An International Analysis:
Enhancing the Regulation of Genetic Tests Through Responsive Regulations
Stuart Hogarth

MR. HOGARTH: I think David has made very clear that the science is moving fast, and the science is moving very fast into the clinic. For instance, the U.S. company InterGenetics has launched the OncoVue test in Europe this year. This is a polygenic test which is intended to inform women about their risk of breast cancer by using a whole panel of markers and interpretive algorithm, the kind of thing David was just talking about.

Of course, we have just had the launch of deCODE-me by deCODE genetics, an Icelandic company. This move into susceptibility testing is closely linked to the risk of consumer genetics, companies offering their tests direct to consumers over the Web. In the case of deCODE, they are offering genetic risk assessments for 17 common diseases, including AIDS-related macular degeneration, breast cancer, asthma, colorectal cancer, multiple sclerosis, heart disease, and prostate cancer. Their list of diseases will be continually updated as new discoveries are made.

We have just seen the launch of a very similar service from a company called 23-ME in the States, and of course, we have Navigenics and Smart Genetics very close behind.

Another aspect of this market is that it is really very international. So, deCODE based in Iceland, but the test is available in the U.S. InterGenetics are based in the U.S., but their test launched in the U.K. The company Genetic Health, the one whose website is shown here, offers a range of susceptibility tests from their base in London, but the tests are provided by an Austrian company called Genosense. This Austrian company offers their tests through intermediaries in a number of countries, including Canada and the United States. So we really are facing what is a very international market.

So, what are the concerns about some of these tests. Well, this is a quote from someone who took one of Genetic Health's susceptibility tests for a range of diseases, including heart disease and breast cancer. As you can see, she understood herself from the test results to have a 140-fold increased risk of cancer, but she was very optimistic that she could deal with this by eating more fruit and vegetables.

The reaction from another piece of media coverage from Genetic Health's tests from the British Society of Human Genetics very recently was that they were very concerned that the tests that were being offered were more or less useless and that they were being promoted with unsubstantiated and overblown claims.

Of course, this really is nothing new. There has been longstanding concern about genetic tests moving into the clinic far too fast, particularly in the area of where tests are for more common diseases. Perhaps BRAC is the most high-profile example to date of a test where the claims at market launch went way beyond the data behind the test.

So this policy concern has resulted in a huge amount of work by a series of high-level committees just like yourselves in the U.S., Canada, Australia, Europe, and elsewhere, looking at the policy issues around oversight. I think one of the key conclusions that has come out of many of those reports is that genetic tests shouldn't enter routine clinical practice unless they have had some kind of independent evaluation.

Linked to that concern about evaluation is a concern about trying to deal with the issue of getting good, comprehensive, accurate information to patients and doctors about tests. So we can think of this in terms of regulation as regulation by information disclosure, which is a concept that is now very popular in the consumer protection field, where it is seen as a way of dealing with the asymmetries of information between creators and consumers.

So there is a real concern, as David touched on earlier, where companies aren't even telling people which snips and which genes they are actually testing. In the case of Genetic Health, there is complete secrecy over the panel of genes. So this issue of an asymmetry of information is really important to the whole oversight debate.

The other thing that has come out of the oversight debate to date is a clear idea of what needs to be evaluated and the categories of information that patients and doctors need to be informed about. This Committee would be very familiar with the framework, so I won't dwell on it.

So we want to enhance oversight to ensure more independent evaluation of tests and better information for doctors and patients. But sadly, at the moment we don't have such a system. What we have is really a regulatory system without real teeth and a whole lot of gaps.

Now, of course, you all would be intimately familiar with the gaps in the regulatory system in the United States, but I just want to speak a little bit now about the situation internationally. It is interesting that although we have all gaps in our regulatory systems, there are actually different internationally.

If we look at the United States, we know that the primary kind of gap in terms of pre-market review of tests is that historically the FDA has not regulated laboratory-developed tests as medical devices. Of course, now the FDA has identified a small subset of tests, IVDMIAs, which they are going to subject to pre-market review.

In Europe, it has really been rather different. The primary regulatory gap in Europe is that we classify nearly all diagnostic tests as low risk. They are therefore exempt from pre-market review. They are the equivalent of a Class 1 device in the U.S. That includes all genetic tests except tests for PKU. Do not ask me why PKU got singled out, but there you go.

Whereas our treatment of laboratory-developed tests is quite different, we think of laboratory-developed tests as medical devices, although we give some exemptions. For instance, healthcare institutions. If you are a pathology laboratory within the National Health Service in the U.K., you are not subject to our device regulations.

