The Role and Economic Impact of Gene Patents in Drug and Diagnostics Development
Mark McCamish, M.D., Ph.D.

DR. LEONARD: It's a pleasure now to introduce Dr. Mark McCamish, Chief Medical Officer from Perlegen Sciences, who will give us more of an industry perspective.

Welcome.

DR. McCAMISH: I believe I'm here representing the dark side of the force.

(Laughter.)

The only thing I was fortunate to is have the schedule rearranged so I wasn't presenting after the snacks so you guys could have food to throw at me.

(Slide.)

In reality, what I'm here to talk about is perhaps the future of using genetics as we're trying to help patient care. As Dr. Leonard mentioned, she was talking about single gene defects and a lot of work that is going on. I'll be talking almost exclusively in my presentation about multiple gene areas or polygenic contributions to disease or drug response, and the absolute need for patent protection to support this research as we go forward in really trying to enter the future of using genetics to help with patient care.

Now Perlegen is a pre-IPO company. It's a private company. Right now we don't have any products so I'm not trying to sell a diagnostic and I'm not trying to sell a drug. We've conducted a lot of research in the area of looking at polygenic contributions to various disease associations. And Francis Collins can testify to the work that we've done in contributing to the science and contributing to the HAPMAP, et cetera.

I will have to confess, however, that with our work, which has been with a lot of the big pharma companies, we've not been able to make traction to get them to move this area forward as fast as we would like, probably because in reality they see that by targeting a patient to drug treatment that the perception in the marketing arena is that you will sell less product. So we are entering some of these difficult times with our collaborators. Therefore, we have licensed in drugs because we felt that it is the way that we can push the technology forward to apply this polygenic approach to improving patient care. So those are my claims as we move forward.

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As you all know, genetic variation is responsible for all inherited components. The one thing I'll be talking about now is variability in drug response and that's what we'll be talking about. I'm trying to introduce the technology and a little bit about how it's used so that you can get a background into the importance of intellectual property and patents to advance this science.

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As you know from a standpoint of drug development, and that's my background is drug development for the past 20 years, one size fits all is not working for everyone. In terms of patients, drugs are not precise, oft times it's too long to get the right drug or the right concentration, the right dose. Many patients don't respond at all to drugs and if you're dealing

with antidepressants a patient can be on an antidepressant for four months without having any benefit to that drug, and patients certainly are suffering.

Drug companies are not falling forward in terms of using the advancements in science and they're not winning enough. They are playing these billion dollar bets. And as we saw yesterdays from Janet's presentation, even half the time you enter into Phase III with a program that's costing you $800 million, half the time you fail. So the blockbuster model is dying and many stalled drugs are even better than existing drugs for treatments of a subset of people. This is an important point for patent protections. Let me just expand on this.

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If, for example, a company spends a lot of time working on a drug, taking it to Phase III, and then the product fails, at that point in time you have lost a substantial amount of patent protection because you've taken, let's say, 10-12 years of developing that drug. If you then have to rescue that drug, by the time you take a genetic targeting approach to taking that drug forward, when you get out in terms of launching that drug, you may only have three or four years of patent protection.

If, on the other hand, you can link that drug to a genetic test that subclassifies a specific patient population and you gain that intellectual property, you can expand the potential protection of that drug for many years and that would allow for industry to then support the further development of the targeted treatment.

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Why are we dealing with this area? We really are focused on improving patient care by better selection of therapies, getting the right patient on the right drug. We feel this can change the health care paradigm. We've seen this in the oncology area with herceptin. We're working in the non-oncology areas, metabolism, cardiovascular disease to try to do the same thing, and we think it can capture sustainable market value if you can have some exclusivity.

How? Identify genetically important questions where there's genetic variability in drug response. If there's no genetic variability in drug response then it's not worth pursuing.

We do this primarily by minimizing adverse events or excluding non-responders and we think this can impact the science and add science to the art of medicine. As you know, when physicians prescribe medications it's based on their past history and the mechanism of action but they still can't predict how that drug will respond in that particular patient.

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So what I'll talk about today are these bullet points that in a polygenic pharmacogenomic diagnostic you're really talking about a probability assessment. It's not an exact diagnostic. It's not like HIV or HCV where you have to have a 99.9 percent positive predictive value and negative predictive value. It's a probability assessment.

In our view options to care must exist. Because it is a probability assessment, if you only have one drug to treat and there's no other options, why do you want a probability of that drug working or not working because there's only that one option? However, if you're in the field of let's say diabetes and there's five different drug classes and you can give an idea to the physician that that

particular patient would not respond well to a specific drug class then perhaps you have an option that you can utilize. Therefore, the results of that diagnostic should alter patient care.

