Editorial: Rethinking the Definition of Diabetes for Precision Medicine

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In his State of the Union address on January 20, 2015, President Barack Obama announced his administration's intention to promote precision medicine. "Tonight I'm launching a new precision medicine initiative to bring us closer to curing diseases like cancer and diabetes and to give all of us access to the personalized information we need to keep ourselves and our families healthier." Experts may have diverse opinions on whether individualized or personalized or precision medicine all convey the same message (1–4). According to the White House Office of Science and Technology Policy, "Precision medicine is not just about genomics. Health and disease are influenced by many factors. Precision medicine aims to also leverage advances in medical imaging, such as magnetic resonance imaging and three-dimensional X-ray technologies, and utilize advances in health information technology, as well as other fields, to better understand each of these factors and to apply this knowledge in the development of new treatments. The potential for precision medicine to improve care and produce new treatments has only begun to be tapped. Translating initial successes to a larger scale will require a coordinated and sustained national effort" (5). The President's 2016 budget will provide a $215 million investment for the National Institutes of Health, the Food and Drug Administration, and the Office of the National Coordinator for Health Information Technology to support the Precision Medicine Initiative (6).

"Can the idea of precision medicine which has been successful for some types of cancer be extended to diabetes?"

As a researcher and clinician, I was pleased that my specialty, endocrinology-diabetes-metabolism, received some well-deserved publicity in the President's address. Diabetes mellitus, defined as an elevated blood glucose due to lack of insulin or failure to respond to insulin, is a major health problem worldwide (7). In the United States, it is estimated that 29.1 million people (9.3% of the population) have diabetes, of which 8.1 million are undiagnosed (8). Among adults, diabetes is a major cause of coronary artery disease, blindness, kidney failure, and nontraumatic amputation and is the seventh leading cause of mortality (8). A person diagnosed with diabetes has a shorter life expectancy and about twice the risk of dying in comparison with a person of similar age without diabetes (8). In 2012, the total cost of treating diabetes was $245 billion, the direct medical costs were $176 billion, and the indirect costs related to disability, work loss, and premature death were $69 billion (9). On average, the medical expenses for those with diabetes are more than twice as much as those of a person without diabetes (9). Eighty-six million people have prediabetes, and if the current trend continues, an estimated one of three people in the United States will have diabetes by 2050 (8).

What's in a name?

A fundamental principle of medicine is that a disease diagnosis is based on criteria specific to the disease, and the diagnosis should guide the treatment. Type 1 diabetes results from insulin deficiency due to pancreatic β-cell damage by autoimmune or other factors, accounts for 5%–10% of cases of diabetes, and is often diagnosed in children and young adults, although it can occur at any age. Type 1 diabetes requires insulin treatment. Type 2

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diabetes accounts for 90%–95% of diabetes cases, and it is associated with obesity, older age, physical inactivity, family history, or race/ethnicity, with Native American, African American, Hispanic/Latino, and Asian/Pacific Islanders having a greater risk compared with Caucasians. Type 2 diabetes is often treated with oral medication but insulin therapy may be necessary. Gestational diabetes is diagnosed during pregnancy, often in obese women with a family history of type 2 diabetes, and requires insulin therapy to avoid complications in the infant. Other rare types of diabetes result from genetic conditions (such as maturity onset diabetes of youth), pancreatic disease, medications, infections, or other systemic diseases.

More than a century after the discoveries of insulin and key metabolic pathways, the clinical classification of diabetes falls short of diagnostic criteria connected to pathophysiology. Type 1 diabetes can occur in lean as well as obese people. Type 2 diabetes is strongly associated with obesity and characterized by several metabolic abnormalities including insulin resistance, impaired insulin secretion, and glucagon hypersecretion, which vary from patient to patient and contribute to a highly variable onset and progression of hyperglycemia in affected patients. Nonetheless, clinicians often rely on blood glucose and glycated hemoglobin as the sole laboratory tests for the diagnosis and treatment of diabetes. Although insulin resistance can be assessed by homeostasis model assessment index of insulin resistance or hyperinsulinemic-euglycemic clamp in clinical research, these measures are not practical for routine clinical use. Changes in adipokines, inflammation, and excessive lipid accumulation in tissues (steatosis) have been associated with insulin resistance and diabetes, but these biomarkers have not been validated for clinical management of patients. A relative insulin deficiency is deemed necessary for the onset of hyperglycemia in type 2 diabetes, but there are no established standards for assessing insulin deficiency in the clinical setting. Genome-wide studies have revealed interesting gene associations with type 2 diabetes, but these may account for less than 5% all cases (10), suggesting that most patients at risk of developing type 2 diabetes are likely to be undiagnosed or misdiagnosed due to lack of diagnostic tools. Despite the availability of several classes of drugs for type 2 diabetes, the treatment is often based on trial and error or availability or affordability of medications, rather than the underlying pathophysiology. Indeed, most patients with diabetes do not achieve adequate blood glucose control (11). Moreover, studies suggest that tight control of blood glucose may not prevent macrovascular complications and may actually increase the risk of death in type 2 diabetes (12–14).

