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Intellectual Property/Ownership Issues

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AFFYMETRIX[1]

A review of the agenda for this conference is a reminder of the tremendous challenge before all of us who are trying to build an ethical, legal, social, and economic bridge as we cross into this next era of genomics and proteomics, and all the other "...omics" buzzwords that seem to be coming out of biotechnology. I notice there is a question mark after "Revolution" in the program title. I have to object to that question mark, because I think there is no question; there is a revolution. But I also appreciate the fact that there is not an exclamation mark up there, because there is an awful lot of hype that runs through all of this. I think it is good to, on the one hand, think about all of these tough questions we are going to confront, but on the other hand, we should be grounded in reality and think about where we are today. We should contemplate how we need to literally put one legal, ethical, and social foot in front of the other to move forward responsibly.

Publication of the human genome, and the realization that we are all 99.9 percent the same, that we essentially share those three billion base pairs,[2] is a significant rite of passage. And yet, so much of this is about that one-tenth of one percent that we are all trying to figure out—the small percentage of DNA variation that differentiates us and makes most of us susceptible to some diseases.

Affymetrix is in the business of making a tool that, we think, is one of the fundamental points in understanding how to catalogue, how to decipher, how to interpret, and how to use this information. Our existing technology includes fitting the human genome on a chip the size of a postage stamp.

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* J.D., V.P. Government Affairs, Affymetrix. This work is based upon a live presentation made on February 5, 2004, and does not necessarily reflect events and changes thereafter.

1. Information about Affymetrix, a bioinformatics company based in California, is available at http://www.affymetrix.com.

2. For information about the Human Genome Project and related advances, visit the site of the National Human Genome Research Institute, http://www.genome.gov.

There are two great dimensions to the genome, and you can think of them as micro and macroeconomic if you will. On the bottom is DNA analysis, and that is sort of macroeconomic—for example, looking across an entire population to understand the differences among people within that population. And this gets back to the point that Michael was making about biobanks. A dimension above that, we ask the microeconomic question. We look out and we ask Michael, "What, specifically, is happening in your genome that would tell us if you have a certain condition, how you'll respond to certain medication, what your prognosis might be?" And so on and so forth. How do we take that understanding of you and reduce it to a molecular level? The word "reduce" is a misnomer because "reduce" sounds like there is less of something. But, in fact, by taking things down to a molecular level, the amount of information we are getting is so much more powerful that we are actually exponentially expanding our understanding of the human condition.

Affymetrix's founder's great idea was to take the principles of combinatorial chemistry and marry them to the principles of semiconductor manufacturing in Silicon Valley.[3] And this really predates, by almost a decade, the publication of the genome because, even as early as 1991 when our founder's paper was published in *Science*,[4] people were starting to understand that completion of a map of the genome would bring an abundance of information. It would bring all of those As and Cs and Gs and Ts, which could stretch between Portland and Chicago fifty times over, or between here and the moon, or fill up 9,000 newspapers. We use a bunch of these wonderful illustrations to capture how much information is involved.

Affymetrix was founded with a focus on moving from fusing transistors on a chip to fusing DNA and RNA on a chip.[5] Increasingly, foremost for developing pharmaceuticals with genomics, including drug discovery, is the notion of looking across a population to understand genetic variance and how that might impact a condition. Secondly, drug validity must be understood on a genetic level—meaning understanding what will and will not work based on genetic insight for what drug targets would be valid,

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3. Affymetrix's "GeneChip" technology was invented in the late 1980s by a team of scientists headed by the company's founder, Stephen P.A. Fodor, Ph.D. *See* Affymetrix, Corporate History, http://www.affymetrix.com/corporate/history/index.affx.

4. Stephen P.A. Fodor et al., *Light-Directed, Spatially Addressable Parallel Chemical Synthesis*, 251 Science 767–73 (1991).

5. *See id.*

rather than based on the outcome of a winding process of clinical trials involving some 5,000 people. The goal is to be smarter, more selective.

Our whole paradigm of what constitutes success, or lack thereof, in drugs is changing. In the old days, we said, "Well, this drug works for sixty-five to seventy percent of the people. That means it is a pretty good drug." If you are in the thirty percent that it did not work for, you are not going to be very happy about it. But on the other hand, there may be a drug for which people said, "Well, it is not all that effective, it only works thirty percent of the time." If you are in that thirty percent, it is one hundred percent effective. So, being able to stratify patients and the kinds of pharmaceuticals we develop is a powerful application of the technology.

