NIH Precision Medicine Initiative: Implications for Diabetes Research

Judith E. Fradkin,[1] Mary C. Hanlon,[2] and Griffin P. Rodgers[3]

DOI: 10.2337/dc16-0541

In his January 2015 State of the Union address, President Barack Obama announced a new Precision Medicine Initiative (PMI) to personalize approaches toward improving health and treating disease (www.whitehouse.gov/precision-medicine). He stated that the goal of such an initiative was "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." Since that time, the National Institutes of Health (NIH) has taken a leadership role in implementing the President's vision related to biomedical research (www.nih.gov/precisionmedicine). Here, we discuss the NIH component of the PMI, related ongoing diabetes research, and near-term research that could position the diabetes field to take full advantage of the opportunities that stem from the PMI.

NATIONAL INSTITUTES OF HEALTH PRECISION MEDICINE INITIATIVE

Precision medicine is built on the premise that most current treatments are based on the average patient and can be successful for some people but not for others. Precision medicine aims to move away from such generalized approaches so that treatment decisions are personalized and based on individual variability in genes, environment, and lifestyle. Precision medicine will take into account these differences between individuals and allow health care that predicts more accurately which treatment and prevention strategies will work in specific people. Already, precision medicine has limited applications across a number of diseases, including diabetes. For example, the American Diabetes Association (ADA) recommends that all children diagnosed with diabetes in the first 6 months of life should have genetic testing. Correct diagnosis of neonatal diabetes is important because these patients should be treated with sulfonylureas (1).

Several factors make this an ideal time for embarking on this visionary new initiative: the recent development of large-scale databases (e.g., the human genome sequence); the emergence of new and powerful methods to characterize patients (e.g., genomics, metabolomics, and proteomics); advances in data science and bioinformatics and the availability of computational tools for analyzing large datasets; increased use of electronic health records (EHRs) and mobile health platforms; availability of new data from the microbiome to sensor data; and Americans' interest in being partners in biomedical research (2).

The National Institutes of Health (NIH) Precision Medicine Initiative (PMI) aims to extend the benefits of precision medicine to many diseases, including diabetes. Its major component involves building a national research cohort of 1 million or more U.S. volunteers who broadly reflect the diversity of the country's population. Initially, medical data and other health-related information will be provided by the participants. Then, as the cohort infrastructure is built with appropriate protection for broad research use, participants will be asked for access to EHRs, behavioral data (e.g., mobile health data related to lifestyle), and collection and extensive

[1]*Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD*
[2]*Office of Scientific Program and Policy Analysis, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD*
[3]*National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD*

Corresponding author: Judith E. Fradkin, fradkinj@mail.nih.gov.

Received 11 March 2016 and accepted 24 March 2016.

characterization of biological samples (e.g., DNA, RNA, proteins, and metabolites). The information will be accessed by qualified researchers to tease out how genetics, environment, lifestyle, and other factors contribute to health and disease. Privacy and security safeguards will be of paramount importance. In return for their participation, the volunteers will have access to their own study results and aggregated study results, and they will also be given tools to help them understand the results to inform their own health decisions. In this model, the participants will be active partners in the development, implementation, and governance of the research. The PMI Cohort Program will be enrolling new volunteers of diverse social, racial/ethnic, and ancestral populations living in a variety of geographies, social environments, and economic circumstances, and from all age-groups and health statuses.

In March 2015, the NIH Director created a PMI Working Group of the Advisory Committee to the NIH Director and charged them with developing a plan to create and maintain a PMI cohort. In September 2015, the Working Group released a report that included several recommendations on cohort assembly, participant engagement, data, biological specimens, policy, and governance (3); the report and recommendations were informed by extensive input from stakeholders external to the NIH. The NIH Director accepted the Working Group's recommendations, and the agency is now building the infrastructure to begin enrollment this year. In February 2016, the NIH announced that it made an award to support a Direct Volunteers Pilot Studies Program to explore optimal ways to engage, enroll, and retain participants in the PMI Cohort Program. The NIH's goal is to enroll 79,000 people by the end of 2016 and at least 1 million people by the end of 2019. Additionally, the NIH expects to make a number of 5-year awards in the summer of 2016 that stem from recent PMI Funding Opportunity Announcements. For example, in June 2016, the NIH anticipates making an award to create a biobank to store and manage biological specimens provided by Cohort participants (4), and an award to establish a coordinating center to provide centralized support and infrastructure for the PMI Cohort Program (5). In July 2016, the NIH plans to make up to seven awards to establish a set of health care provider organizations as partners in the creation of the PMI Cohort Program (6), and one award to create a participant technologies center to harness the latest opportunities in mobile phone and sensor technologies to assess health outcomes and various influences on health with greater precision than in previous cohort studies (7). These activities are summarized in Table 1.

