During the 2015 State of the Union address, President Obama unveiled plans for a $215 million Precision Medicine Initiative. The details of this plan were laid out by past and present directors of the National Institutes of Health, Harold Varmus and Francis Collins, in a commentary in the New England Journal of Medicine.\textsuperscript{1} While the announcement stood as a public statement of support for funding, it was likely the first introduction the American public had to a concept that has been close to my heart for more than a decade. In 2005, I founded the Personal Genome Project, the world’s first open data set of genomic and patient data. The Precision Medicine Initiative offers many opportunities to promote the progress of chemistry, and chemistry in its turn can do much to satisfy the aims of the Initiative.

The term precision medicine generally refers to the personalization of healthcare (decisions, practices, and products) for a given patient based on his or her unique history and genetic makeup. Because cancer is widely recognized as a disease born out of mutations, many of them being patient-specific, the precision medicine stereotype emphasizes pharmacogenomics, cancer, and especially their intersection.\textsuperscript{1} Despite this close association, other fertile opportunities are beginning to blossom. The number of allele-specific drugs (e.g., Ivaçafòr aimed at the 5\% of cystic fibrosis patients with a specific G551D mutation) and allele-specific treatment decisions (e.g., warfarin dosing based on CYP2C9* type) are increasing rapidly across many diseases. The fact that this growth is occurring despite initial concerns over the commercial viability of such tiny markets demonstrates the power of precision medicine and suggests the importance of this initiative. Nevertheless, even classic cases (like warfarin) can lose significance upon careful examination\textsuperscript{2}—indicating an urgent need for more precise and novel approaches.

Regardless of the fate of the Precision Medicine Initiative, the broad ideas raised by the President’s proposal highlight some exciting new areas for chemists and chemistry.

Environmental Precision. Choosing the right drug and dose goes far beyond peering at genomic DNA—necessitating the inclusion of many environmental and internal variables. These could include such disparate factors as the seemingly innocuous consumption of grapefruit (furanocoumarin affects the rate of cytochrome P450-catalyzed drug metabolism) to past immune exposures. Analytic chemistry can now monitor numerous chemical differences not just from person to person but moment to moment—radically breaking with one-size-fits-all medication and litigation-fueled fear of multiple analyses. One of the great challenges in personalized health is monitoring and changing what we eat and breathe. As we get better at 24/7 monitoring...
of health factors, we may extend such measurement and regulation to include personal variation in exposure and sensitivity to cholesterol, sugars (fructose and lactose), carcinogens (UV and estrogens), microbes, viruses, allergens, toxins (synthetic and natural), micronutrients (iron, vitamin D), and metabolites not yet on our radar. Rather than making food labels ever longer, more complicated, and easily ignored by patients during impulsive buying decisions, we might instead create personalizable cell phone apps that integrate diverse emerging wisdom with each dynamic personal file of big data.

**Resistance.** Unfortunately, despite their benefits to specific patients, drugs targeted at specific genomes, whether cancers or infectious diseases, do not often escape the difficulties of emerging resistance. These Darwinian moving targets are particularly challenging. Here, precision should be combined with revolutionary forms of “vaccination.” We don’t fight drug-resistant smallpox because we eliminated it at the source. The new precision chemistry available to add malaria to the globally extinct list includes “gene drives.” This powerful ability to engineer “selfish DNA” to carry payloads making invertebrate disease vectors resistant to carrying specific microbes must be tested with great care.

