My remarks focus on 4 topics: What is personalized medicine? Why now? When will it be real? And what is the specific call to action that I see for pathology?

First, let me note what personalized medicine is not. It is not trial and error medicine. Yes, trial and error medicine has been the tried and true way we have achieved so much to date. I still believe it is the old paradigm that we will need to change to move forward. The way I see trial and error medicine is that a patient goes to a physician with an observation. The doctor then takes an action and says, “Come back and let’s see how it works.” This system is inherently a circular process loop that calls for action, observable response, change, and action. It is successful when we use it and learn from those trials and errors, and we indeed move medicine forward. It is a failure when this loop is the only way to do it and we do not learn from patient to patient or even within an individual patient’s progression.

I think the new paradigm is not a loop but a straight line. It starts with the same observation, but before the physician goes into action, he or she includes a test or a diagnosis that may very well still be the same action, but instead of an observable response, we now have a predictable response. This is not the personalized medicine in the 1980s and early 1990s, which was going to cure all disease and be 100% effective. I would love to think that was the case, but it is not going to be. We have moved the likelihood from observable to predictable, and that I believe will break the cycle of trial and error.

So why is this important? Fundamentally it is because diagnosis saves lives and diagnosis saves money. I get a bit tired of everyone saying drugs save money, drugs save lives, surgeries save lives. Diagnosis saves lives, too, and in the current environment, we have to think about the fact that you have to save money and at the same time you are saving lives.

Where does that happen? What is personalized medicine? There has been a lot said about trastuzumab and drug selection. Personalized medicine is much more than that and there are actually 6 different pieces to it. It starts with drug selection, which is as classic as HER2-positive or HER2-negative and trastuzumab, but it moves to drug dosage—UGT1a1 and the use of irinotecan. It then moves to drug efficacy. Can we predict problems with the drug and can we predict when you will get a lack of drug efficacy?

Next is disease status. With minimal residual disease testing, the example is alemtuzumab, a monoclonal antibody for the treatment of B-cell chronic lymphocytic leukemia. Do you need to go with 2 courses of action or can you stay with 1 treatment paradigm? New kinds of technologies assess disease recurrence risks, including OncoType DX (Genomic Health, Redwood City, California). Then, lastly, something that has been around for 15 years now is the Myriad Genetics (Salt Lake City, Utah) BRCA analysis looking at predisposition. So when we talk about personalized medicine, it is not just which drug a patient takes, it is 6 different dimensions of how that patient can be treated more effectively. Ultimately, however, I believe personalized medicine will be more than just drug interventions. It will be known as personalized health care and will involve surgical and other interventions as well.

Where is this happening? People ask when will it happen? “Give me a date like March 12, 2011.” Personalized medicine is already happening in the key area where it has already saved lives, in blood cancers.

One hundred years ago, if a patient came in with lethargy, bruising, and night sweats, the best that the physician could say is you have a disease of the blood. Twenty years later we understood leukemia and lymphoma were different. Twenty years after that, we knew chronic, acute, indolent, and aggressive. What happened next created the initial work on personalized medicine—we can now quantify 90 or perhaps as many as 150 different genotypes for leukemia and lymphoma. If you talk to a lay audience, they say who cares? I now know I have mature B-cell lymphoma type 12. The “so-what” is that 5-year survival during this period has gone from 0% to 70% and for many of the pediatric cancers far higher than 70%. Why has this happened? Because in hematologic cancer, we have the ability to not just do morphology but also fundamental molecular level analysis with flow, cytogenetic, and DNA analysis to get an expanded characterization and to get to that very specific diagnosis.

Personalized or specific medicine is about getting to the least common denominator. It gives pharmaceutical com-
panies the ability to take that small subsection of patients and look for a drug, and it gives the treating physician the ability to differentiate between one patient and another. But this is not just blood cancers. Very recently, cetuximab and its use in colon cancer was discussed at the American Society of Clinical Oncology. With colon cancer and cetuximab, you treat 10 patients and get 3 successes, which is typical of our past experience. But with personalized medicine, with the addition of K-ras testing, you take those 10 patients and screen out 4 who will not get any clinical benefit from the drug. You then treat 6, and end up with 3 who are treatment-successful, but you are avoiding the toxicity for those patients who would not have benefited. Another benefit is cost savings. The average treatment cost per person is $22,000 with K-ras testing versus $38,000 without. What is very interesting is cost per success—just the 3 patients who are going to be successfully treated. For the 30% of the colon cancer patients who are going to be treated with cetuximab, you see a huge difference of $100,000 versus $156,000. This is why we are proving that personalized medicine and accurate diagnosis not only saves lives but saves money.