Then, if we look at a couple of other countries, Canada essentially has the same regulatory gap as the U.S. insofar as its authority over laboratory-developed tests is unclear. Australia in fact has been busy revising its medical device regulations. It treats laboratory-developed tests as medical devices, and it treats genetic tests as moderate risk. So most of them are subject to pre-market review.

Of course, in a sense, this is rather depressing. We have been talking for over 10 years about how to enhance oversight. We have been talking about in Europe. We have been talking about it in Canada and Australia, and the U.K., and we still have a whole lot of significant gaps in our regulatory system.

But I guess the important thing is in fact policy is moving, as well as the science is moving. It is being commercialized, and the commercial aspects are moving. Policy is moving as well. Of course, you know what is going on in the States, so again I won't bore you with that.

But in terms of elsewhere, in the United Kingdom we did have a couple of years an advisory code that looked after direct consumer testing, although it fell into abeyance for reasons I won't go into now.

We have a new system for evaluating single-gene tests within the National Health Service, the U.K. Genetic Testing Network. The National Screening Committee has been looking at the regulation of commercial screening services, and in the last year the Human Genetics Commission has renewed its interest in the regulation of direct-to-consumer genetic tests. There will be a new report out from the HGC within the next couple of weeks on that issue.

Within Europe, we have had the creation of EuroGenTest, a kind of network of clinicians and lab people across Europe who work on quality assurance issues and other issues around the quality of genetic testing. Our IVD device regulations are imminently going to be revised, and we have been in discussion with the European Commission and member states about ways of enhancing the regulatory system.

Of course, we have had a drug regulator, EMEA, working on pharmacogenetics, not least in collaborations with the FDA. People in Europe have been participating in international initiatives such as the OECD's guidelines for quality assurance for molecular genetic testing.

The Council of Europe, which is something separate to the European Commission, is working on a protocol on genetic testing which really addresses the issue of direct-to-consumer testing and recommends that tests be offered with individualized medical supervision and predictive tests for monogenic diseases and susceptibility tests should only be offered with counseling. So we have quite a lot going on in Europe.

In Australia, they decided to completely revise their IVD regulations, in part to deal with the laboratory-developed test issue, in part to deal with the issue of genetic tests. They have also issued guidance in the regulation of nutrigenetic tests, which is an international first.

In Canada, they have issued guidance on pharmacogenetic tests, and then if we look internationally, I have already mentioned the OECD guidelines on quality assurance. The Global Harmonization Taskforce, which is a forum within which device regulators get together to talk about how they can harmonize regulation, has been working on issues around IVD regulation.

The International Committee on Harmonization has been working on pharmacogenetics. Muin Khoury, with colleagues in the public health genetics area internationally, not least with some of our colleagues in Cambridge, has been working on HUGENet, which has been a very important initiative.

Of course, in the U.S., probably the most significant issue around pre-market evaluation of tests and the FDA's role has been issuing of the IVDMIA guidance. I would suggest that the IVDMIA guidance probably has correctly identified the area where FDA intervention was most urgently needed. The guidance has brought clarity to FDA's position in a situation where it had been intervening with individual companies on a piecemeal basis.

But really, it opens up the question of what to do with the rest of the laboratory-developed test sector. Obviously, that is an issue which this Committee has been considering in some detail as it has developed its draft report.

Clearly, the guidance leaves most LDTs outside of FDA regulation. It doesn't cover all monopolistic providers. It doesn't cover homebrew tests, where an unlevel playing field would remain between kits and the homebrew test. For example, the Roche Amplichip, an FDA-approved kit for pharmacogenetic testing, has to compete with non-approved tests. It doesn't deal with other tests that we might consider high-risk, perhaps pharmacogenetic tests, perhaps direct-to-consumer testing.

So we spend a lot of time talking about the whole issue of how the technology and the tests are moving very fast and the ethical, legal, and social consequences. We think of these as areas where rapid change is causing disruptions which need today to be dealt with at a policy level.

But I just want to say something about the way that the IVD industry is moving because I think when we are talking about regulation we need to think about what we are regulating. I think that underlying all this technological change, clinical development, and scientific progress are changes in the business of IVDs that are really very significant. It is really crucial to understand this to thinking about how we deal with oversight issues.

In the traditional model of the IVD sector, companies hold intellectual property platforms and they tend to compete with each other. They develop different versions of testing for the same biomarkers, and they compete with each other over who has the best platform and so forth.

