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FROM THE BROAD BRUSH TO THE FINE POINT: How to Enable Personalized Medicine

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I am very grateful to the Manhattan Institute for this opportunity, and to all of you, for taking this time out of your day to hear my thoughts.

I understand that many of you are supporters of the Manhattan Institute's work, and for that I also thank you, as a citizen. I wish I could say that the importance of free markets and individual responsibility was widely understood, and that the Manhattan Institute was therefore a pleasant luxury. But that is not the case.

Markets and the free choices of individuals are not always perfect. The current mortgage crisis makes that clear once again, along with the need for prudent regulation. However, if I may recast Winston Churchill's comment about democracy, the free market is the worst possible system except for all of the others! This argument must be made constantly and applied to all manner of policy, no matter how unfashionable the argument might be. Far from a luxury, therefore, the Manhattan Institute is a foundational necessity, and I hope that you will continue to keep it strong.

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This is a milestone event for me. I will retire as chairman of Eli Lilly and Company in less than three weeks, so these will be my last public remarks as the leader of a large pharmaceutical company.

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Do not fear the worst! I promise that I will not use this time either to talk about the "good old days" or to unburden myself of a growling complaint about how the industry has been mistreated. As tempting as these approaches might be, neither would leave us with much more than indigestion.

Instead, I want to look forward—to speak about the promise of the life sciences and about what we can do to realize that promise.

I firmly believe that we stand on the cusp of an unprecedented period of discovery and invention in the life sciences, in which our understanding of individual human differences replaces our pursuit of generalized well-being as the main driver of medical progress.

That is a mouthful. So let me try to explain by bringing to mind, 10 blocks from the MOMA in this city of art and culture, the image of a painter at work. The masterpiece in this case—and it is worthy of that name today—is the improvement of human health.

Prior to the 20th Century, this canvas had been barely touched. There was a pencil outline perhaps, the contours of an image that would have seemed fanciful throughout most of history—the image of more and more children surviving infancy, of infections and plagues that could be stopped rather than simply endured, of chronic diseases that could be held at bay or even cured, and of lives that were not only long but also robust and productive.

During the last century, we began to paint rather than merely to sketch this masterpiece. We began with broad brush strokes—including major public health improvements through the build-out of a sanitation infrastructure, immunization programs, health education on a mass scale, and the training of medical practitioners on the basis of science rather than superstition.

At the same time, innovative pharmaceuticals—along with medical devices and new surgical techniques—added more and more layers of color and texture to this masterpiece. No one describes these shadings more effectively than Frank Lichtenberg, a Columbia University economist whose work the Manhattan Institute has encouraged.

For example, Professor Lichtenberg published an analysis of disease data and death rates from 52 countries—rich and poor—and correlated this information with data on the availability of new medicines. He controlled for income, education, and other factors. And he found that new drug launches accounted for 40 percent of the increase in life expectancy during the two decades that he studied—the 1980s and 90s.

In other words: for every year that life expectancy increased, five months can be attributed to the availability of new medicines.

And so, as the 20th Century came to a close, improvement in human health already qualified as a striking masterpiece. Today, the average life expectancy at birth in the U.S. is 78. A century earlier, it was 47. This increase of 66 percent is unprecedented in human history. And the rates of increase have been equally dramatic throughout most of the world.

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Not bad for a work in progress, and I am proud to have been part of an industry that contributed mightily to the brush work. But we are not done.

Wagers are being placed these days, at some scientific conferences, about whether the first person to live to 150 already has been born. (I must say, I have no idea how these scientists propose to collect on their bets, unless they are the ones who will live to 150 and beyond!)

As for me, I will not place a bet on a specific number. Sadly, some of the lifestyle factors that plague us today—such as poor diets and lack of exercise—conspire to actually reduce life expectancy. What I do feel confident in sharing with you is this: Whether lifespans increase by 10 percent or another 66 percent in the century ahead, it will not be as a result of using the same broad brush strokes that filled the canvas during the last one hundred years. Further improvements will require a fine-pointed brush—detail work at the level of the individual patient.

This is the vision that some have called "personalized medicine," and I can assure you, from the front lines of pharmaceutical innovation, that it is no illusion.

So the massive task for our scientists, now, is to combine insights from the human genome with the growing field of systems biology, use informatics to organize complex data, and apply new research tools to develop highly targeted molecules that prevent or stifle disease.

The Human Genome Project was necessary to this vision, though not sufficient. It has allowed scientists to pin down the location and chemical composition of every gene that defines a human being, but this effort did not reveal the "master code" of disease that some had hoped for. Genes interact with many other biological systems to determine whether a particular disease develops in a particular human being—or not.

