Testimony of Dr. Tom Coburn—July 14, 2015
Senate Subcommittee on Space, Science and Competitiveness

First, I'd like to thank Chairman Cruz, Ranking Member Peters, and the other members of the committee for inviting me to speak today about an important subject that is near and dear to my heart: advancing cures for the tens of millions of American patients and their families battling life threatening or disabling disorders.

The battle is personal for me in many ways. As a physician, I see elderly patients suffering from symptoms of early dementia, and eventually Alzheimer's, without a real treatment in sight. The burden of the disease falls not only on patients, but on their families and caregivers. Their plight is agonizing. And I can't offer them any effective treatments.

As a three-time cancer survivor, I'm excited by the progress we've made against this deadly disease, but also mindful of how much further we have to go to conquer it. Cancer remains the second leading cause of death in the U.S.; for patients diagnosed with metastatic solid tumors—of the lung, colon, pancreas, or ovaries—far better diagnostic and treatment options are desperately needed. Diagnosing these diseases late—as we do all too often today—means that we can only delay the inevitable, at great human and financial cost.

But I'm also deeply optimistic, because I've seen firsthand the inventiveness, dedication, and entrepreneurship of America's leading researchers and companies. I'm watching a flood of new information emerge that is helping researchers map out cancer's vulnerabilities at the genomic level and develop personalized treatment programs for patients tailored to their unique tumor profile. These approaches are being made possible by advanced computing platforms for rapidly sorting through this torrent of information, guiding doctors and patients to the best treatments. For instance, IBM's Watson is analyzing millions of journal articles, patient records, and data on approved and experimental drugs to help developed personalized cancer-care regimens faster than any single physician alone could ever do. Watson and other "big data" and machine-learning approaches are literally getting smarter every day—and will, one day, expand state of the art oncology services to every cancer patient in America in their own communities, not just patients with access to leading cancer centers.

The advent of systems biology and, more recently, quantitative systems pharmacology are helping us unravel the molecular networks of complex diseases at an unprecedented pace; simulate the effects of candidate compounds in computer models; weed out drugs likely to fail; and identify those most likely to succeed, all before a single human patient is dosed. Companies are also perfecting the art of developing targeted medicines, including genetically modified T-cells, monoclonal antibodies, and new gene-editing technologies. This approach heralds a day when researchers will use molecular scalpels to target disease-causing cells and genes—and kill or replace them with healthy versions.

Is this the Golden Age of Medicine? Not yet. How long it takes us to get there rests with you. It depends on the 21st Century Cures legislation just passed by the House, on steps that you can take to improve it even further, and on decisions that Congress will make over the next few years to enhance the climate for breakthrough innovation in the United States.

The way we approve new medicines and diagnostics must change. It's got to be completely transformed. I know that word is overused and we've been talking about transformation for a long time. We don't need another committee to study it, or hold another conference about it. We need to do it.

I'm honored today to be testifying beside Keith Yamamoto, vice chancellor for research at UCSF, one of America's leading medical-research universities. He is one of the visionary leaders of the precision-medicine movement, and one of the architects of the pivotal National Academy of Sciences committee report *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. That report talked about the need to develop a true molecular taxonomy of disease through a knowledge network that patients and physicians could consult and upload information to in real time—moving us away from an outdated classification of disease based on clinical symptoms and toward one based on molecular pathways.

We've made and continue to make rapid progress toward precision medicine. But the way the FDA approves new medicines is still mostly rooted in those clinical signs and symptoms. It is based on cutting edge science—cutting edge in 1962, when we couldn't identify the molecular mechanisms of disease, let alone design drugs to target them. It's how we got the double-blind, placebo-controlled trial (preferably two of them) as the "gold standard" for approving new drugs. That gold standard is increasingly out of date, as we gain confidence that we actually are targeting the pathways causing the disease or disorder in question. And we can also design trials that, as they proceed, help unravel those pathways in a learn-as-we go strategy using targeted medicines. We can't continue to ask one narrow question at a time, in one trial at a time. The current drug development and approval system is too expensive, too time consuming—and, frankly, likely unethical when there are better approaches available.

What we should be doing instead is ensuring that all trials that we run attempt to match new medicines to the biology of the patients taking the medicine: we know that different patients with the same clinical symptoms can respond differently because of a variety of genetic factors that affect drug metabolism (or indicate that one patient actually has a totally different disease that needs a different treatment).

We're moving in this direction—rapidly in cancer and much more slowly for other indications. Far too many drugs are still tested and developed based on 1962-era science. It's a one-size-fits-all approach to innovation that causes too many drugs to fail that could succeed if they were tested in the correct order, in the correct groups of patients.

While the FDA remains concerned about approving ineffective or dangerous drugs, alternative approval pathways—based on molecular signatures called biomarkers, followed over time in patient registries via electronic medical records—could bring potential treatments to desperate patients much sooner, with appropriate requirements for post-market trials verifying long-term safety and efficacy. That approach is the exception today but should be the rule. Despite its best intentions, and despite repeated pronouncements since 2004, it's clear that the FDA isn't embracing clinical-trial transformation to the degree that it could. The rapidly falling cost of genetic testing, the ability to share tens of thousands or hundreds of thousands of detailed patient medical records and the rise of analytic infrastructure, "bioinformatics," that can rapidly comb through massive, complex datasets all make it increasingly possible for individual physicians to develop personalized treatment profiles that leap ahead of the FDA's approved drug labels—which might be years or decades out of date.