This means it is a very competitive industry with low profit margins compared with the pharmaceutical sector. With low profit margins, little protection of investment, and little experience or infrastructure for doing large-scale clinical validation, the traditional sector has really not focused on doing large studies to demonstrate the clinical validity or clinical utility of new tests.

A model where we have weak IP and biomarkers has meant that no one party is responsible for developing the clinical data and the clinical validity of a new test. So we have academic studies and professional advocates filling the gap, often promoting tests on the basis of ad hoc experience.

There is really a disincentive for doing large-scale clinical studies because any one manufacturer who made such an investment and brought a test to market would immediately find themselves competing with other companies. Indeed this issue is exploited by some IVD companies who specialize in being fast followers. There is an industry maxim which says it is hard to be first.

Now, things are changing. If you look at many of the companies in the molecular diagnostic space, what we see is that they are disrupting the traditional business model. Companies are developing tests based on protection of the gene or the association with the disease, and the emerging market for gene expression and proteomic tests is based, for instance, often on strong IP rights and biomarkers.

Many of these companies are seeing, for some of their tests, significantly higher levels of reimbursement than traditional diagnostics. So potentially, stronger IP and biomarkers, if it gives the company a monopoly on the test and it reduces competition, gives them an incentive to generate clinical data. What we are seeing is companies developing tests, offering them on a

monopolistic basis through their own reference laboratories or licensing them to another company, who offers them on a monopolistic basis, and companies are starting to compete in some areas on the quality of their clinical data.

I think that is very important. When we think about oversight, it is all very well to think about how we can improve the evaluation of tests. But if companies don't have any incentives to generate clinical data, then there isn't really any point in creating better systems for evaluating what simply won't be there.

Now, having said there may be some advantages to this new business model, clearly it poses some challenges, as monopolies often do. Obviously, many people have expressed concern that tests offered on a monopolistic basis are not subject to the traditional kind of peer review in the field where lots of different lab directors can take on a test, try it out for themselves, see its strengths and its weaknesses.

There is also a concern that where companies had significant investment to bring a test quickly to market that there is a danger that it will make overblown claims for its tests too soon. We have seen a number of companies in this kind of field where such concerns have been expressed.

That is not to try and say that all companies that are developing tests in this business model are bad players, but in the absence of an effective oversight mechanism, we don't actually have a way for patients and doctors to distinguish between good players and bad players.

So this is a rather provocative slide entitled "Six Reasons to Require Pre-Market Review for Laboratory-Developed Tests as Medical Devices." I hope some of the kind of issues there are fairly straightforward. Obviously, they can pose the same risks as tests. Laboratory-developed tests are big business. Leading companies are bigger than many kit manufacturers. Even for the small laboratories, they don't get a CLIA exemption, so why should they receive an FDA exemption.

It is clearly possible to do pre-market evaluation of laboratory-developed tests because we have the example of New York State, where many, many, many of the LDTs in the U.S. are subject to pre-market evaluation through the NY state lab regulations. We have the example of FDA regulating and evaluating laboratory-developed tests.

It is also clearly the international trend, if you look at Europe and Australia, and we do have this issue around the business model for reference lab monopolies, which might in some senses pose a particular kind of risk.

So there are lots of different reasons why we might think about regulating laboratory-developed tests as medical devices. But we still have this concern that maybe we might be overreacting. Do we really want to apply statutory pre-market review to all laboratory-developed tests or is it in fact unduly burdensome. So, does one size really fit all. This issue obviously is particularly pertinent in the area of rare disease tests.

So maybe what we need is a range of alternative oversight options. You can really see the implementation problems we have had with trying to deal with the recommendations from successive committees has come up against the issue of how to balance evaluation, innovation, and access. The lack of clarity, I would suggest, on the respective roles of different gatekeepers; so, what is the role of reimbursers, what is the role of clinical practice guidelines, what is the role of the FDA.

We also have the issue of FDA resources, or the equivalent regulatory agencies in other countries. Of course, we have industry reluctance for any kind of enhanced oversight.

So, can we have our cake and eat it. Is there some way that we can develop some kind of more comprehensive system of evaluation whilst ensuring adequate protection to the public and encouraging innovation.

I want to suggest that there is a number of solutions. These are ideas that have come out of our research with stakeholders right across the spectrum from industry through to FDA, patients' groups, et cetera.

One of the solutions is to focus pre-market review on truth in labeling. Another one is to have a far greater emphasis on post-market controls and clarify the role of different gatekeepers. Our research has shown some quite strong support amongst many stakeholders, although not all, it should be said, for the idea that pre-market review should be focused on truth in labeling.