The clinical utility of the probability assessment must be valid, and that's something that FDA is working on. How do we deal with the validity of that predictive market?

What I'll get down to is reimbursement is key. The single test generates less value in this situation because it's not a multiple diagnostic test. In other words, it's not like glucose where you have a diabetic and you have to check glucose on a routine basis or hemoglobin A1C where you check on a routine basis. But a genetic diagnostic, it's a one time test. It's hard to create value on that one time test without charging a substantial amount for them.

As it turns out, the approved label is critical and I'll talk a little bit about that. It's not only the patent that you have, it's not only the information that you can publish but it's the label that you're able to garner specifically when you're dealing with drug.

And then incorporation in the clinical practice has many barriers that we've already seen. There are labels out there with drugs that have a recommendation that the patients should be tested but it's not mandated, and those tests are not often used by clinicians to understand, let's say, drug metabolizing enzymes for particular patients. So there are barriers that we have to go through.

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So back to this area about probability assessment. This is just simply a Gausian distribution. If you consider this, let's say, response to an anti-diabetic agent, so on this axis this would be decreasing hemoglobin A1C, a measure of glucose control, in patients here. So a Gausian distribution and I've just plotted out two genotypes.

For those of you in the back who can't see, the yellow area here I'm calling Y genotype. This would be what we would classify as non-responders. There is-essentially the mean response is a little bit less than no change in hemoglobin A1C after treatment.

The gray is a genotype X that we would call responders.

The only point here is that there's an overlap. This is not a precise diagnostic. You will be a responder or you won't be a responder. It's a probability assessment and then it provides information to the clinician about making that judgment call on the drug that they would use.

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And here's an example of a probability that's in an existing label. This is Meridia currently marketed as ibutramine by Abbott Laboratories. Basically what happens is if you treat patients with this drug--it's a weight loss drug, if you treat them for four weeks and they lose four pounds of weight, they've got a 60 percent probability of going on and achieving clinically significant weight loss, which is five percent initial body weight. However, if you treat for four weeks and they do not lose four pounds, they've got an 80 percent probability of not going on to achieve clinically significant weight loss.

The point is that you have to treat the patients for four weeks before you know this probability assessment. We feel you can use pharmacogenomics in this way testing across the broad spectrum of genes to find out if a patient has a probability of responding or not. That's the

benefit here is that you could get this type of a probability without treating the patient for the first four weeks and this would enhance not only patient care but it would be beneficial for sales of this particular drug.

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The question becomes who will order this particular test? Who pays for it? Who is interpreting the test? This is where all of your background really comes in, whether it's genetic counselors and helping individuals understand this probability assessment or in terms of ensuring that there's reimbursement.

These tests must have clinical utility. There's two publications that I'm mentioning here. One from China showing a striking association with one allele with carbamazepine induced Stevens Johnson Syndrome, a very severe dermatologic manifestation or adverse event to this drug. And they showed a very high predictive power, 93 percent positive predictive value, 100 percent negative predictive value. The problem was that there are only eight cases of Stevens Johnson Syndrome per one million patient years. So you're not going to test all of China to find a few of these patients. It's not very useful in terms of the cost of screening, et cetera. It's scientifically very relevant.

The second one is Chasman published looking at two SNPs that were significantly associated with reduced efficacy of a statin therapy. In this case patients with a single copy of the minor allele had a 22 percent smaller reduction in LDL cholesterol. It wasn't that they didn't have a reduction. They just had less of a reduction. So in this case the physician would not avoid treating the patient if they did this test. They would just have a prediction of less of a response. So what we're trying to do is get multiple genes that are predictive and then in an additive sense give the clinician advice about whether to use a particular drug or not.

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So how is this discovered? When I show this slide it reminds me of a trip I took to Mexico City. They've got a law there, just like in California, where you have to wear a helmet when you're riding a motorcycle. I was in Kentucky recently at the University of Louisville doing a presentation and there they don't have the law so it's not that big of an issue but in Mexico City this was actually one of the last World Cups I was driving. Everybody was crazy and screaming about this but all the people riding a motorcycle had their helmet on their elbow as they were driving around. So the law stated you had to wear a helmet but it didn't say where.

(Laughter.)

So finding these and applying this is almost that difficult. We've got to not only have the technology but we have to be able to apply it in the right way. I'm going to use genotyping as a technology to serve as an example of the importance of patents and exclusivity. There's all sorts of other technologies, proteomics, expression profiling, things of that nature, these are tools and genotyping is simply a tool to use as we go forward.