Eliminating disparities in health and health care has been a long-standing public health goal. The NIH is collaborating with the Health Resources and Services Administration (HRSA) to begin partnerships with Federally Qualified Health Centers to identify approaches for bringing underserved individuals, families, and communities into the Cohort Program, particularly those historically underrepresented in biomedical research. The PMI Cohort Program will help to address questions about how differences in genetics, environment, lifestyle, or interactions among those factors contribute to health disparities. Since racial and ethnic minorities and economically disadvantaged populations bear a disproportionate burden of the diabetes epidemic, information on health disparities emerging from the PMI will be particularly relevant to diabetes.

The PMI Cohort Program is early in development. The NIH has valued the input it has already received from participant, scientific, and other stakeholder groups in the early planning stages, such as through Requests for Information and a series of public workshops. The NIH will continue to engage these communities as partners as it develops plans for the Cohort Program.

BUILDING ON ONGOING DIABETES RESEARCH

The PMI has the potential to provide novel insights about diabetes on an unprecedented scale. It may benefit from substantial efforts already underway to develop information on genetic and environmental factors important for pathogenesis of diabetes that may be incorporated into personalized approaches to prevention and treatment.

The great majority of type 1 diabetes heritability has been identified, with HLA class II alleles accounting for up to 50% of genetic risk for the disease (8). The association of type 1 diabetes with HLA-DR and HLA-DQ genes made possible an ongoing National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)–supported study of unprecedented scale designed to identify environmental factors contributing to development of autoimmunity and type 1 diabetes in genetically susceptible neonates. Beginning in 2004, The Environmental Determinants of Diabetes in the Young (TEDDY) study screened 421,000 newborns and enrolled 8,667 at high genetic risk (9). To date, longitudinal follow-up has yielded >663 children

Table 1—NIH PMI Cohort Program Implementation

Major activity	Time frame
PMI announced by President Barack Obama	January 2015
PMI Working Group of the Advisory Committee to the NIH Director established to develop a plan to create and maintain a PMI cohort	March 2015
Report issued by PMI Working Group with recommendations on creating and maintaining a cohort	September 2015
Direct Volunteers Pilot Studies Program award to explore ways to engage, enroll, and retain participants into the cohort	February 2016
PMI Cohort Program Biobank award for storing and managing biological specimens	June 2016*
PMI Cohort Program Coordinating Center award to provide centralized support and infrastructure	June 2016*
PMI Cohort Program Healthcare Provider Organization Enrollment Centers awards	July 2016*
PMI Cohort Program Participant Technologies Center award to harness mobile phone and sensor technologies	July 2016*
NIH-HRSA collaborations to establish partnerships with Federally Qualified Health Centers to bring underserved people into the cohort	Ongoing

*Expected award date.

with islet autoimmunity and 226 with type 1 diabetes. The study is currently following over 6,000 children until they are 15 years old and has collected over 2.7 million specimens (e.g., blood, stool, urine, and nasal swab) from TEDDY subjects. Nested case-control studies are analyzing these samples for the microbiome and virome, gene expression, proteomics, metabolomics, and dietary biomarkers. Whole genome sequencing of the case and control subjects will soon be under way, and genotyping using the Immunochip has already been performed on the entire cohort.