The issue of the role of other oversight mechanisms and the role of other gatekeepers is linked to the idea of responsive regulation. So the idea that state agencies, whether it is the FDA or its equivalent in other countries, are not the only people who have a role in gatekeeping. We need to think about what the appropriate role of all the gatekeepers are.

Although your draft report doesn't mention the idea of responsive regulation by name, I think it has a very cogent analysis of different kinds of compliance mechanisms, ranging from mandatory to incentive-driven, to voluntary and informal.

Clearly, when we think about the three core functions of regulation, information-gathering, standard-setting, and enforcement and compliance, we can see that there are many ways in which a whole range of bodies, organizations, and gatekeepers can be involved in the process of oversight.

So the crucial issue that I want to explore now is really around this issue of providing accurate, comprehensive information to doctors and patients and the way in which we can use oversight to improve that. I will focus a bit on pre-market review, as well.

What can IVD device regulations do. We think that they should be primarily focused on pre-market review of analytic and clinical validity. They should set clear evidence standards for market entry. They can also monitor performance in the post-market environment. Most importantly, they can ensure truth in labeling and truth in promotion. These are the core functions that we think can be carried out by IVD device regulations.

But there are many things that they can't do. They can't deal with ethical and social issues such as genetic discrimination. They can't regulate clinical practice issues such as informed consent, and they can't evaluate clinical utility, which our research suggested most stakeholders was best left to health technology assessment and clinical practice guidelines.

If we focus on pre-market review and truth in labeling and truth in promotion, again I come back to this idea of regulation by information disclosure. We are trying to balance the need to protect the public with a desire to encourage freedom of choice. This is a kind of minimal approach which reduces the regulatory burden and passes on the responsibility for risk management to doctors and patients, allowing them to make informed choices about when and how to use a test.

But our research also suggested although there was support for this kind of idea there were concerns that doctors generally will not have time to do detailed surveys of the literature on new tests. In fact, we need to think of ways to simplify the information that we provide to doctors and patients, rather as we sometimes do, for instance, with food labels so there is kind of a clearer and easier to understand guide to the quality of evidence that supports new tests.

A scheme like this might take the form of kind of a simplified schema which could indicate where a test lies on the development spectrum from research to well established clinical use, or it might be based on evidence-based medicine standards as developed by the Cochran Collaboration.

Linked to this issue is the whole question of expanding the definition of a label. If we are going to focus on truth in labeling, then we really need to think about the issue that tests are quite different to drugs. With a diagnostic test, in general it is the laboratory, not the patient and doctor, who see the label. So device regulators need to broaden their concept of a label and ensure all those that are offering tests meet the necessary information available to clinicians and the general public. So test manufacturers and test developers should be obliged to keep their labels online, where they can be accessed by all, with samples of test result sheets which show reference ranges and so forth.

In the provision of information, the issue of labeling is another area where there is a clear difference between test kits and laboratory-developed tests. At the moment we don't have the regulatory equivalent of a label for a laboratory-developed test. That is a clear definition of the information that LDT developers should be providing to the users of their tests. This is an issue that FDA has started to address in the IVDMIA guidance, but it is clearly one where some more work is needed.

Regulators can also facilitate information disclosure by making public their device reviews and subsequent post-marketing data. Now, in this respect, FDA is far further ahead on this than Europe. In the U.S., OIVD publishes review summaries on its website. Sadly, such data is currently treated as confidential in Europe.

However, even in the U.S., it is possible that more might be done. I think FDA could maybe make a better job of making the information easier to find and presenting it in a more understandable way.

So, this kind of model of a very minimal approach to pre-market controls. We found support for this idea, but it was predicated on the idea that that would be balanced with enhanced post-market controls. When I say "post-market controls," I mean all those other forms of oversight that exist once a test is on the market. The role of reimbursers here is really crucial.

I think in the oversight debate there has been real concern in the past about health technology assessment and lack of HTA of genetic tests. That has led to initiatives such as EGAP. But I think although that has been very true in the rare disease field, what we are starting to see with tests with a broader application is that health technology assessment is operating as an effective form of oversight and effective gatekeeper.

If we take the example of the Roche Amplichip, it was approved by the FDA but it has subsequently been subject to a series of very critical HTA reports both in the United States and Canada and in Europe. So I think we can see a really strong and important role for health technology assessment emerging now as tests with broader applications emerge.