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The goal here in terms of genotyping is to understand that we've got 3.2 billion base pairs in a genome and the variances between individuals is less than one percent of that or .1 percent, and with that we're primarily focusing on single nucleotide polymorphisms. There can be between

six and ten billion of these common single nucleotide polymorphisms. Ultimately we want to end up with a test of let's say 10 to 50 of these polymorphisms because it's polygenic that give us information about the predictive power of either the patient having a disease or responding to a drug. There's a process of getting to this that is quite onerous and many people when they look at this in terms of the numbers think that we just don't have a prayer of a chance of finding these 20 SNPs out of eight billion as we go forward. But the technology is improving and we do have some technologies necessary to find this.

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Let me give you an example of a risk stratifier, and this will point out again some of the importance of patent protection. If you are looking for a risk stratifier for myocardial infarction, we already know that subjects with a comorbidity such as hypertension, diabetes, hyperlipidemia are already at risk for myocardial infarction, and these patients that you treat with these types of drugs for these indications are already at high risk. But which subset of these individuals that you see in patient—are seen all day in clinic with these types of diagnoses, physicians are judging patients' care and medications and balancing it. There are many classes of medications available for treatment of these diseases and multiple drugs are often required for the treatment of any one of these. Evidence exists that optimal control in each area is associated with less events, less MIs if you have better care.

Also, multiple surveys reveal that these diseases are not adequately controlled. Hemoglobin A1C is not controlled as well as it should be. Blood pressure is not controlled as well as it should be. Can we find out what subset of the population should be optimized with currently available treatment so that those individuals at greatest risk, perhaps the clinician can spend more time with them in terms of adjusting these medications trying to get them as normal as possible.

Having a patent around that diagnostic test would be important because you don't control the treatment of the drugs or reimbursement based on those drugs.

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The way this is done--and the reason I'm illustrating this is simply the cost of doing some of this research. The way that we are performing this research is we take individuals that have, let's say, myocardial infarction and individuals that don't. In this case we have between two and five hundred cases of myocardial infarction, two and five hundred controls. And in this case the control for myocardial infarction is really critical. You can't just have individuals like Jim Fixx who are healthy and are running around one day but in the next day they have myocardial infarction. The control is probably more important. You have to have people that have undergone angiography and show no coronary disease and that's your control that you're looking at. So finding those patients, five hundred of those individuals is very costly and expensive. So you get those individuals and in our hands we have a couple approaches but basically we're using either 1.5 million of these SNPs or a subset of these tag SNPs in the cases and controls, and comparing them statistically to see if there's an association between SNPs of interest and that event or that disease.

The difficulty is that the single study association gives you no value because there are so many false positives that are there. You've got to replicate it in some way or validate it in some way to then find those SNPs that are predictive. These become the diagnostic tests. All the work that we're doing in these huge wafers and arrays is exploratory and the diagnostic test can be a very simple five SNP genotyping array but that's the process of discovering these.

Just in finding some of these characterized phenotypes can be multiple millions of dollars as you go forward so you can see the cost of investment is fairly substantial.

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Now even after you do this and you provide this information, would that test generate value? The value of the diagnostics—they are extremely limited as I mentioned because it's a one time test and due to this fact most tests are expensive. The expense may preclude general use for guidance on aggressiveness of treatment, particularly with the genetic drugs and so reimbursement becomes key. Even who performs the test. Is it the physician that asks for the test? Is it a central lab doing the test? Is it a pharmacist that actually orders this and then uses saliva, for example? Who reimburses the genetic test? And how do you market this test once it's approved?

It can be perceived purely as a barrier to the physicians as they have to write a test before they figure out which drug that you use. So without exclusivity and patent protection, this approach really won't be pursued. People aren't going to fund this type of research without at least some basic protection.

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FDA, as you saw from Janet's presentation, is supportive about combining diagnostics with drugs and published this concept paper. They realize the value of having this additional information to judge the benefit and risk of treatment with this type of a drug.

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So let me give you an example of a drug diagnostic development approach to decrease an adverse event. So we talked about using genetics to look at predictors of disease so you know which treatment to use. This is looking at an adverse event. So let's assume that your goal was reduce a class effect adverse event by 50 percent and simultaneously introduce a new drug in that class. So this is a diagnostic drug co-development process.

In this case the adverse event was not immediately life threatening. We talked about reducing adverse events by a certain percentage but not eliminating them because genetics can't predict with 100 percent surety.

Other drugs in the class are available for treatment of this disease and outside this class so there's options.

Providing information to the physician about the increased risk of this adverse event would allow other options to be explored.

And this requires simultaneous development of a diagnostic with the drug and also requires identification of an acceptable diagnostic prior to entering in the pivotal trial. And the reason I'm going into this is also talking about the difficulty of producing these data and without patent protection, people won't be pursuing it.