Of note, the TEDDY cohort includes participants from four nations, with multiple discrete HLA genotypes and various phenotypes (e.g., patterns of appearance of islet autoantibodies). Data that emerge from –omics analyses are being stratified by genotype, phenotype, and nationality, which may enable us to identify environmental triggers associated with specific subgroups. It is possible that TEDDY will uncover triggers that interact with certain genotypes or are specific to a particular pattern of disease progression or geographic location. TEDDY is also assessing celiac disease because of shared HLA risk variants between type 1 diabetes and celiac disease. Swedish children in TEDDY had nearly double the risk of celiac disease autoimmunity compared with American children with the same genetic risk variants (10), suggesting that the extra risk may come from a geographically specific environmental factor. Rigorous and creative approaches are needed to define subgroups that may be at risk for specific modifiable environmental triggers of autoimmunity and type 1 diabetes so that we can develop precision prevention approaches.

Although many genes associated with type 2 diabetes have been identified, no single gene region accounts for such a large percentage of the familiar clustering for type 2 as HLA does for type 1, and the known risk or protective loci in aggregate explain much less of the type 2 diabetes heritability. Moreover, the mechanisms linking most known diabetes loci to the disease remain to be elucidated. To address this deficit, the Accelerating Medicines Partnership, a joint effort of the NIH and the pharmaceutical and the nonprofit communities, has developed a portal providing access to comprehensive results from 28 large human genetic association studies of type 2 diabetes and more to be added with the goal of identifying disease targets and expediting therapeutic development (www.type2diabetesgenetics.org/).

Another important resource for precision diabetes medicine research is the National Heart, Lung, and Blood Institute (NHLBI)–supported cohorts that were established to study cardiovascular disease (e.g., Framingham Heart Study and Insulin Resistance Atherosclerosis Study [IRAS]). The cohorts provide the opportunity to study biomarkers associated with incident diabetes. For example, a recent study in IRAS participants provided new insights into heterogeneity of type 2 diabetes by showing that branched-chain amino acids, which were identified from metabolomics studies as possible biomarkers for type 2 diabetes, were associated with incident type 2 diabetes, with the associations generally stronger in Caucasians and Hispanics (11). NHLBI is now investing in genotyping participants in their large cohorts through the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) initiative (www.chargeconsortium.com/main). They are also supporting the Trans-Omics for Precision Medicine (TOPMed) program (www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed) that is coupling whole genome sequencing and other –omics data with molecular, behavioral, imaging, environmental, and clinical data from their studies. These efforts can further open up new opportunities for precision medicine for type 2 diabetes.

The ADA recommends a patient-centered approach to pharmacologic therapy of type 2 diabetes but acknowledges the paucity of current knowledge regarding the choice of agent to be added when metformin alone is insufficient (1). Considerations for choice of pharmacological agents include efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia, and patient preferences. Pharmaceutical agent choice will also be informed by future results from the NIDDK-supported Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) study. GRADE is comparing the long-term benefits and risks of four widely used diabetes drugs (sulfonylureas, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 receptor agonists, and insulin) in combination with metformin for treating recently diagnosed ($<$5 years) type 2 diabetes in about 5,000 people. The study is also assessing the differences in study outcomes within subgroups defined by baseline characteristics, including race/ethnicity, sex, age, diabetes duration, weight, BMI, HbA_{1c}, and measures of insulin sensitivity, insulin secretion, and the glucose disposal index (12). While GRADE's primary outcome is based on average responses, the focus on demographic, clinical, and metabolic factors that are associated with response to and failure of the different treatments will promote understanding of how to individualize therapy. Pharmacogenetic studies have yielded important information on how variants affecting metformin transporters (13) and PPAR-γ binding sites (14) modulate drug responses, and future genetic studies should augment the contributions of GRADE to understanding what makes people more or less responsive to different drugs, both in terms of glycemic lowering and associated side effects.

ADA recommendations for individualization of targets for glycemic control focus on known risks and benefits of intensive therapy, with more or less stringent targets based on duration of diabetes, comorbidities and life expectancy, and risk of hypoglycemia. Information on the relationship between glycemic control and complications is based on the average reduction in complications in response to intensive treatment; yet some individuals develop complications despite tight control, whereas others with poor control are resistant. If we knew which individuals were more or less prone to microvascular complications, this could be factored into risk-benefit assessments. Some ongoing studies such as the NIDDK-supported study of Joslin Medalists (people who have lived with type 1 diabetes for at least 50 years postdiagnosis and are relatively free of complications) may identify factors that protect against complications. However, the size and scope of the PMI Cohort Program holds great potential to shed more light by allowing us to compare larger numbers of people with diabetes who will and will not develop complications. Additionally, the Cohort Program

could identify new biomarkers of diabetes complications, which could also pave the way toward precision medicine, so that people showing early signs of disease could be treated more aggressively.