And at last, clinical genomics. Today, most of this technology is what the Food and Drug Administration ("FDA") calls "research use only" (RUO) technology. But Affymetrix can move quickly, as can others in the industry and the FDA, and there are the folks in the clinic who would like to take this technology today and be able to say with great definition from what types of conditions people suffer.

I will tell you one quick, anecdotal story from a friend of mine, Terry, who is the Medical Curator of the Smithsonian in Washington, D.C. It is a story about Ulysses S. Grant, our only president to have died from cancer.[6] A series of biopsies were taken, before and after he died, of the tumor that had lodged in his throat.[7] Those were kept at Walter Reed Army Hospital over the many years that followed. In 1999, the Army decided to bring in a group of pathologists to look at Ulysses S. Grant's tumor slides and to try to discern what we would know today that we did not know when Grant died in the 1880s.[8]

The results were interesting, which Terry reported in "What's in Grant's Tumor?," which I think is a great pun.[9] They brought all of these great pathologists in, and they all looked at a slide.[10] And more than one hundred years later, what could they definitively say that had not already been deduced in the 1800s?

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6. *See generally* Josiah Bunting, III, Ulysses S. Grant (Arthur M. Schlesinger, Jr. ed., Times Books 2004).

7. *See generally* T. Ready, *Access to Presidential DNA Denied*, 5 Nature Med. 859 (1999); G. Terry Sharrer, *What's in Grant's Tumor?*.

8. Sharrer, *supra* note 7.

9. *Id.*

10. *Id.*

The answer was nothing.[11] They reached the same conclusion because they had the same basic baseline of evidence to go on. Now, that is not to suggest that the treatment of cancer has not progressed; it certainly has. But the molecular understanding of cancer is just beginning.

Now let me contrast that with some work that has been done recently. Scientists started out looking at leukemia classifications and leukemia cells. They began with this baseline of looking under the microscope. But then they employed a chip-based technology and they were able to decide which classification of leukemia patients had, with ninety-five to ninety-nine percent accuracy.[12] In fact, they updated this study in 2002 and found an entirely new classification of leukemia that had not existed before, just based on the gene expression profile.[13]

Now, why is that important? Medicine, as good doctors tell you, is still a lot of art mixed with a lot of science. But the therapy path, as with some of these treatments for leukemia, can be dramatically different. They are excruciatingly difficult, they are painful, and they are hard on families as well as patients. They are certainly expensive for all of us as a society. And how would you like to be the person who is halfway through the treatment protocol for acute myelogenous leukemia ("AML"), only to hear, "Oh, gee, you really had acute lymphoblastic leukemia ("ALL")?" Clinically, we are talking about being able to give patients a definitive diagnosis with understanding of the disease at an unprecedented level of certainty, which is starting to happen now and will arrive before we get way out there with the futuristic world of personalized medicine.

The use of these technologies is quite far-ranging, for everything that lives has a genome—plants, animals, viruses, and bacteria. Consider the news starting around Christmas 2003 that incidents of bovine spongiform encephalopathy ("BSE"), mad cow disease,[14] were occurring again, and see the importance of livestock and being able to tell the kind of feed that livestock consumed. We have a chip that does that. Similarly, Affymetrix is doing a lot of very interesting work with the Environmental Protection Agency ("EPA") to think about how to come up with a

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11. *Id.*

12. *See generally* Scott A. Armstrong et al., *MLL Translocations Specify a Distinct Gene Expression Profile that Distinguishes a Unique Leukemia*, 30 Nature Genetics 41, 41–47 (2002).

13. *See id.*

14. For information about BSE, visit the website of the U.S. Food and Drug Administration, http://www.fda.gov/oc/opacom/hottopics/bse.html.

whole new way of doing environmental impact assessments aside from the thing we have been doing for fifty years, that is, taking these poor mice down to the lab and seeing how many of them make it and how many of them do not. There has got to be a smarter way to do that, and we think we can find it.

What are the intellectual property issues and implications? I approach this discussion, by necessity, from a parochial point of view—as a private sector company that has evolved over the last decade. And it may not go in the direction you think it is going to go when I use the word "private sector," which is why it is a lot of fun to talk about this. At Affymetrix, we started asking some very fundamental questions about gene patents, and about their justifiability based on, not just legal grounds, but also ethical, economic, social, and commercial grounds. For instance, we use many gene probes on our chips; the latest chip we just introduced has 50,000 genes, which is actually more than the genome—it is, in fact, the genome with redundancy built in. The feature size on that chip is eleven microns, which means millions and millions of bits of information, millions and millions of probes of information, on that chip. Now, what if we had to pay a patent royalty for every one of those probes that was on the chip? That is the most far-out example I can give.

