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**“Targeted Medicine: What Progress Has Been Made? What’s Holding It Back?”**

It is always a pleasure to visit the Boston area, and it’s an honor to share some thoughts with you today.

I particularly want to thank Raju for this opportunity and for his ongoing commitment to our field. Your Center is implementing on a day-to-day basis many of the approaches that I’m about to propose to accelerate this field.

There is no doubt that the Harvard Partners Center, and those of you who work in concert with them, will help shape the future of personalized medicine and the future of health care.

Please take a look around you. We are here today with some of the most innovative leaders in our field, including:

- Senior executives from some of the world’s largest pharmaceutical, biotech, and molecular diagnostic companies, who are driving the pipeline of personalized medicine products,
- Executives from the world’s largest IT and software corporations, who are enabling the convergence of IT and life sciences,
- Founders of new start-up companies,
- Nearly a dozen analysts and directors from venture capital firms with a focus on life sciences and health care,
- World-class clinicians from major hospitals in this region,
- Heads of disease foundations,
- Leaders from the National Institutes of Health,
- Representatives from Secretary Leavitt’s office at HHS,
- And senior leaders from payor organizations.

If there was any doubt in your mind that this field cuts across every silo in life sciences and health care, the list of attendees at this conference should put those doubts at rest.

And we are all here because we are committed to moving personalized medicine forward, and we know that we must collaborate to achieve our shared goals.

## Introduction

I believe that we are at a crossroads. We must clearly decide what we are committed to achieving, we must take action to achieve those goals, and we must monitor our progress and continue to be flexible in our approach until we achieve the promise of personalized medicine.

The challenge we have, to put it bluntly, is that our pace is not matching the promise of personalized medicine.

I am very concerned that as a community, we seem to be willing to wait 20, 30, or even 40 years — the traditional amount of time it takes for new technology to be fully adopted — to achieve what we should be pushing to achieve in 10 years.

Why is that? Let's start by taking stock of where we are today:

- We are near an inflection point in the history of medicine. The exponential increase in biomedical knowledge will entirely disrupt traditional health care institutions and systems.
- We can no longer pretend that the old system of medicine, which is structured around empirical evidence, is the best guide to clinical practice. As we are at the beginning of a new era in medicine, we are also in the waning years of an era when the standard of care included reactive treatment of disease symptoms, usually well into disease progression.
- We are also realizing that this dynamic change will disrupt not just clinical practice, but everything about health care, including the basic business structure that is skewed toward activity-based reimbursement, rather than evidence-based medicine.

Why is there such an imperative to change business as usual?

First and foremost, the disease burden is unacceptable:

- Heart disease — the number-one killer of adults in the United States — accounts for nearly 40 percent of all deaths each year.<sup>1</sup> Out of 2.4 million death certificates issued each year in our nation, cardiovascular disease is listed as the cause of death on approximately 1.4 million.
- Cancer, in all its forms combined, kills over half a million Americans each year.<sup>2</sup>
- Diabetes and Alzheimer's disease also continue to claim lives at increasing and alarming rates.

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<sup>1</sup> National Center for Health Statistics. Health, United States, 2006. Table 31., <http://www.cdc.gov/nchs/data/hus/hus06.pdf>

<sup>2</sup> National Center for Health Statistics. Health, United States, 2006. Table 32, <http://www.cdc.gov/nchs/data/hus/hus06.pdf>

And tragically, while it is difficult to pinpoint precise numbers, we also know that adverse drug reactions take the lives of as many as 100,000 people each year, which could, unfortunately, make ADRs one of the leading killers in the country.<sup>3</sup>

If we persist in this course, where will we be as a nation in a few years?

- In 2004, the United States spent 16 percent of its overall gross domestic product on health care, far more than any other nation. And it's projected that the percentage of GDP spent on health care will reach 20 percent in the next decade.<sup>4</sup>
- This out-spending is making U.S. industry less competitive in the global economy. Consider that health care costs add \$1,500 to the price of every General Motors automobile.<sup>5</sup>

And remember, these numbers will only increase as our Boomer generation, having entered retirement age, drives a *new* boom in our nation's elderly population.

The inefficiency of the U.S. health care system, combined with the demographic reality, threaten to overwhelm our society, and undermine our entire economic stability.

### **A Better Way**

But let's stop for a moment. Let's just take a step back and consider our alternatives.

What if we are able to interrupt these terrible trends? Can we imagine a future in which we identify disease earlier, treat it more accurately, and target treatment for specific genotypes? Can we imagine an era where we don't waste precious health care resources, where we maximize our health care investment to find disease earlier, where success rates are generally higher and treatment costs are generally lower?