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So this is the type of an approach. This is a very simple trial approach that one would utilize in trying to look at both getting approval for the drug as well as for the diagnostic and, theoretically,

by doing this you would create this intellectual property or patent portfolio to protect this use. Most drugs you would then—you would stratify based on treatment with a placebo or the drug itself.

Here you're doing a pharmacogenomic test. What you're trying to do is provide this clinical utility for that diagnostic test at the end. You stratify patients for high risk of the adverse event versus low risk. In each strata you then randomize to drug treatment or placebo treatment.

At the end of this type of conduct you can look at a primary efficacy analysis comparing the placebo and treatment of low risk patients which you think is what your label is going to reflect.

The safety analysis looks at all patients as it usually does and then the diagnostic clinical utility analysis compares the percent of adverse events and the group at high risk for the adverse event given the drug versus the individuals at low risk for the adverse event given the drug. The replication in this situation might require an additional Phase III program.

All of this is done to generate that intellectual property but it's also done to generate the label that is necessary to restrict the use of the drug.

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So the patent—the diagnostic itself is not sufficient. It's almost like a polygenic test. One gene is not sufficient to have a high probability of the disease. The patent alone is not sufficient but it's important. The clinical utility must be adequate to convince FDA to restrict use of the drug only to those people tested.

Let me give you an example of an even extending the use of drugs if you would provide this type of information. Yesterday you had a discussion about what you could recommend to the Secretary about stimulating the use of this technology. One thing you could easily recommend is something similar to the pediatric exclusivity where industry are granted an additional six months of exclusivity if they provide information about pediatric testing, pediatric labeling. You could suggest the Secretary do the same thing, the same approach where you provide an additional six months or year of exclusivity to companies that provide this type of pharmacogenomic information, subsetting of their information regarding their own drug. That's one way that industry could do that.

(Slide.)

So the IP will not predict use of the drug without use of the diagnostic in this case. Reimbursement is not likely if the test is only informative. That's the problem we're running into now. Clinicians are resonant to adopt a technology that is only informative. There are current drugs that have recommendations for drug metabolizing enzyme tests and they're not used.

The threat of litigation I put in an alternate color because I don't enjoy the threat of litigation just like Debra doesn't enjoy receiving some of the letters that are there but it may be an incentive for clinicians to adopt.

And incorporation of clinical practice has many barriers that can be overcome by a label if the label suggests or demands that you use this prior.

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So the genetic diagnostic targeting efficacy could also be useful and it provides that you have options that are available so this allows subjects to be assigned to beneficial treatments sooner. Instead of just getting more subjects on this same drug, more appropriate subjects are being treated and others who would not benefit can also be treated with other therapies.

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And due to time let me just skip through this.

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And talk about the benefits of genomic and proteomic research and the NAS document that was put together. The recommendations by the committee on IP, again from my viewpoint, were excellent. They're informative overall, concurrence with most of the recommendations. I have additional suggestions.

Recommendation 7, I would suggest that they add "industry scientists" in developing these technologies to the Patent Trademark Advisory Committee. That we also endorse the utility of a standard that patent applicants show specific benefit in currently available form so it's not just patenting a gene or a protein but what does that gene do. What does it predict?

And then recommendations 10 through 12 on the validity, features, properties, inherent characteristics of the invention or the diagnostic, what they were suggesting is a way of then independently validating. I guess I struggle with that from the perspective of when we're looking at these and trying to validate them clinically and getting a label approved for its use that's usually under the FDA domain right now when you're using a pharmacogenomic marker to use or not use a drug.

We don't often ask for independent verification of drug efficacy. If the drug is approved there's not another independent board doing a verification of that so I struggle with that recommendation.

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So my view on this is how do we lower the barrier to routine use of these types of activities, of these types of tests?

FDA support and the Critical Path Initiative are critical.

Finalization of this co-development guidance would help industry as they move forward and patent protection of discovery of validated genetic and proteomics is really critical to provide protection for the investment in the research necessary to go through the multiple steps of getting these things out in the clinic.

Education of the patent office on this emerging science.

Continued NIH support of basic clinical science. The new translational medicine efforts now, I think, are critical.

Also, supporting anonymous access to samples for exploratory research. The guidance document we talked about yesterday for consent of iv diagnostic device studies.

And then also continue to focus on reimbursement, which you guys have already discussed. How do we improve reimbursement for these tests? So Debra is now having difficulties getting the tests done because of reimbursement. They reimburse an adequate and validated diagnostic as we go forward.

So those are my comments in terms of focusing on these particular areas and, hopefully, that will contribute to the discussion we have.

Thank you.

DR. LEONARD: Thanks, Mark.