But equally important is the role of clinical governance. Many, many committees, including this one, have pointed out the need for increased use of and better funding for clinical guidelines.

There is also a role for independent sources of information. We have some wonderful examples and lab tests online, the GeneTest website, and clearly this Committee has spent some time thinking about how those mechanisms could be used to enhance oversight and they can clearly play an important role. We will talk a little bit more about that.

I focused on the role of the FDA as looking after pre-market evaluation, but clearly there is still quite a lot of concern expressed by industry and other stakeholders about an enhanced role for FDA and there is some concern expressed by FDA about having to take on far more work. I'm sure any of you who know Steve well will know that it is not unusual to get Emails from him on a Sunday afternoon, and it is not terribly clear that people in OIVD can actually work any harder than they are at the moment.

So, are there other alternatives to simply expecting the FDA to do more. I come back to this idea of the enforcement pyramid and responsive regulation and the role of other gatekeepers.

Now, a few years ago when your predecessor committee was working on the issue of oversight, there was a discussion in one of the meetings in which Steve pointed out that in fact FDA had been thinking quite hard about the ways in which it could develop more flexible mechanisms, including self-certification, the use of smaller data sets, different data sets. They clearly got a whole range of flexible regulatory tools that they might be able to bring to bear on this issue.

So what we have seen recently in the last year or so is a discussion about alternative regulatory mechanisms. One of these ideas is the idea of a data registry. It has been around for a while now. It has support from a range of stakeholders. It would appear to address the problem of information asymmetries without placing an undue burden on test developers.

I think it is also very much the kind of idea your predecessor committee was moving towards as they kind of wound up their work on oversight. I think they were thinking very much about the issue of how do you provide independent sources of information on tests.

Obviously, your draft report recommends a voluntary approach based on expansion of the role of the GeneTest website, and you recommend the registration of the lab and the list of tests offered and, in the case of tests not reviewed by FDA but by other bodies, a statement that they have passed through this review process.

Now, some stakeholders have suggested a more comprehensive registry which provides detailed information about the tests which labs provide. This is a useful suggestion, but it raises two issues, I would suggest. The first one is really the issue that, to act as a trusted source of credible information, a registry must be able to guarantee the quality of information on the registry and it must be able to deal with complaints.

So, how do we address this issue of having a registry but having a registry that has some real kind of authority. What I want to suggest is that one of the ideas is that we actually look upon the role of the FDA as a meta-regulator. When I say a "meta-regulator," what I mean is that the FDA has some kind of overarching role that in certain instances it can be the guarantor of quality. It can ensure, for instance, if there is a complaint, that it will address that. Whilst you can have something like a data registry that would in fact be maintained and managed by other parties.

We can see that it is possible for regulatory agencies to act in this way as a kind of meta-regulator when we look internationally. So if you look at the European model for IVD device regulation where tests are subject to pre-market review, it is not done by the equivalent of the FDA, the regulatory agency. It is done by a notified body, an independent third party who carry out the review.

Now, the model that the Australians are developing is that the Therapeutic Goods Administration, the equivalent of the FDA, has also adopted third-party review. So the professional pathology bodies will act as reviewers, but TGA has a role in standard-setting, can step in where there are complaints, and will review tests which are in the highest-risk category.

So FDA has the authority to empower third-party review and has experimented with it in the past, although I know Steve is not entirely satisfied with his experience of it.

Clearly, there are other agencies within the United States who could act as third parties. We already have the example of New York State, who are conducting pre-market review of a very, very large proportion of the laboratory-developed tests that are currently available in the United States.

In the rare disease field, we have recently seen the example of the CETT initiative, which has developed a system for evidence-based introduction to rare disease tests.

So I think there are some parallels here with the report's recommendations for private sector or public-private partnerships to review LDTs which aren't reviewed by FDA. I think the crucial difference here in the model that I'm suggesting is that the FDA retains an overarching role as the meta-regulator.

We still lack a comprehensive system of oversight which can provide doctors and patients with creditable, comprehensive, and accurate information on genetic tests. The new wave of consumer genetics companies makes this issue all the more pressing. We need to find ways to balance innovation and regulation. The idea of regulation by information disclosure, the concept of responsive regulation and its tools, including a more flexible approach to pre-market review and a greater emphasis on post-market controls, are perhaps some of the ways we can enhance patient protection whilst nevertheless encouraging innovation.

I just want to mention briefly that David and I are part of a bigger research team with colleagues in a number of places in Cambridge. Thanks a lot.