Let us now look at another area. Pancreatic cancer, which Jared Schwartz, MD, PhD, mentioned, has come into the news again with Randy Pausch, the professor who wrote The Last Lecture. What is the process now? Suspected pancreatic cancer goes 1 of 2 avenues: watch and wait or pancreatectomy. If you go with watch and wait, expected pancreatic cancer goes 1 of 2 avenues: watch and wait or pancreatectomy. If you go with pancreatectomy, there is a risk of insulin insufficiency—not to mention the mortality of the surgery itself. I would call that 2 bad choices.

Now move into the era of molecular and personalized medicine. Take that suspect pancreatic cancer and move to a test by a company called Redpath (Pittsburgh, Pennsylvania), Pathfinder TG, and get a more accurate diagnosis of pancreatic cancer. Now you move to truly confirming the diagnosis of cancer in 30% of the cases that are then treated aggressively, but 70% have a benign condition and do not need to be treated, reducing by more than a third the number of pancreatectomies. Not ideal choices but more informed than the 2 choices one has without the test.

We are not going to focus on the financials today, but there are a lot of data that say personalized medicine and accurate diagnosis reduce, not increase, costs. But this is an industry about patients. Most important to me is that it is not only about the cost but about time. Patients can have good or bad insurance coverage, many or few resources, but the one thing they do not have with a cancer diagnosis or any serious diagnosis is time. So if you try that circular loop of trial and error medicine and you let that lung cancer patient try chemotherapy and not try an epidermal growth factor receptor test first, you can only work with 40% of the patients at the end of the year—because 60% of patients have died in that first year. With colorectal cancer, you have lost a quarter of the patients at the end of a year. This is most dramatic in chronic myelogenous leukemia. Before imatinib, there was 63% 1-year survival and post-imatinib, 93% survival. A great drug, but it does not work on other blood cancers. It works on other cancers that may be related to that kind of mechanism and neurology changes, but it is not for everyone. It works when that diagnosis is right. In blood cancers, getting that diagnosis right and going through that cascade has become so common it is not even called personalized medicine, it is just called medicine, and that is the way we need to move. Personalized medicine will no longer be something that we have special conferences on. It is something inherent in the base of the profession.

Where do we go from there? Why is this happening now? It is the human genome project that has really made the difference. It is the emergence of the explosion of “omics.” Everyone knows proteomics, but this is just for starters; Google now shows 76 new “omics.” These new areas of study are all about diagnostics.

If you look at diagnostic technology in the past, it is macro: disease versus nondisease. Disease (particularly cancer) was solely defined by the organ in which it was found. Today, it is molecular level testing that is based on the DNA of the person, the tumor, or a virus.

What does the future look like? First, the future is much more predictive testing. There are multiple technology platforms that require the integrative role of a pathologist. There is multifactorial testing for common and complex disease, which I believe is going to start in the immune modulation area. There are multigene signatures, so that we are not going to be looking at a single gene with all the answers, but more complex disease, more specific diagnosis, and multiple genes. There are new sample types, not tissue and blood, but saliva, breath, and urine. There is the increased use of diagnostic imaging. I believe that imaging is going to come together in a way that will make it relevant to virtually all of our testing in the future.

Second, there will be increased government interest. The government and politicians are getting involved; before Ted Kennedy was diagnosed with cancer, he talked about personalized medicine and declaring a war on cancer and he was working on a bill around the next war on cancer. The US Food and Drug Administration (FDA) has issued draft guidance on what is called in vitro diagnostic multivariate assay, the most complex gene signatures. It is not clear when the final guidance will be issued, but this is a high priority for the FDA. Pharmacogenomics as voluntary data submission continues to increase and is a key part of the critical path initiative. The Secretary’s Advisory Committee on Genetics, Health and Society (Secretary of Health and Human Services Michael Leavitt), on which I serve as a member, just came out with a major report containing a lot of findings, but the key finding is to close the gap in the regulation of these tests. Ten years ago there was no interest in doing this because people did not think diagnosis truly saved lives. They did not think or spend enough time on diagnosis. It was considered a commodity and something nice to have, but not the critical role that diagnosis is playing now.