**Prevention.** While it is obviously very desirable to stop diseases before they start, there is a higher bar to developing treatments that work on healthy individuals than on severely affected ones. The points of intervention are typically pre-conception, prenatal, newborn screening, and adult onset. A huge breakthrough is occurring in noninvasive circulating blood DNA tests for fetal, transplant crisis, or cancer cells—rapidly growing to millions per year. Single-molecule and single-cell measures are becoming the new standards, not just for sensitivity’s sake but for the accuracy of not blurring different measures. The ability to repair tissues depends on such feedback on diverse sets of epigenetic landscapes. Speaking of repair, by far the most common lethal disease in wealthy regions of the world is aging. As large, long-lived animals like the bowhead whale survive many more cell divisions than small rodents, and whereas some people survive a century of smoking, we suspect that some aspects of cancer (and aging) are preventable. Progress in finding mechanisms for youth extension and aging reversal has taken off in invertebrates and rodents, encouraging movement toward preclinical trials.

**Costs.** Bringing down the price of medicine may be one of the great opportunities ahead. The cost and accuracy of DNA analytic chemistry improved over a million-fold in eight years (far faster than the analogous decline in the cost of computing dictated by Moore’s Law) and these continue to improve. Similar gains are being made in DNA synthetic chemistry, including precise genome engineering. How do we direct this momentum toward drug development costs? Orphan drugs are quite expensive (e.g., Glybera at 1.1 million euros per dose). Precision chemistry can reduce R&D costs by reducing cohort sizes needed to capture a given genotype while maintaining high efficacy and low toxicity. Gene therapy may become one of the most precise chemical interventions ever—some genome editing occurring with fewer than one off-target event in 300 trillion base pairs. If we wish systemic delivery, then we might need 5 orders of magnitude greater precision to avoid tumor suppressor inactivation or oncogene activation. The ability to test hypotheses flowing from the sequencing of cohorts may leverage high-throughput testing in human organoids, which might be less costly and more informative than animal trials.

**Cohorts.** As the cost and quality of measuring and altering our personal chemistry improve radically, the ability to interpret accurately must keep pace. This depends on cohorts such as the Personal Genome Project, specifically consented for open sharing of complex and highly identifying big data on individuals (of the type that physicians need to make decisions)—not merely population-averaged case-control DNA variant frequencies. To avoid off-target chemistry in such tests or genome editing therapies requires whole genome sequence of the specific patient cells, not just a generic reference genome. We seek not just weak effects found in genome-wide association studies (GWAS), but extreme values and strongly epistatic effects which override hundreds of small factors, and we seek rare individuals (like supercentenarians) with personal chemistry capable of overcoming common risk factors. To establish precise standards for new diagnostics, the National Institute of Standards and Technology (NIST) and the U.S. Food and Drug Administration (FDA) are collaborating to produce sharable DNA and cells in a project called “Genome-in-a-bottle.”

**Innovation.** Just as President Obama’s State of the Union address in 2013 lead swiftly to the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, his 2015 address introduced a major push into precision medicine.

As the cost and quality of measuring and altering our personal chemistry improve radically, the ability to interpret accurately must keep pace.
These two projects may overlap at some points, and innovative analytic and synthetic chemistry will be central to both.

Details of the Precision Medicine Initiative

The $215 million investment in the President’s 2016 budget includes:

- $130 million for the construction of a one million volunteer cohort with data accessible to both researchers and patients
- $70 million to the National Cancer Institute to spur research into drug discovery programs, looking particularly at the genomic drivers of cancer
- $10 million to the Food and Drug Administration for database expertise and support
- $5 million to Office of the National Coordinator to support the exchange of data and to protect patient privacy

Beyond these monetary commitments, the initiative more broadly aims to use precision medicine to target cancer via supporting novel clinical trials of targeted drugs, expanding the use of combination therapies, and promoting research to combat drug resistance. An important component of the initiative involves the call to both public and private sectors to partner and collaborate.

The cohort, or biobank, aims to synthesize data from medical records, assays, and personal devices to provide information ranging from genomic and proteomic, to metabolite and environmental exposures and behavior and make it widely available. The proposal also calls for the engagement of patients and volunteers, going beyond permission to participation; this includes trying to use mobile devices to encourage healthy behaviors.

In order to support these endeavors, significant updates to regulatory processes are required.

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