What are the obstacles to personalized medicine? And, more to the point, how do we remove them?

I want to concentrate today on how we can achieve the goals that are most immediately critical and, I think, addressable by those of us in this room and beyond.

Before I offer these goals for your consideration, let me tell you that I believe completely in the promise of personalized medicine. As some of you know, I've staked my company on genomics and the broader concept of molecular understanding of disease. This concept is the bedrock of both Applied Biosystems and Celera. You could say that Celera's DNA encodes the idea that genetic and other molecular diagnostic tests are an

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<sup>3</sup> 2002 FDA report (<http://www.fda.gov/cder/drug/drugReactions/default.htm>)

<sup>4</sup> Borger, C., et al., "Health Spending Projections Through 2015: Changes on the Horizon," Health Affairs Web Exclusive W61: 22 February 2006.

<sup>5</sup> Statistic widely quoted by General Motors, see [http://www.pbs.org/newshour/bb/business/jan-june06/gm\\_3-23.html](http://www.pbs.org/newshour/bb/business/jan-june06/gm_3-23.html)

essential component of the personalized approach to health care.

So let me be very clear. I believe that the science driving personalized medicine can:

- Reduce and, in some cases, eliminate human suffering,
- Make the delivery of medical care much more clinically effective and more economically efficient,
- Mitigate the unsustainable rise in health care costs that will be our legacy if we continue with a business-as-usual approach,
- And provide an effective response to the demographic challenge posed by the aging U.S. Baby Boomer generation.

Personalized medicine is not about immortality, but it is certainly about maximizing the quality of our mortality.

### **Successes**

The good news is that we have made some progress away from the old models.

The human genome was decoded only about five years ago, and was, as my company always said, only a parts list for understanding human biology. We also said the “race” to sequence the genome was merely the race to the starting line.

Building on the foundation of the human genome sequence, academic groups and some businesses are conducting disease-gene association studies analyzing thousands of patient samples using high-throughput discovery platforms.

These studies are yielding discoveries of genetic and protein biomarkers of disease — some of which have been validated and are now becoming the foundation of new tests and potential therapies.

Personalized medicine is a concept in search of proof points. We now have a few products that are saving lives:

- It is often overlooked that the standard of care today for treating HIV in the industrialized world is, in essence, a personalized medicine approach. HIV viral load and genotyping tests are routinely administered to guide the choice of anti-viral therapy. Harvard scholars recently published a paper estimating that, in the aggregate, 3 to 5 million years of life have been saved due to the use of multi-drug antiretroviral therapies and diagnostics since the first protease inhibitor was approved by the FDA 10 years ago.<sup>6</sup> I am proud that Celera, through its relationship with Abbott Laboratories, is a leader in providing nucleic acid assays for HIV, as well as for hepatitis C.
- The well-known poster children of personalized medicine — Herceptin and Gleevec

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<sup>6</sup> *Journal of Infectious Diseases*, July 2006.

— have helped hundreds of thousands of patients. Herceptin, in particular, demonstrates just how powerful the alignment of molecular diagnosis and targeted medicine can be. By specifically inhibiting the HER2 receptor, Herceptin has greatly improved the survival rate of women with this deadly form of cancer. And Herceptin would not have even made it to the market if not for molecular diagnostic tests that identify patients who will benefit from receiving the drug.

The reality is that personalized medicine needs more success stories, and I am very hopeful that we will have several more very soon.

- At Celera, we are excited that the first genetic test based on original Celera research was launched this fall by Specialty Laboratories. The test predicts risk for liver fibrosis and, more broadly, cirrhosis in HCV-infected patients. The test uses seven single nucleotide polymorphisms to rate the relative risk of progression to liver fibrosis and cirrhosis.

From a medical perspective, the Celera cirrhosis risk score is expected to help many thousands of HCV-infected patients and their physicians in identifying those at high risk and at an early stage of disease who previously might not have been eligible for pegylated interferon therapy.

Patients who go on the drug following a positive test are also more likely to put up with the severe flu-like symptoms of PEG-A therapy if they know they are in a high-risk group.

- Celera also has been very active in cardiovascular disease. For example, we are working toward commercializing a panel of genetic risk markers for predisposition to coronary heart disease.

Additionally, Celera researchers and academic collaborators have discovered and replicated genetic markers in two large clinical trials that predict a survival benefit from statin therapy. If further study substantiates the work done to date, it is conceivable that within two years physicians may be able to prescribe one test to measure a patient's heart disease risk and another to assess the probability that the patient will benefit from taking a statin.