I want to start at that baseline and analyze the genome as a resource, because I think it is probably our ultimate natural resource. Part of what makes this conference so interesting is that we are really charged with the stewardship of that resource, in ways large and small. How are we, as a society, going to derive the greatest benefit from this wonderful discovery?

All that I've told you about the genome, and all that we have learned and all these wonderful slides that you are going to see over the next few days is vastly outweighed by all we have yet to learn. Francis Collins, who heads the National Human Genome Research Institute, is always fond of saying that this is "the end of the beginning of where we are right now."[15] Essentially, we have just put down a baseline. We also know that there are about 35,000 genes in the human body, depending upon whose estimate you want to believe.[16] What does that tell us from the start? Well, we probably cannot say there is just one gene that gives you blue eyes, one gene that gives you cancer, one gene that gives you heart disease, and so on. There is a fair amount of single-gene disorder,

15. *See* Ania Lichtarowicz, *The End of the Beginning*, (2005), http://news.bbc.co.uk/2/hi/sciencenature/1100726.stm.

16. J. Michael McGinnis, *Population Health and the Influence of Medical and Scientific Advances*, 66 La. L. Rev. (Special Issue) 9, 10 (2006).

but they are not the norm. In fact, we at Affymetrix just did some very interesting work with such disorders, which leads me to believe we are going to end up with sub-biobanks in specialized populations.

We just did a fascinating project with an Amish community in Pennsylvania and, in one month's time, isolated the gene for a birth defect called Swyer Syndrome, a single gene disorder.[17] But most of the common complex diseases we are looking at are going to be an interaction, we believe, of multiple genes doing multiple things with one another, and interacting with the environments that they are in. So there is an enormous amount of complexity out there to understanding why certain genes on Mondays, Tuesdays, and Fridays are doing this, and then on Thursdays and Saturdays are doing that, and why they are interacting with one another in a real social environment, if you will. Thankfully, this identification of the added dimensions of complexity is accompanied by more enabling technologies. More and more technology is coming online, which is enabling scientists to address and interrogate the whole genome, or significant chunks of the genome at one time, rather than looking gene, by gene, by gene.

Now, what happens when the ability and the need to do this research collides with property rights in that genome, created by an intellectual property regime? Affymetrix has over 250 patents on our technology and another 300 patents pending. So we are the living embodiment of the importance of the patent system. This intellectual property is very important, and it has been a singularly important thing in building the commercial value of our company. And that goes back to something Michael said which I think is not even a debatable point: going forward will be an interaction of government, academia, and the private sector, all commingling with one another—sort of like the gene interactions I talked about. Where are we going to set the property right bar along that genome so that society gets the maximum benefit? How do we build incentives into the system so that everyone can take advantage of it, and yet recognize that inevitably there is going to be a request for a return on value and investment? Eric Lander, of the Whitehead Institute at the Massachusetts Institute of Technology,

17. Information about Affymetrix's research is available at http://www.affymetrix.com. More recently, Affymetrix worked with an Amish community in Lancaster, Pennsylvania to identify the gene responsible for a new form of sudden infant death syndrome following the death of twenty-one Amish babies from the disease. *See* Dr. Holmes Morton et al., A Modern Miracle in the Most Traditional of Communities, Oct. 2004, http://www.affymetrix.com/community/wayahead/modern_miracle.affx.

is a pretty provocative guy. At a seminar in Washington, D.C. a few years ago on these issues he questioned, "Aren't we awarding limited time monopolies on mindless genetic innovation?" Of course, what constitutes "mindless genetic innovation" is a debatable point.

In addition to the basic genome I talked about, there is a whole second order of discovery issues that are coming down the pike as well—notions about what we do with proteomics, MRNA, and so forth. And we will have a very difficult time setting legal standards for those when, in my mind, we have not been able to reach the right perspective for what we need to do with the essential parts of the genome. We have been trying to break out of the sort of traditional notion of gene patents, right or wrong, to instead think about what our approach should be going forward. How should we differentiate all these different pieces of genomic information that are out there?