So the massive task for our scientists, now, is to combine insights from the human genome with the growing field of systems biology, use informatics to organize complex data, and apply new research tools to develop highly targeted molecules that prevent or stifle disease.

All of this will permit the biopharmaceutical industry to make essential contributions to personalized medicine. At Lilly, we call our goal "tailored therapies"—or "tailoring" for short.

Already, it is possible to design and engineer molecules that target patients, based on their genetic makeup, who have not been helped by existing therapies. At Lilly, we're doing this right now—for example, with a molecule for the significant percent of patients with non-Hodgkin's lymphoma who do not respond well to Rituxan, which is today's standard of care for that disease.

And we are coming away from clinical trials with better and better information about the benefit-risk profile for new molecules in different groups of patients. That has been our experience, for example, with prasugrel, a molecule Lilly developed alongside Daiichi Sankyo for acute coronary syndromes. It is currently being reviewed by the FDA.

Even after a product is on the market, it is increasingly possible to determine why it does not work in certain patients and to spread that knowledge to doctors, perhaps in conjunction with a diagnostic tool that identifies the right patients. We are close to delivering on that vision with Xigris, Lilly's product for severe sepsis.

Today, there is hardly a molecule or an approved product anywhere in Lilly's pipeline or portfolio that is not the subject of tailoring. Our goal is to give doctors the ability to prescribe for individual patients—with a much higher level of confidence—the right dose of the right medicine at the right time.

The therapeutic value of tailoring is fairly obvious, even from the few examples I've given. But there is potentially large economic value as well—which is quite important in a world of aging populations and struggling payers. The economic argument for personalized medicine has at least three dimensions.

First, the more predictive that medicine becomes—using genomic information and other tools to identify the patients likely to be at risk for certain diseases—the more that can be done to prevent the onset of expensive chronic conditions or medical crises.

Second, the more tailored the therapies that doctors

prescribe, the less money that will be wasted in trial-and-error medicine—not to mention precious time—and the fewer side effects that will arise, which carry their own costs to remedy.

Third, even as personalized medicine can reduce the immediate expenditures on health care, it also promises to improve the long-term return on investment, if you will.

The wide brush strokes of the last century added years of productivity and personal fulfillment to the average lifespan. In the same way, the detail work of 21st Century medicine should increase the value that each of us adds to the economy and to the lives of those around us.

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I hope that my report on the early progress at Lilly makes clear that, as I said, personalized medicine is no illusion. However, personalized medicine is also not guaranteed. There is nothing automatic about the innovation that will be required to improve human health even further and to realize the economic value of human potential. This is why I have come to an elite institution of policy research to press my case.

Far from guaranteed, innovation in the life sciences depends on a set of basic requirements that seems perpetually under threat in political debates and policy deliberations.

In understanding the basic requirements of innovation, it helps to envision a three-legged stool—the kind which a painter might sit on, to keep our metaphor intact!

The first leg is intellectual property protection, without which the incentives to take financial risks on health-care R&D simply would not exist.

The second leg is pricing freedom: the ability to price our products in a manner that reflects their true value compared with other alternatives in an open, competitive health-care market.

And the third leg is market access: the ability to make our products available to prescribers—-who, in turn, can inform their patients about the attributes and the benefits of what we have developed.

The average investment today in the pharmaceutical industry, to bring a single new product to market, is around $1.5 billion. We are not happy with that number and we are working on a number of fronts to improve our productivity. However, the complexities of tailored therapies and the growing demands of regulators make it unlikely that 21st Century drug-development will come cheaply.

The necessary investments simply cannot and will not be sustained in the absence of the three-legged stool. The image is appropriate because, like other three-legged stools, this one will collapse if any of the legs are sawed down or removed.

And right now, saws are being wielded against all of these legs in the U.S., with potentially serious consequences for the development of tailored therapies—and I won't even speak about markets outside the U.S., where it is more like chainsaws that we are facing!

With regard to intellectual property protection, the U.S. Congress is considering various pathways for the approval of generic biotechnology products—so-called "follow-on biologics." Biomolecules, I should note, lend themselves particularly well to the kind of targeted engineering that I mentioned earlier.

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On the innovation side of the industry, we have no complaint at all with the role of generics. We will not be able to develop anything worth copying, however, if the new laws do not guarantee a significant period of what is called" data package exclusivity" for our inventions.

This kind of exclusivity would assure that, for a fixed period of time after FDA approval, no one other

than the owner of a patent could use data about the resulting product and its manufacturing process in a regulatory application. Some key Members of Congress, unfortunately, envision follow-on biologics legislation with no data package exclusivity whatsoever.