The need for earlier intervention in heart disease is crystal clear. Consider this statistic: Of the 1.4 million Americans who die from heart disease each year, over 400,000 die in an emergency room or before they can even reach a hospital.<sup>7</sup>

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<sup>7</sup> Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. *Circulation*. 2001; 104: 2158–2163. Available at: [http://circ.ahajournals.org/cgi/content/abstract/104/18/2158?ijkey=a9cdd4b268352265e5d7573b34aca3822f1ecfee&keytype2=tf\\_ipsecsha](http://circ.ahajournals.org/cgi/content/abstract/104/18/2158?ijkey=a9cdd4b268352265e5d7573b34aca3822f1ecfee&keytype2=tf_ipsecsha)

There are many in the science community who relate our expanding molecular knowledge to Moore's Law in the IT field. Better technology continues to add fuel to scientific discovery. Biological information is increasing exponentially, and costs per data point continue to decline sharply.

Yet, our ability to address complex biological systems is not advancing as rapidly as the accumulation of raw information about them. This discrepancy is a problem that demands more interdisciplinary research and, most likely, more of a systems biology approach, as well as further advances in bioinformatics.

There has been a modicum of progress toward creating new structures that are favorable to personalized medicine.

- NIH and the FDA have demonstrated leadership with initiatives such as the Critical Path and guidance on voluntary genomic data submissions.
- Other federal health care agencies are starting to cooperate to advance the new science. One recent example is The Cancer Genome Atlas pilot project co-sponsored by the National Cancer Institute and the National Human Genome Research Institute.
- Initiatives like this link multiple institutions in large-scale projects that not only seek to make exponential progress in discovery, but also mandate a sharing of data through standardized IT language and systems so that all boats are lifted in the search for knowledge.

### **Challenges and Goals**

But these are early advances in the revolution of medicine. We must ask ourselves: What more can we do to increase the development of safe and more effective products?

What goals must we achieve in order to realize the promise of personalized medicine?

The white paper called "The Case for Personalized Medicine," released this month by the Personalized Medicine Coalition, illustrates the potential impact of personalized medicine on the health care system and outlines a realistic scenario for its evolution.

In my opinion, the PMC correctly notes the need for:

- A regulatory environment that will foster the emergence of personalized medicine,
- The realignment of reimbursement policies to support a more preventive, proactive approach to medicine,
- And the development of a health care information technology infrastructure that will support the widespread adoption of electronic health records.

The report, which I'm proud to say was supported in part by my company, presents evidence that personalized medicine will be increasingly significant to health care, while at the same time acknowledging that there are many uncertainties about the timing of its ultimate impact.

I promised you I would put forth goals for your consideration. Today I will highlight five

key areas in which we must all play a part in order to speed the development of drug, device, and biologic products that will drive personalized medicine.

### **Goal 1: Increase research funding**

First, we must sustain and increase funding for the research that drives personalized medicine.

Basic science still has much to learn, and it needs the funding support to connect the layers of biological complexity more quickly.

We must make it clear to Congress that the future of health care is written into their NIH appropriations. This task is not someone else's job: As leaders in this field, it is uniquely ours.

NIH is at the heart of our nation's preeminence in the life sciences, which is the envy of the world. Yet NIH budgets have been flat to declining in real terms over the past five years. The public investment in mapping the human genome has laid the foundation for tomorrow's better drugs and cures. It's time to build on the foundation.

It's time to make the investments in translational research that can improve the health care of Americans for many years to come.

We can't prove the proposition just yet, but I believe delivering "the right drug to the right person at the right time at the right dose" should help ease the financial crunch that Medicare is certain to face when charged with covering the health care costs of millions of Baby Boomers.

### **Goal 2: Support Economic Impact Studies**

This brings me to what I believe must be our second major goal: We must support studies that test our hypothesis that personalized medicine reduces cost.

Nothing will demonstrate the worth of personalized medicine more quickly than showing not only that the approaches work clinically to achieve a certain endpoint, but also that they result in significant cost savings and an increase in quality and quantity of life.

The two-part trial recently launched by the Harvard Partners Center for Genetics and Genomics to investigate using genetics to determine the right dose of warfarin for patients, and to analyze the cost/benefit of incorporating genetic information to make better clinical decisions for using warfarin — is a step in the right direction.

But showing the economic value of personalized medicine is by no means a simple matter. With the health care system still mired in the paper age, documenting the true cost of current therapies and the comparative economic advantages of personalized medicine is extremely difficult.

But it is not impossible, and more work must be done. Kathryn Phillips, a well-known health economist at the University of California at San Francisco, made this point very

well last month at a symposium in San Francisco. She cited a paper she published two years ago, which found only 11 published studies that evaluated the cost effectiveness of pharmacogenomic interventions.