So far, our efforts have been largely to differentiate between those items we think are cataloged in nature and those that demonstrate some real functionality from which, in our view, there would be true innovation in the art of discovery. By cataloging, I mean sort of like the Sears catalog. There is quite a bit of information out there that we think sort of falls into that category. For example, the periodic table of elements. You could not walk out of here tomorrow and patent iron. You could not walk out of here and patent gold. We consider those to be part of nature. Mr. Gray may have gotten a copyright on his drawings, but he could not copyright part of the anatomy. The first person to ever see a spleen could not have pulled that out and said, "Oops, this is mine. No one else can use it without a license from me." There is a culture of understanding that there are some things that are just obvious, and obviousness is one of those terms that comes up a lot in patent law. I am going to try very hard not to have us go down into patent law minutia for this conversation but, rather, to stay with some of the policy questions that I think are really preeminent.

As a company that has 250 patents, I cannot say that we do not believe in intellectual property. We certainly do. And I think the question is the point at which you say, "This entity has done enough innovation to justify some degree of exclusivity taking hold." We have discussed a commerce clause for the genome. An interesting analogy is to think of the genome as a river. To illustrate the point, consider the great Mississippi River flood of

1927, which is wonderfully told in a book entitled *Rising Tide*.[18] The good people of New Orleans decided that they did not like the flow of the Mississippi so they got the Army Corps of Engineers to build a very complicated and wonderful series of levees up and down the river, which resulted in a disastrous flood and an enormous social displacement of the whole mid-range of the south.[19] Anyway, if you said to people, "Well, if you go out to the river, buy a piece of land on the side of the river, and develop that and put a resort or some other facility there—something that adds economic good—well, we will recognize and protect your rights in that," that would be understandable. But if you were to allow people to put up a toll booth every twenty feet along the Mississippi today, how would commerce move up and down the river and how would that benefit people?

Now, legally, are we going to be able to change the existing scheme of intellectual property rights in the genome? Probably not, but I do think there are some measures that could be taken to mitigate this. One that I would like to talk about is the notion of pooling in a resource. Incidentally, a few minutes ago, Michael talked along similar lines and mentioned a potential role for the World Health Organization ("WHO"). I think the Office for Economic Development ("OECD") is another organization that could be useful for working through issues and accomplishing some collective good.

Affymetrix has advocated the establishment of a Biomarker Pool. There was some precedent set earlier last year through establishment of an agricultural pool by Rockefeller University.[20] The notion was that there were a great many universities—and I believe LSU was one of them—that had done great work in developing agricultural products. They then had licensed that work to companies like Monsanto, DuPont, and others, which took these innovations and sort of put them on the shelf rather than carrying them through to fruition. Consequently, there were a lot of products that could, potentially, be very helpful in alleviating hunger around the world that were not developed. And so the Rockefeller Institute convened a meeting of all of the parties and said, "Look, why don't we create a pooling arrangement where we'll bring all of those patents back into a centralized database, and then we'll allow other people who are doing non-profit

18. *See generally* John M. Barry, Rising Tide: The Great Mississippi Flood of 1927 and How it Changed America (Simon & Schuster 1998).

19. *See generally id.*

20. *See* Richard C. Atkinson et al., *Public Sector Collaboration for Agricultural IP Management*, 301 Science 174, 174–75 (2003).

research, or who might even want to commercialize it in some way, to take advantage of it. Let's get more people in on the action and use the intellectual property that's there."

If you know anything about the computer industry, they function with a very complicated pooling system as well, but it does work. For example, DVD technology was stalled for a long time because you had sixty companies holding different kinds of patents. Finally, when the bulk of those companies came together and put their patents in a pool, they moved the technology forward.

Affymetrix thinks that the concept of bringing some of the patents, especially on gene sequencing, and especially for non-profit, basic research is a good idea. The court of appeals for the Federal Circuit has made it very clear that there is no research use exemption under U.S. patent law.[21] The options are to wait for Congress to pass a research exemption, in which case I would argue that we would all be very old before that happens. Alternatively, we could do something that, hopefully, would bring some of the interested players to the table and try to create the kind of framework that at least allows basic research to go forward and researchers to feel like they are not going to get a cease and desist order from a patent-holder somewhere trying to block their work. As I said at the outset, these are enormously complex issues, and I embrace the remainder of this conference and the opportunity to engage in further discussion of them.

21. *See* Integra Lifesciences I, Ltd., v. Merck KGaA, 331 F.3d 860 (Fed. Cir. 2003), *vacated*, 125 S. Ct. 2372 (2005), *remanded to* 421 F.3d 1289 (Fed. Cir. 2005). *See generally* Lawrence B. Ebert, *In Favor of The Federal Circuit Position in Merck v. Integra*, 87 J. Pat. & Trademark Off. Soc'y 321 (2005).