want to take on the world here, but I think that the point that you made about redundancy and too much regulation or duplicative regulation does have an impact in the sense that a number of these companies are in fact offering these tests in different markets.

In some of the rare disease tests, we have international aspects where the only laboratory that is doing it may be in Italy or Norway. How do we get samples from here to there. I know that some European laboratories have actually undergone CLIA certification so that they can actually provide these tests within the legal construct of the United States healthcare system.

So it seems like perhaps it should at least be reflected in our report that it seems that there are reasons for international discussion so that we can at least achieve some relatively common goals and possibly even look at how the regulators in different places may work together to ease some of the regulatory burden for companies that want to bring things worldwide. So I would appreciate comments on that.

The question I have is that, obviously in the context of this particular discussion, we have been talking about genetic tests, as is appropriate since that is the name of the report, but one of the things we always struggle with in these discussions is whether genetic tests in and of themselves are exceptional compared to other types of tests.

That wasn't something that you addressed in your presentation, and so I guess I would just be interested in your opinions as to whether there are reasons in regulation to treat these types of tests as exceptional.

DR. MELZER: Yes. Post-market review, test review and marketing and then testing it in situ, that is going to be pretty difficult for these predictive markers. Many of them are predicting outcomes late in life and so on. The actual model of how it would be released and how it would be used is going to be pretty difficult to work out.

There is also an issue of where research ethics come in. It has been suggested that some companies are actually using the samples that the public are sending in for testing as research fodder without any kind of institutional review board and without flagging out to people that that is what their samples are actually being used for.

So it is actually quite a difficult situation. I don't think we have any experience yet for these new complex disorders, and I guess we are going to have to see how systems could help generate evidence. It seems, certainly for prediction, to be more an epidemiological problem rather than a health service problem. But there may be specific niches that people are going to come up with wonderful clinical applications that we can't even imagine. That will have to be worked through.

Its national aspects. I'm sure you are very aware that these are before the Harmonization Taskforce. It does look as if, under the constraints that the various major markets have, you are grappling with identical problems in moving towards kind of similar solutions.

The problem in Europe, obviously, is that we are a loose confederation of countries with much less central authority, much less of a track record of authority than the FDA has. So the whole system has been built on the central regulator reviewing these secondary ones, being a meta-regulator. It is very much seen as a first stage, so people have been thinking about it as an incremental regulatory regime, starting with some very simple that could work across Europe, and then gradually racking it up.

So within the confines of the "real politick," I'm sure there is an enormous scope for harmonization. The companies we talked to seem to be very thirsty for that. They do not want to have to produce different evidence for different markets. I'm sure that a common evidence requirement could be arrived at fairly easily.

What was the third point? Right, genetic exceptionalism. Our team has endless debates about this, and I'm sure you have had it. How can I summarize it. It is true that many other tests have very similar characteristics, if not all the characteristics, of genetic tests, but genetic tests do stand out for a number of reasons. The first is that the public think they are different. The level of education is very low and the gullibility is very high.

So in terms of "real politick" again, there does seem to be something different about genetic tests certainly in the U.K.. Although the strict regulatory system is harmonized with all other tests, it is just part of the device regulations. There are special committees looking at genetic testing.

I think the second issue is we have had these very recent explosion of results. Now, that is probably happening, or going to happen, in proteomics and so on, and it is going to throw out very much the same issues.

So I would argue as a public health person that genetics should probably be seen as an opportunity, a trigger, to improve test regulation throughout. So it shouldn't be ignored because it is just a test because they are different, but it does offer us a political opportunity to get some of that basic information to doctors and patients so they can make sensible decisions.

It is a really good trigger because it is a bit different. When you get tested, you are revealing something about your family, and in the current environment you are likely to overestimate the importance of that and make decisions that would affect other family members.

Do you want to say anything?

MR. HOGARTH: Just something to follow onto the exceptionalism issue. I think once it comes down to what you are asking the device regulator to do, or the regulator or clinical laboratories, they really have to take their standard criteria for the evaluating the risks of the tests and apply them to the genetic tests and decide within those standard criteria are these high-risk tests, moderate-risk tests, low-risk tests. If people aren't happy with that, then you have to say, well, does the regulator have to redefine its criteria for risk classification.

I actually think that you can deal with this just by using the traditional kind of risk classification schema that the regulators have.

On the issue of international cooperation, I was fascinated. I was speaking to an IVD regulator from Canada recently. They said to me, the problem is we don't actually have time and resources to kind of write our own guidance documents, often. So we just take FDA's and we put a slightly Canadian spin on them."

So maybe Steve should be being paid twice or getting some kind of consultancy, although I'm sure the government would never allow that.

So there are lots of interesting examples of international cooperation that I think are very important: the OECD guidelines on quality assurance for instance, FDA's work with EMEA on voluntary genomic data submissions and looking at very complex genomic data for pharmacogenetic tests and so forth together, and of course, very well established mechanisms like standards development and so forth.

I think it is really important to think about how we can lower the burdens for companies by making more consistent standards internationally.

DR. FERREIRA-GONZALEZ: Thank you very much.

Because of time, we are going to cut the questions at this point. If we do have more time at the end, we can invite back our two presenters. So, hold those questions for the end.

Thank you very much, Mr. Hogarth and Dr. Melzer, for being here today and sharing your insights to inform the Committee.