Dr. Phillips estimated that today, there may be only 15 such studies in the literature.

I believe that we must perform more economic impact studies, and that every development program should have built in cost-benefit measurements.

### **Goal 3: Improve clinician understanding**

Third, we must increase clinician knowledge about personalized medicine. Since 1993, the number of individuals who achieve certification in clinical genetics has been declining.<sup>8</sup>

Today, more than half of the positions in approved medical genetics residency training programs remain unfilled.

We can make all the scientific progress we want, but if we can't get it into the doctor's office, the patients will not benefit. We need to change the way we educate our clinicians, and that change must start in the academy.

Most medical schools and postgraduate education programs do a good job of teaching standard Mendelian patterns of inheritance and X-linked inheritance, generally a one-gene view of disease, which are certainly relevant to medicine, but only a small part of what we must achieve.

As you know, the so-called "common diseases" are a result of highly complex inheritance patterns, and the functional genome scans and population-based association studies we perform — among others — are almost utter strangers to the medical school curriculum.

Many conditions that look alike to a physician in the clinic — or for that matter, look alike to an expert histopathologist — are really different conditions at the molecular level.<sup>9</sup> Naturally, these molecular differences will require a more sophisticated perspective on prevention, screening, diagnosis, and treatment than is currently being practiced, much less taught.

The medical education system must be revamped to address applications for diagnosis and therapy in situations where the decisions are made on a panel or network of genes, rather than on one gene.

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<sup>8</sup> Korf BR, Feldman G, Weisner GL. (2005). Report of a Banbury Summit meeting on training of physicians in medical genetics, October 20-22, 2005. *Genetics IN Medicine* 7: 433-438

<sup>9</sup> Dave SS et al. (2006). Molecular Diagnosis of Burkitt's Lymphoma. *New England Journal of Medicine* 354: 2431-2442.

In addition, medical curricula must move from the reliance on “classic” anatomical orientation in teaching diseases, to more emphasis in favor of courses built on understanding and unifying diseases by genetics and molecular pathways.

As a first attempt to address these issues, the Applera Charitable Foundation has made grants to Harvard Medical School and other institutions to develop new teaching modules. These new models offer one way to prepare the next generation of medical professionals about polygenic diseases and new treatment paradigms. We will continue to make genomics education our Foundation’s priority. But this Applera approach is not enough. We need a concerted effort of all major parties — all of you — to improve genetics education for all clinicians, and to support medical genetics as a medical specialty.

#### **Goal 4: Address regulatory issues**

The fourth issue is regulation.

The FDA, in developing its Critical Path Initiative, has noted on numerous occasions that industry stimulated its efforts to become more proactive in providing guidelines that strike a balance between protecting public safety and encouraging innovation to improve the safety and efficacy of drugs and diagnostic tests. Pharma, biotech, and diagnostic firms told the FDA that we were very concerned about conducting this new science without a better understanding of how the regulators were going to review and interpret it.

That is why today, the FDA is challenging the status quo in numerous ways, including leading and participating in collaborations between government, industry, and academia.

Dr. Andy von Eschenbach, the FDA’s acting commissioner, has noted that the FDA is recognizing that our regulatory system is not organized to deal with future developments in personalized medicine.

We’re going to have to participate in a total reinvention of our regulatory process as this technology rolls forward, so that as individualized therapies are developed, we have a regulatory system capable of approving them.

#### **Goal 5: Establish better models for collaboration among diagnostic and pharmaceutical developers**

The fifth area we must address is the need for workable business models for how drug and diagnostic developers can share value from the combination of their products.

This is a big challenge. Drug and diagnostic manufacturers often seem to have opposite points of view and differing incentives, and it’s clear that there’s a cultural as well as a business gap.

Consider the case of a drug that is in clinical trials and a diagnostic genotypic test that could help select patients in order to improve the efficacy and safety of the drug.

The diagnostic manufacturer wants a high price for its test to maximize revenue and deliver an ROI. He is leery about taking the up-front development risk when clinical success and regulatory approval of the drug is uncertain.

At the same time, it is in the interest of the pharmaceutical company for the test to be as inexpensive as possible, in order to encourage use that will drive acceptance of its product. Moreover, the pharma company is by nature resistant to the concept of sharing in the cost and risk of developing the test.

I would offer that a new “companion products” business model will emerge in coming years, probably catalyzed by numerous factors, including the realization in the executive suites that both parts of the diagnostic and therapeutic combination have value and bring value to the other part.