One of the hallmarks of the President’s Council on Science and Technology, a very unusual group in Washington, is that all of their reports have to be fewer than 50 pages. Their final report in this administration will be about personalized medicine and the importance to the next generation of health care, so the government is taking notice and this will become a bigger and bigger issue as we move forward.

It is great that this is happening now, but when will it truly be real? There is always a 3-stage process to adopt any technology. The first stage starts with fear. No matter how good a new technology is, everybody is nervous about what it is going to be like when they use a new technology. There is a tremendous amount of fear of what
personalized medicine means today and how it is going to change the pathologist's world.

Then the second stage, which is value. How does it provide value? How can it help me in what I do? Only after that is acceptance. Physicians will say, "yes, I will take this and move forward." And there are a lot of data on physician acceptance for everything from Papanicolaou smears to vaccines showing that they typically take 15 to 20 years to go from fear to acceptance.

Where are we in personalized medicine? Let's talk about fear, where the fear is, and the major stakeholders. Physicians are saying, "we are going to add a test, not focus on the result, and still do what they want anyway." There are some real data that says that. For instance, a small number of trastuzumab prescriptions are written within minutes of writing a request for a HER2 test. The HER2 test may have a fast turnaround time, but it is not instantaneous, so on Monday morning they are asking for the test and they are asking for the drug at the same time. It appears they are saying, "it would be nice to know the patient's HER2 status but I am going to use trastuzumab anyway." Now, clearly that is changing, but that is the payer's fear and we have to deal with that head on.

Physicians are saying, "personalized medicine is great but do not tell me what to do. I need to use the art as well as the science to treat my patients. Do not tell me what to do but give me the rules and give me enough flexibility to think it through myself." So there is not an easy answer, but a lot of fear that this changes what they do every day. What is the balance between art and science?

It is easy for patients to say personalized medicine sounds good. My mother imagines that somebody is compoundng drugs at the pharmacy just for her and that is fine because if you tell her that the drug is created just for her, she will actually take it. But patients are saying that personalized medicine is terrific only if they get the drug they want. But try telling a 30-year-old woman with HER2-negative breast cancer that there is nothing more we can do. It is very difficult to say personalized medicine means that you cannot get the drug. In our culture, some action and some drug is better than saying we have nothing to do. Few patient associations come on aggressively for personalized medicine. I believe that we have to do the education that changes the mindset that action is always better than nonaction.

Regulators have done a great job, particularly the FDA, of trying to attack this, but it is not easy. If we want tests on labels, how does the FDA put a test on a label if they do not approve that test? If they do approve the test, do they now need to look at a different level of analytic and clinical validity to actually put on a drug label? Putting things on a drug label is one of the biggest things the FDA does.

Diagnostic companies talk to pharmaceutical companies, which say, "Wow, personalized medicine is going to be a bonanza for diagnostic companies. This is terrific. You are going to be doing all those new tests." Well, from the diagnostic company or laboratory view, if every test loses money, it is not better to do more of them! The reimbursement system does not reward diagnostic companies in a reasonable way to truly embrace personalized medicine.

Lastly, I am going to focus on pharmaceutical companies and pathologists. I do not believe we can have personalized medicine without pharmaceutical firms creating the drugs that really increase survival. Pathologists are central to the diagnostic process. I think in some ways pharmaceutical firms and pathologists may be thinking about personalized medicine in the same way, that "it is taking away part of my world."

The first piece of pharmaceutical fear is justified fear—spending on research and development is going up and drug approvals are not. This has been a consistent pattern for the last 7 to 8 years and shows no sign of abating. Blockbusters are going off patent. There are 105 blockbusters today with more than $20 billion in sales, 37% of all prescriptions. In 2006, 7 of 10 of the top launches were generics, and by 2012, 85% of all prescriptions will be generics. But we have to acknowledge that their profitability will change dramatically during these next 5 years. Eighty percent of sales go away in the first 80 days of postgenerics. The pharmaceutical industry will continue to go forward; generics only work when innovative pharmaceutical firms are making branded drugs, so we need to protect the idea that we have innovative drugs coming out of the system.

Where else is the fear and where are there opportunities? The most important one, and an area that is most disturbing but really enables personalized medicine, is that the average drug efficacy is 50%—so half of the time drugs produce no positive clinical value in the patients they are given to. It is not because they are bad drugs. It is that they are not given to the right people at the right dose at the right time.