Another potential bonus for diabetes is the planned incorporation of new sensor technology to monitor the health of the PMI cohort. The NIDDK has made a substantial long-term investment in glucose-sensing technology that has now come to fruition with the advent of accurate continuous glucose monitors. Software is now being developed to incorporate glucose monitoring data into EHRs. Having such extensive data over long time frames linked to EHRs can be especially valuable in chronic diseases like diabetes, in which complications develop over decades. For example, if incorporated into the PMI, such information may help remedy the limited data currently available on whether variability in glucose levels, versus average glucose levels (HbA_{1c}), contributes to the development of diabetes complications.

PAVING THE WAY TOWARD PRECISION MEDICINE FOR DIABETES

To achieve the goal of personalizing treatment for patients, it is imperative to better define the many subgroups that represent the spectrum of type 1 and type 2 diabetes. The current classification of the disease into two major forms of type 1 and type 2 is a gross oversimplification. It is increasingly being recognized that both type 1 and type 2 diabetes are heterogeneous syndromes (15). Even people who present with a classic form of the disease could have hallmarks of the other form. For example, some youth with type 2 diabetes have autoantibodies typically associated with type 1 diabetes (16) and some patients with type 1 diabetes have insulin resistance associated with obesity (17).

Currently, type 2 diabetes subgroups are often defined based on traditional measures such as waist circumference, insulin secretion, or insulin resistance. Approaches based on data mining and/or –omics technologies have the potential to identify subgroups without bias and to generate new hypotheses regarding pathogenesis. Such approaches are already being used to study heterogeneity in type 2 diabetes. A recent study used a precision medicine approach to characterize populations of patients with type 2 diabetes based on EHRs and genotype data in over 11,000 people in a racially and socioeconomically diverse cohort. The study identified three distinct subtypes characterized by distinct comorbidities and genotypes (18) and demonstrates the potential that the much larger PMI Cohort Program holds to provide critical data in this area.

As information emerges from the PMI, identifying specific subgroups within the larger population with or at risk for diabetes who may be prone to specific comorbidities or benefit from specific therapies, simpler and more cost-effective methods will be needed to test precision medicine approaches. One way to address this is to invite specific PMI subgroups to participate in more detailed studies or clinical trials. Other insights could be gained through the NIH Health Care Systems Research Collaboratory (https://www.nihcollaboratory.org), which was established to improve the way clinical trials are conducted. The Collaboratory is engaging health care delivery systems in research partnerships to provide a new infrastructure for collaborative research and supports the design and rapid execution of pragmatic clinical trial Demonstration Projects.

Diabetes research is increasingly utilizing high-dimensional and high-throughput technologies that generate enormous amounts of data and require an interdisciplinary workforce. To encourage application of bioinformatics science to the study of diabetes and obesity, the NIDDK is supporting a training program for predoctoral and postdoctoral level researchers with backgrounds in bioinformatics, mathematics, or computational sciences and mentorship in both mathematics and computer science and diabetes or obesity (19). This effort will help prepare the next generation of scientists who will be instrumental in analyzing the complex datasets that emerge from the PMI Cohort Program and applying it to metabolic diseases. The NIDDK is also encouraging high-impact, interdisciplinary science projects (20) to lay the foundation for new fields of investigation and to accelerate critical breakthroughs, and early and applied research on novel tools, technologies, and services that foster new approaches to interrogate information arising from the PMI and to improve the synergy and interactions among multi- and interdisciplinary research teams.

CONCLUSIONS

The PMI Cohort Program can transform our knowledge of diabetes toward the goals of precision medicine for people with and at risk for the disease. Now is the time to leverage ongoing and future diabetes research to take advantage of knowledge stemming from the PMI to advance diabetes research and make precision medicine a reality for diabetes care and prevention. The NIDDK is taking a proactive approach with initiatives building on new technologies and established cohorts together with a focus on creating an appropriately trained scientific workforce and supporting high-impact, interdisciplinary projects. These efforts are ushering in a new era of biomedical research that holds tremendous potential for identifying more precise and personalized ways to prevent and treat diabetes.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. J.E.F. and M.C.H. wrote the manuscript. G.P.R. reviewed and edited the manuscript. J.E.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Prior Presentation. Parts of this article were presented at the 76th Scientific Sessions of the American Diabetes Association, New Orleans, LA, 10–14 June 2016.