Other saws are being sharpened around pricing in the U.S. For example, some in Washington appear poised to repeal the so-called "non-interference clause" in the Medicare drug benefit, which today relies on private competition among health plans. Companies such as Lilly would face de-facto government price controls if the non-interference clause were to be eliminated.

Used wisely—as one element in medical decision making—data on comparative effectiveness can help to improve patient outcomes. However, I believe that we should be very skeptical about calls for a centralized or government-run center for such research, and we should resist policies that would turn favorable comparative effectiveness reports into yet another requirement of market access.

A second pricing issue concerns the rebates that pharmaceutical companies are required to pay as a condition of doing business with the government through the Medicaid program. There is growing support for increasing both the percentage and the scope of the rebates, possibly requiring them in Medicare as well.

The common fallacy of these proposals, in my view, is the notion that the government can somehow generate real savings by reducing near-term outlays for prescription medicines. The actual impact is likely to be the opposite.

Since our current revenues pay for future innovation in the pharmaceutical industry, price controls and expanded rebates will mean less progress in tailored therapies—which, in turn, will make it harder for society to realize the economic benefits of personalized medicine that I described earlier. Short-term savings will be swamped by long-term opportunity costs.

The case study leading to this conclusion is the story of pharmaceutical innovation in Europe. In the course of my own career—about 40 years—Europe went from being the primary location of R&D on new medicines to a distant Number Two. To explain this, I can do no better than to quote Ken Kaitin, director of the Tufts Center for the Study of Drug Development.

Kaitin said: "Investors tend to invest in places where there is less control over prices." For the sake of innovation in personalized medicine, let us hope that the remaining island of opportunity in the U.S. is not swamped as well.

The third leg of the stool—market access—also is threatened in a variety of ways. Indeed, the U.S. Food and Drug Administration's growing risk aversion has contributed to a serious decline in the number of drug approvals in recent years—only 19 new molecules in 2007, for example, the lowest number in a quarter century. The FDA has also been slow to embrace some of the implications of personalized medicine, such as adaptive clinical trial designs—research that evolves in mid-stream based on what is learned about individual patient responses.

Meanwhile, policymakers appear to be considering yet another hurdle to market access based on something called "comparative effectiveness" research. It compares the clinical effectiveness, risks, and benefits of different options for treating a medical condition.

Used wisely—as one element in medical decision making—data on comparative effectiveness can help to improve patient outcomes. However, I believe that we should be very skeptical about calls for a centralized or government-run center for such research, and we should resist policies that would turn favorable

comparative effectiveness reports into yet another requirement of market access.

Such approaches simply fly in the face of personalized medicine—reducing the range of options available to doctors and patients on the basis of research that almost by definition favors the broad brush over the fine point.

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To conclude, I would like to offer a few thoughts on how we can use policy to favor the fine point, thereby helping to make the masterpiece of human health improvement even more spectacular in the 21st Century.

I'll group these ideas into three areas, calling the first one "choice for patients and doctors"; the second one "tapping health information"; and the third one "working together."

Let's start with choice. To enable personalized medicine, we must increase both the options available to patients and their freedom to choose among these options.

Single-payer health care systems accomplish neither goal, which is yet another reason to avoid them.

Instead, I believe that we should be looking at insurance and payment-system reforms—such as the Health Savings Account model—that elevate the role of individual patients, working with their doctors, in weighing one set of interventions against others based on their particular needs.

Universal access to health care is completely consistent with choice and with improved outcomes for individuals, since larger markets are better markets. But the emphasis must be on giving new entrants meaningful power. Too often, existing universal systems simply entitle patients to receive care, passively, from a fixed and limited inventory. We must do better—creating more savvy consumers, equipped with the knowledge and the choices to realize the promise of personalized medicine.

This leads us into the second area of policy innovation that I foreshadowed: tapping health information—with the aim of converting such information into real knowledge.

In the disaggregated, paper files of tens of thousands of doctors' offices, we are squandering one of the greatest untapped resources in health care: namely, the knowledge of what works and what does not work in the treatment of patients based on their particular characteristics and medical histories.

Tapping this resource—in conjunction with the rise of genetic testing for individual patients—could yield a true wealth of insight on personalized medicine, making treatments safer, more predictable, and more effective across the board.

Getting to that point requires things that policymakers can enable, including: an infrastructure for building and sharing health records electronically, a rigorous privacy code that prevents disclosure and discrimination, and a far more pervasive system for detecting "signals"—both positive and negative—in the real-world use of prescription medicines.