This is most dramatic in oncology where only 25% of the drugs given have efficacy. Many people say that cancer is a tough disease. Cancer is a tough disease, but I do not think it has to be as tough as we currently see it. We saw that for the cetuximab example. The average cancer patient will get 2½ drugs during the course of therapy, but if we can reduce that to 1 drug and make it more effective, we have saved cost and we have bought that patient time, which is what he or she really needs to survive.

Adverse events in the United States affect 2.2 million people and cause 100 000 deaths a year and $177 billion in costs. It is the single largest reason drugs are withdrawn. This is taking medication as prescribed. We do not know enough about how drugs are metabolized person by person and when we do know it, we do not implement it. One hundred thousand deaths, and a real opportunity is dramatically reducing that number.

Lastly, what is called the most known secret in the pharmaceutical industry is compliance. Only 25% of prescriptions are filled and taken as prescribed. Seventy-five percent of the market is not being accessed now—that can increase. I do not believe that personalized medicine drugs will shrink the market for any individual drug company. Indeed, if the drug works, it will increase the market.

There is a major change in Europe potentially coming that reconsiders how we reimburse drugs. It is a risk-sharing system for which reimbursement only happens if the patient benefits and the refund happens if the patient does not. Six years ago I asked about these types of systems at a large meeting of the American Society of Clinical Oncology. The question was greeted with laughter. Now it is beginning to happen outside the United States. This risk sharing may indeed be the single incentive that brings personalized medicine to fruition.

The biggest current example is a Johnson & Johnson...
product in Europe, bortezomib (Velcade), for multiple myeloma. Johnson & Johnson and the government payers in the United Kingdom came up with a system with a full refund if the patient does not respond to bortezomib (Velcade) therapy based on the results on a biomarker test. Another example is Genomic Health and their new contract for OncoType DX test with United HealthCare. From public information, it appears that the contract confirms United's use of the test with its members but with an option to renegotiate after an agreed-on period based on the results seen. Genomic Health in essence is saying, we believe in our test—use it and if it doesn't show the benefit we expect, then we can renegotiate, but get it into patient's hands because we believe it will save lives and save money.

The protocol is that the patient is treated with a maximum of 4 cycles, US $25000. Serum M protein is the biomarker that is looked at in normal plasma and they make a determination after the 4 rounds of therapy. If there is a complete response, the company is paid. If there is a partial response with a reduction of 50% or more, the company is paid. If there is a minor or minimal response, there is a refund and the company is not paid for the drug. This is a real incentive to get that biomarker in place because you only get paid for the ones that work.

The pathologist will have to deal with new types of samples, such as molecular blood tests, breath tests for Helicobacter pylori, and tests using urine, and new technologies, such as microarrays that challenge the current laboratory system.

An interesting example of this is Burkitt lymphoma. According to the National Cancer Institute, Burkitt is misdiagnosed 17% of the time based on morphology alone. But the work at the National Cancer Institute says that if we use gene expression technology either in addition to or instead of morphology, we get a very, very clear picture and, they would say, no misdiagnosis between Burkitt and diffuse large B-cell lymphoma. This is personalized medicine, the use of new technologies, and I would say they present both fear and opportunity.

Molecular tests are exploding. There are 6 to 12 in vitro diagnostic multivariate assays that the FDA calls a device in the market today, depending on how we define them. Recent research on how many are in development indicates there are 200 in the United States alone. Let's say half of them succeed during the next 10 years. This is an inflection point that I would say has never happened in diagnosis: a wave of new kinds of tests coming into the system.

If you do not believe that might happen, just look at venture capital focus on diagnostics. It peaked in the 1990s at a level much below today. They have come back in a strong way and continue to increase these dollars. Based on the first quarter, it looks like 2008 will be another record year for venture capital investment, specifically in diagnostic companies and molecular diagnostics.

Lastly, consider what is a shared fear for pharma and pathologists: drug labeling. Right now there are 121 drugs that have genomics in the label: the label says the use of this drug is determined by pharmacogenomics, but how many of those drug labels link to a test? Two. Three have a test recommended and 16 mention the test for information only. So 100 of those 121 tell the physician, yes, there is a pharmacogenomics effect here, but they do not tell you what to do about it. This is key, and I believe it will change in the new era of personalized medicine.