References

1. American Diabetes Association. Standards of Medical Care in Diabetes—2016. Diabetes Care 2016;39(Suppl.):S1–S112
2. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med 2015;372:793–795
3. Precision Medicine Initiative Working Group to the Advisory Committee to the Director, NIH. The Precision Medicine Cohort Program—Building a Research Foundation for 21st Century Medicine, 2015. Available from https://www.nih.gov/sites/default/files/research-training/initiatives/pmi/pmi-working-group-report-20150917-2.pdf. Accessed 11 March 2016
4. RFA-PM-16-004: Precision Medicine Initiative Cohort Program Biobank (U24). Available from http://grants.nih.gov/grants/guide/rfa-files/RFA-PM-16-004.html. Accessed 11 March 2016
5. RFA-PM-16-001: Precision Medicine Initiative Cohort Program Coordinating Center (U2C). Available from http://grants.nih.gov/grants/guide/rfa-files/RFA-PM-16-001.html. Accessed 11 March 2016
6. RFA-PM-16-002: Precision Medicine Initiative Cohort Program Healthcare Provider Organization Enrollment Centers (UG3/UH3). Available from

http://grants.nih.gov/grants/guide/rfa-files/RFA-PM-16-002.html. Accessed 11 March 2016
7. RFA-PM-16-003: Precision Medicine Initiative Cohort Program Participant Technologies Center (U24). Available from http://grants.nih.gov/grants/guide/rfa-files/RFA-PM-16-003.html. Accessed 11 March 2016
8. Prasad RB, Groop L. Genetics of type 2 diabetes-pitfalls and possibilities. Genes (Basel) 2015;6:87–123
9. Hagopian WA, Erlich H, Lernmark A, et al.; TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY): genetic criteria and international diabetes risk screening of 421 000 infants. Pediatr Diabetes 2011;12:733–743
10. Liu E, Lee HS, Aronsson CA, et al.; TEDDY Study Group. Risk of pediatric celiac disease according to HLA haplotype and country. N Engl J Med 2014;371:42–49
11. Lee CC, Watkins SM, Lorenzo C, et al. Branched-chain amino acids and insulin metabolism: the Insulin Resistance Atherosclerosis Study (IRAS). Diabetes Care. 19 February 2016 [Epub ahead of print]
12. Nathan DM, Buse JB, Kahn SE, et al.; GRADE Study Research Group. Rationale and design of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes Care 2013;36:2254–2261
13. Jablonski KA, McAteer JB, de Bakker PI, et al.; Diabetes Prevention Program Research Group. Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the Diabetes Prevention Program. Diabetes 2010;59:2672–2681
14. Soccio RE, Chen ER, Rajapurkar SR, et al. Genetic variation determines PPARγ function and anti-diabetic drug response in vivo. Cell 2015;162:33–44
15. Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. Lancet 2014;383:1084–1094
16. Klingensmith GJ, Pyle L, Arslanian S, et al.; TODAY Study Group. The presence of GAD and IA-2 antibodies in youth with a type 2 diabetes phenotype: results from the TODAY study. Diabetes Care 2010;33:1970–1975
17. Polsky S, Ellis SL. Obesity, insulin resistance, and type 1 diabetes mellitus. Curr Opin Endocrinol Diabetes Obes 2015;22:277–282
18. Li L, Cheng WY, Glicksberg BS, et al. Identification of type 2 diabetes subgroups through topological analysis of patient similarity. Sci Transl Med 2015;7:311ra174
19. PAR-15-182: Interdisciplinary Training in Bioinformatics and Diabetes, Obesity and Metabolic Disease (T32). Available from http://grants.nih.gov/grants/guide/pa-files/PAR-15-182.html. Accessed 11 March 2016
20. PAR-16-103: Institutional Research and Academic Career Development Awards (IRACDA) (K12). Available from http://grants.nih.gov/grants/guide/pa-files/PAR-16-103.html. Accessed 11 March 2016