> Much more will be asked of companies such as Lilly. Tailored therapies will not arise in isolation from our own labs and sales forces using the R&D and delivery models of the past. That is why we are quietly transforming ourselves from a company that once did everything by itself into something more like conductors of a global orchestra.

To that end, I am proud of something called the Observational Medical Outcomes Partnership (OMOP), which our industry association, PhRMA, launched with almost no fanfare together with the FDA and the Foundation for the National Institutes of Health. OMOP, to use the acronym, will develop and test new tools to mine vast databases of information on the outcomes of therapy.

Finally, there are the policy innovations that I have labeled, simply, "working together." The insight here is straightforward. No single company, industry, agency, or even nation will add very much to the canvas of human health by working on its own. The fine point, ironically, depends much more than the broad brush on collaboration, flexibility, and trust.

Much more will be asked of companies such as Lilly. Tailored therapies will not arise in isolation from our own labs and sales forces using the R&D and delivery models of the past. That is why we are quietly transforming ourselves from a company that once did everything by itself into something more like conductors of a global orchestra.

Using virtual collaboration tools, risk-sharing arrangements, new financing models, and many more innovations, our goal is to tap expertise at its source, accelerating the development of new medicines. The same openness and spirit of partnership will be required in our relationships with patients and doctors.

As an industry, we are beginning to share non-proprietary assets, including libraries of molecules and imaging data, in an effort to avoid unnecessary duplication of work. And we have launched a very promising consortium, working with the FDA and the National Institutes of Health to validate so-called "biomarkers"—biological "tell-tales" that have been a key to progress in tailored therapeutics.

And we are learning—finally—that transparency with regard to our clinical trials, research grants, and payments to doctors is the best way to build trust with patients, which in turn will be crucial to their engagement in personalized medicine.

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Ladies and gentlemen, almost 40 years in the business of health care leaves me an optimist.

The canvas of human health looks vastly better today than it did when I began my career in the early 1970s. And I remain convinced that it will look much better still—from the vantage point of another generation—with many more of the details filled in, by the artists of personalized medicine.

If I am right in this assessment, then it will be because innovation triumphed. We do not need to be doctors or scientists ourselves to help that cause. But we do need to insist on a reasonably free market, on the possibility of reward for innovation that works, on collaboration and openness towards the outside world, and on the importance of individual aspirations—in health care and otherwise.

So it has been my privilege today to conclude the public portion of my Lilly career right here in the company of the Manhattan Institute, where all of these things are understood and embraced. Thank you!

Fellows

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The mission of the Center for Medical Progress (CMP) is to increase awareness of the indispensability of vibrant free-market institutions to medical innovation. The research and writing of CMP senior fellows David Gratzer, Regina Herzlinger, Paul Howard, Thomas Stossel, Peter Huber, and Benjamin Zycher examine and propose market-based policies that advance the efficiency, quality, and availability of medical treatment. CMP reports are also be prepared by outside scholars.

CMP fellows have published articles in the *Wall Street Journal*, the *Washington Post*, *National Review*, the *Weekly Standard*, and other leading publications, and they have also written a number of widely recognized books. Regina Herzlinger's focus is on health-care delivery and the role of choice in ensuring economical and broad-based care; in 2007, she released *Who Killed Health Care?: America's $2 Trillion Medical Problem—and the Consumer-Driven Cure*. Dr. David Gratzer's work also focuses on consumer-driven health care, as well as drug re-importation and reform of government agencies and programs, including Medicare and Medicaid. His 2006 book, *The Cure: How Capitalism Can Save American Health*, received nationwide acclaim. CMP director Paul Howard focuses on medical malpractice, reform of the U.S. Food and Drug Administration, and health-care innovation.

CMP fellows also produce research reports. Ben Zycher researches the economic and political effects of regulation, government spending, and taxation, as well as the economics of the pharmaceutical industry. Thomas Stossel has written extensively on the interactions between physicians and researchers and private industry. Peter Huber writes on a wide range of topics, from drug development to the future of personalized medicine.

In the fall of 2008, CMP launched Project FDA, a committee organized to influence FDA policy. Chaired by Professor Tomas Philipson, it is composed of physician-scientists, economists, medical ethicists, and policy experts. Their purpose is to show how 21st-century technologies can better inform FDA regulations and accelerate the drug-development and drug-approval process while maintaining drug safety.

CMP also runs the website MedicalProgressToday.com, which provides daily links to news, commentary, and research and analysis written from a free-market perspective. In addition, MPT generates op-ed articles and convenes policy forums. Contributors to MPT have included law professor Richard Epstein, former Speaker of the House Newt Gingrich, American Enterprise Institute scholar Scott Gottlieb, and J. Edward Hill, a former president of the American Medical Association.