In conclusion, what is the call to action? I would say pathologists need to capture the future. Morphology tests are the majority today and we are moving to molecular. There is a stable base of technology, which to a large extent has only been incrementally improved during the last 20 years. I believe we will have many new emerging technologies: single gene tests to multiple gene tests; tissue samples to multiple sample types.

Turnaround time has been controlled by the pathologist. Now, there is an impatience, which maybe comes from the Internet age that says we want it now, we want it at the point of care, and we do not want to send it to any central laboratory. How is industry reacting to that? There are more and more diagnostics that are becoming in vitro diagnostic kits, some would say prematurely, but that is enabling treating physicians to do it in their laboratory, do it right there. There is a financial benefit to doing it, but most importantly they can get it done faster. The pathologist has less control when it happens right in the office with an in vitro diagnostic kit.

The pathologist traditionally interprets and does everything with the diagnosis. What we are seeing now is more and more of these molecular laboratories bringing the diagnosis directly to the treating physician, to the oncologist, and saying you do not need to go through the pathologist.

I believe this is a future that cannot be avoided. The technology is going to change, you cannot hold it back, so how are we going to get on top of it? The pathologist needs to move forward and embrace that. Is personalized medicine a friend or a foe? It needs to be a friend, period. The pathologist needs to own personalized medicine, to be the source of expertise on all tests available, whether they happen in the laboratory or not. To be an interpreter and consolidator of all test results, and the educator, most importantly, of all the other physicians on diagnosis. There will be many more tests that are of that smaller and smaller applicability. You cannot always get an accurate diagnosis based on one test. You have to bring them together and that is what pathologists need to do to move from fear to acceptance.

What are the 3 areas more specifically? First, physician education of your peers. Second, data integration into the health record. And third, policy. The College of American Pathologists has done a marvelous job and needs to continue to be a leader in that area.

In physician education, 15% of medical schools today have no education on genetics. Only 20% of medical schools have more than 40 hours on genetics diagnosis, so there is a piece here that goes back awhile that says we need to generate more interest in and more knowledge on the importance of diagnosis with the new generation.

We need to build commitment through education for community physicians. In the oncology area, 85% of patients are treated in the community, not at academic centers. It is great that the thought leaders are publishing and all of you are here on a weekend to get this done, but the “rubber hits the road” at the community physician's level, and that is where the real change will happen if pathologists get out to educate those physicians.

We need to get more practice guidelines out. The College of American Pathologists and the American Society of Clinical Oncology did an extraordinary job coming out with the new guidelines for HER2 testing, but by my count there are only 4 guidelines that have come out for
the use of personalized medicine tests linking tests to either therapy or a drug. We need to get more personalized medicine practice guidelines out and the National Comprehensive Cancer Network needs to be more active if that average community physician is to truly embrace personalized medicine.

Data integration in the electronic health record. As you know, 70% of the data in the electronic health record will come directly from the laboratory. We need to put together better data for the payers, for ourselves, and for our colleagues in order to be able to say personalized medicine works. It is great to tell anecdotes, but as an industry we need to work together. The diagnostic companies cannot do it. A diagnostic company may come out with a great new test, but they do not have the outcome data to be able to be out there and put together that convincing evidence that it works. The pathologist is the leader in building the electronic health record. I happen to believe a single system nationwide would be the way to do it, but even if it is multiple systems across the hospitals, we need to have that electronic medical record be truly representative of the diagnosis of the patient.

Lastly, policies. We do not have enough time today, but when you look at reimbursement, it needs to be based on value, not activity. We need pay-for-performance guidelines to include diagnosis, which they do not have today, and we need regulatory options that combine personalized medicine, drugs, and tests and embrace the era of diagnostics. When you put this together, the pathologist, I believe, needs to and can lead all of these efforts.

What is the opportunity? Expanding the scope of practice, increasing the impact on patient treatment, becoming the institutional knowledge coordinator, the cutting edge expert, the leader in personalized medicine. It is necessary. It is here today. If you look at the economics of personalized medicine and how it will change, today we spend relatively little when we are all young and healthy and we spend a tremendous amount when we are older and sicker. The promise of personalized medicine is that the investment in diagnostics and prevention delivers improved quality of life and financial savings. The real challenge is, where do we start? This is what I believe the future is but we need to drive it.

Reference