Precision medicine: promise and challenges

Can the idea of precision medicine that has been successful for some types of cancer be extended to diabetes? As our knowledge of the molecular causes of diabetes increases, it is obvious that we need to expand the tools for identifying patients. Once hyperglycemia ensues, the course of diabetes is progressive and difficult to treat. Hence, it would be important to identify individuals with an increased risk of diabetes, while their glucose metabolism is normal, to begin early preventive measures to delay the onset of the disease. Reliable methods for identifying those who are likely to progress from normoglycemia to prediabetes will reduce health costs (15). A better classification of subsets of patients with diabetes can help to identify those who are likely to respond to existing drugs or new therapies. We also need better predictive markers of diabetes complications. Because the pathogenesis of diabetes involves interactions of a wide range of organs, including adipose, gastrointestinal tract, pancreas, muscle, kidneys, and brain, the contributions of these organs to the disease process in an individual is likely to vary. Precision medicine is attractive because it fosters the transformation of our current diagnostic approaches based on clinical and pathological measures to include the use of state-of-the-art molecular tools to create more accurate diagnostic, therapeutic and prognostic strategies to meet specific needs of patients. Precision medicine aims to use the power of advanced computing technology to amass and convert clinical, epidemiological, genomic, and other -omic data, commonly called big data, into new ways of diagnosing and treating diseases.

Although precision medicine strategies have the potential for improving patient care, there are major obstacles to be overcome for this concept to live up to its promise. A fundamental requirement of precision medicine will be a reclassification of diseases, taking into consideration the new understanding of biological pathways. This new taxonomy of disease based on clinical and molecular parameters should enable a dynamic incorporation of disease mechanisms as the information emerges (1). Unlike the traditional laboratory diagnosis, which is based on threshold values, the advent of precision medicine will require handling and interpretation of massive amounts of genomic, metabolomic, phenomic, and other data, far beyond the expertise of medical professionals who are not trained to deal with such complex information. Another potential concern about big data is that the massive information will provide descriptive statistical associations without necessarily advancing the discovery of how various molecules interact mechanistically to produce diseases or lead to rational therapies.

Can the health care infrastructure provide necessary tools for clinicians and patients to enable the acquisition and processing of personalized health information, molecular testing, interpreting results, and facilitating treatment choices based on a deeper understanding of specific pathways affected in individuals? Can precision medicine really live up to the hype that drugs can be truly customized according to individual needs, with maximum efficacy and minimum side effects? How will industry cope with new changes in drug development strategies focused on individuals or select patient groups rather than large groups? Will additional regulatory agencies be created to monitor the implementation of precision medicine and safeguard against the marketing and distribution of fraudulent products?

Ultimately the success of precision medicine will require honest discussions and collaborations among patients, health care providers, governments, industry, and other stakeholders on the key issues outlined above. Expectations must be realistic, costs must be affordable, and accessibility must be universal. Applying precision medicine to diabetes will require an acceptance of the heterogeneity and complexity of the disease and the need to develop rational therapies based on pathophysiological characteristics of individuals or small subsets of patients. Given the enormous burden of diabetes and its complications, any transformation of the current management of diabetes that leads to significant positive medical and socioeconomic outcomes will be a worthwhile investment in our future.

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References

1. http://dels.nas.edu/Report/Toward-Precision-Medicine-Building-Knowledge/13284. Accessed February 2, 2015.
2. **Mirnezami R, Nicholson J, Darzi A.** Preparing for precision medicine. *N Engl J Med*. 2012;366:489–491.
3. **Hamburg MA, Collins FS.** The path to personalized medicine. *N Engl J Med*. [Erratum 2010;363:1092] 2010;363:301–304.
4. **Mega JL, Sabatine MS, Antman EM.** Population and personalized medicine in the modern era. *JAMA*. 2014;312:1969–1970.
5. http://www.whitehouse.gov/blog/2015/01/21/precision-medicine-improving-health-and-treating-disease. Accessed February 2, 2015.
6. http://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative. Accessed February 2, 2015.
7. http://www.who.int/diabetes/facts/en/. Accessed February 2, 2015.
8. **Centers for Disease Control and Prevention.** *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. Atlanta: US Department of Health and Human Services; 2014.
9. **American Diabetes Association.** Economic costs of diabetes in the US in 2012. *Diabetes Care*. 2013;36:1033–1046.
10. **McCarthy MI.** Genomics, type 2 diabetes, and obesity. *N Engl J Med*. 2010;363:2339–2350.
11. **Stolar MW.** Defining and achieving treatment success in patients with type 2 diabetes mellitus. *Mayo Clin Proc*. 2010;85(suppl 12): S50–S59.
12. **Brown A, Reynolds LR, Bruemmer D.** Intensive glycemic control and cardiovascular disease: an update. *Nat Rev Cardiol*. 2010;7: 369–375.
13. **Zoungas S, Chalmers J, Neal B, et al.** ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med*. 2014;371:1392–1406.
14. **Zoungas S, Patel A, Chalmers J, et al.** ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363:1410–1418.
15. **Cefalu WT, Petersen MP, Ratner RE.** The alarming and rising costs of diabetes and prediabetes: a call for action! *Diabetes Care*. 2014; 37:3137–3138.