In 2013, researchers at Stanford University screened FDA-approved drugs with known molecular targets, with the molecular expression profiles of known tumor types. They found a match between a 50-year old class of anti-depressants and small cell lung cancer. They then tested the drug in cancer cell lines and animal ok models, and found that the match predicted by

their software killed tumor cells. It turned out that the anti-depressants caused certain cancer cells, called neuroendocrine tumors, to self-destruct, through a process called apoptosis.

Neuroendocrine tumors are found in subsets of other types of cancer, including pancreatic cancer, so the drugs may be effective there as well. The drug quickly went into mid-stage efficacy testing in small cell lung cancer, potentially shaving years off development timelines. Atul Butte, now a colleague of Dr. Yamamoto's at UCSF and one of the developers of this drug repurposing strategy, observed:

> "We are cutting down the decade or more and the $1 billion it can typically take to translate a laboratory finding into a successful drug treatment to about one to two years and spending about $100,000."

That's tremendously exciting; but imagine if we could do this at scale. By scanning millions of real-world patient profiles, researchers might discover that some patients, "exceptional responders," are already being cured with off-label drugs, or rehabilitate medicines that the FDA considers "failures" in broader populations. Researchers could also discover evidence that patients who take certain types of commonly prescribed drugs (statins, newer classes of anti-depressants, etc.) have lower rates of some types of cancer or Alzheimer's, making them powerful off-the-shelf options for preventing or treating chronic illnesses. With enough data, the right analytics, and the correct strategy for adaptive clinical-trial designs, researchers can unravel the right time and sequence for using existing or experimental treatments to produce better outcomes and even cures.

In short, we can harness the many petabytes of data we're already collecting to discover, test, and validate new treatment approaches without waiting for the FDA's overly cautious bureaucracy to catch up. Properly harnessed, data can deliver new treatments and cures at a fraction of the time and cost required by the FDA's 50-year-old paradigm for testing new drug candidates.

To revolutionize outcomes for patients, Congress must require the FDA to collaborate with the broader scientific community to establish clear guidelines for unleashing the full potential of digital medicine to transform drug development and enable precision medicine prescribing by physicians. Congress must set overarching goals for all federal agencies that touch digital medicine, especially the NIH and HHS: streamline bureaucracy, reduce waste, and coordinate research efforts, and hold agencies accountable for doing so through annual or biannual performance reports.

We need reimbursement reforms that reward breakthrough innovations. Many curative technologies will be very expensive at first, but will save the health care system vast amounts of money in the long run by reducing hospitalizations, use of nursing homes, and the need for repeat physician visits and tests. A one-shot cure for leukemia or sickle-cell anemia may be extremely expensive by historical standards, but may still be extraordinarily cost effective for public and private payers in the long run. New approaches to funding and paying for those breakthrough treatments will be needed if we are to address our massive entitlement spending challenges for Medicare and Medicaid. A cures strategy is a strategy that fiscal conservatives should embrace, as long as we are truly paying for outcomes.

Don't mistake my optimism for naiveté. There are real challenges we have to overcome to embrace a cures strategy for American health care. Existing electronic medical records, for instance, don't capture much of the data we need to support rapid development of personalized

medicine protocols. Many physicians still are not well-equipped to interpret results from genetic testing. While Medicare has required EMRs for reimbursement purposes, they haven't helped streamline the physician's workload or enhance patient care. If anything, they've detracted from it.

But these challenges are largely engineering problems—problems amenable to technical solutions. The basic tools enabling precision medicine are available and are widely used across the internet, as well as in numerous industries, from retail to the Department of Defense. (The Defense Advanced Research Agency is building a machine-learning engine to identify and predict all of the genes and signaling networks driving all cancers.) Several large hospital systems, such as Intermountain Healthcare, are developing sophisticated electronic-records systems and diagnostics platforms that can serve as proving grounds for rapidly scaling up new digital medicine strategies, as well as for sharing such data.

What will it take to enable a cures strategy for America? There are many good ideas in the 21st Century Cures legislation; but the biggest one is yet to be embraced. The FDA will have to pivot from being a gatekeeper to a collaborator, one that works with many stakeholders to develop evidentiary standards for enabling digital, precision medicine on a national scale. Power will have to shift from centralized bureaucrats to empowered patients and physicians. But I have no doubt that the country that brought us Google, Intel, Amazon, and Salesforce can tackle the challenge of disrupting the FDA's nearly 50 year-old framework for advancing innovation. Regulators will resist—just as they resisted the demands of AIDS activists in the late 1980s. Yet now, as before, when successes accumulate, regulators will take credit for embracing reform.

By sending the 21st Century Cures legislation to the Senate, Congress has taken one powerful stride to advance precision medicine. Your responsibility is to put your own stamp on the legislation, to ensure that the transformational potential of digital and precision medicine is realized for patients as swiftly as possible.