While I’m talking about commercial issues, let me address the oft-cited comment that personalized medicine is a threat to blockbuster drugs and is therefore something that pharmaceutical companies are naturally opposed to.

That knee-jerk reaction no doubt persists in some quarters, but my company has seen an evolution of thinking underway in the industry in the last couple of years. Some pharma company executives have stepped up to the plate publicly to support this shift, and others are working behind the scenes to adapt their organizations.

The pharma CEOs I know are focused on building their product pipelines. They worry less about fragmented markets and more about dramatic side effects in a few patients washing their drugs out of clinical trials or, worse, leading to recalls of on-market products.

It has not escaped either pharmaceutical or biotech companies that safer and more effective drugs that address unmet medical needs in serious and life-threatening diseases can generate significant revenues, and that, in many ways, targeted therapies offer not only benefit to patients, but also offer competitive advantage to their developers.

With these five goals in mind, it’s clear that there’s a role for each of us to play in this relentless and massive transformation

### **Glimpses of the Future**

At this year’s BIO meeting, Health and Human Services Secretary Mike Leavitt imagined what the life of the CEO of a biotech firm might be like 10 years from now. For obvious reasons, and as I’m sure you can imagine, I was pretty interested in Secretary Leavitt’s predictions for this imaginary CEO.

Secretary Leavitt painted a picture of a CEO who had been doing drug discovery work since the mid 1990’s. He had been a full participant in the development of the genetic era.

In the year 2016, this CEO has access to real-time health data and detailed health

histories — data that has been fully privacy protected. The data has been provided by researchers funded through institutions such as the NIH, as well as by individuals who provided their genetic information and health history directly to a health data firm.

That information allows researchers at the CEO's lab to analyze data from 120,000 patients in their quest for a possible treatment for Alzheimer's.

The researchers find that of a large number of people who have developed an antibody to a common cold virus, a few have experienced an unusual reaction that has led to initiation of the Alzheimer's disease process.

In a matter of a few days, researchers at the CEO's firm survey the medical histories and blood samples of the entire data set. The data shows that more than two-thirds of the known Alzheimer's disease population has a biomarker for the unusual reaction, and only a small percent of the unaffected population has the biomarker.

The CEO's firm downloads more than 3,000 computer-designed compounds for testing that could block the action of the antibody in question. Then as now, the challenge will still be finding the right key for the right lock. But testing will be much faster and much more economical. Researchers winnow the 3,000 compounds to 20 possibilities that can then be used in a computer-assisted clinical trial.

The CEO then goes to the FDA for permission to start human studies. And in the year 2016, the painstaking plodding of trial and error that characterizes today's discovery and pre-clinical development had been transformed into a six-month sprint.

That transformation has happened because researchers have much more information and many more sophisticated tools at their fingertips. Among other tools, researchers have access to predictive toxicology screens, gene expression systems, and metabolic assays.

Researchers also have access to real-time feedback about adverse events, thanks to on-line patient reporting.

In Secretary Leavitt's story, safety testing of the compound proves successful in a matter of months, not years. And the CEO's company moves forward to a brighter future with the first pre-emptive therapy for Alzheimer's.

### **International Perspective**

Finally, I don't want to miss the opportunity to mention that many of the advances in molecular medicine and its underlying platforms could go a long way to improve the public health of the developing world.

In fact, in addition to the public health, there is a security component to this topic. Unchecked disease and premature, preventable death in the developing world arguably undermine national, regional, and in turn, global stability.

Also, application of genomics in countries in the developing world could pay other big

dividends for the United States and Europe. Knowledge of the genetic differences in populations around the world is increasingly relevant to health care in Western societies that have become more multicultural through immigration.

### **Closing**

In closing, I challenge all of us to become a new type of leader.

I am not here to lecture you, since this type of convocation attracts some of the best minds in the world. But I believe that *we* must lead the transformation in how we define and describe diseases, and thus how we treat and prevent them. I can think of no greater challenge, and no more noble pursuit in our time.

None of this work will be easy, or smooth, or even always popular.

Ralph Waldo Emerson might as well have been talking about all of us here today when he said, “There is always someone to tell you that you are wrong. There are always difficulties arising which tempt you to believe that your critics are right. To map out a course of action and follow it to an end requires courage.”

It is the responsibility of leaders like us to map out a course of action and involve others in achieving it. I believe that is why you are here today.

Please keep thinking imaginatively and critically. Keep educating, innovating and collaborating.

Keep asking the right questions: those that *need* to be answered, not just those that can be answered easily.

Our success in asking — and answering — the right questions will be measured in the health of the entire world. I look forward to working with you during this conference and beyond.

Thank you.

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