Precision Medicine, Genomics, and Public Health

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> Despite the advances in molecular genetics and. . . as genetic tests are proliferating in the U.S. population, their appropriate usage in the public health setting needs careful scrutiny.
> —Muin J. Khoury

The issues that Muin J. Khoury (1) identified as relevant in the intersection of genomics and public health—rapid advances in the molecular technologies available for interrogating the genome, the proliferation of genetic and genomic testing in the clinical setting, uncertainties surrounding the use and value of such tests—are far from surprising. These issues form the basis of much discussion in today's scientific, professional, and popular literature. What is perhaps surprising about the statement, however, is that it was made nearly 20 years ago. As advances in molecular genetics have marched steadily forward and genetic epidemiologists have attempted to generate useful public health knowledge, paradigms have meanwhile shifted and developing disciplines (e.g., epigenetics, metabolomics) now contribute substantively to the conversation. The challenges faced by public health practitioners in this context have stemmed from the shifting landscape upon which the discipline is built. President Barack Obama's Precision Medicine Initiative (PMI), unveiled during his 2015 State of the Union Address, represents a concerted effort to lay the scientific foundation for the careful scrutiny Khoury called for.

How does this PMI impact the prevention and treatment of diabetes? As public health practitioners, we must face the current reality of the high and increasing global prevalence of diabetes. Between 1980 and 2008, the global age-standardized diabetes prevalence increased from 8.3 to 9.8% in men and from 7.5 to 9.2% in women (2). Precision medicine (PM) may offer new strategies to prevent and reduce diabetes in populations. PM seeks to integrate a bounty of data from each person's genome—combined with data from his or her environment and lifestyle (i.e., behaviors)—to tailor medical treatment to the individual rather than what has been characterized as "treating to the average." We contend that PM will add to—not replace—traditional public health strategies. Prior lessons from genomic research has taught us that for common diseases like diabetes, environmental factors have the greatest impact on prevalence. While the human genome evolved over thousands of years, two key determinants of diabetes prevalence, diet and physical activity, have evolved very dramatically over a very short "genomic" period of time. It is this intersection between lifestyle factors and the genome that will be critical to halt the rise in the epidemic of diabetes. As public health experts, we must do everything possible to understand and ameliorate the environmental effects on diabetes. The PMI offers the opportunity to explore both existing and new public health strategies that address both environmental and genomic risk factors. The PMI proposes to recruit 1 million individuals; this will identify many subjects with prediabetes and diabetes who could be connected with known lifestyle interventions to prevent diabetes incidence or improve adherence to lifestyle or medical management. With its approach of engaging participants with their own data collection for lifestyle factors, proven clinical and population-based interventions could then be tested in high-risk individuals in relation to their genomic profiles to ascertain important gene–diet and gene–physical activity interactions.

At first glance, PM, with its resolute focus on the individual patient and its apparent inevitable eminence, might alarm some public health professionals.

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Such concerns are largely unwarranted: the PM paradigm is no more at odds with public health than traditional patient care. That said, the integration of genomics (and other biomolecular technologies collectively known as "omics"), mobile technology, electronic medical records, data analytics and warehousing, and all the other elements of PM will surely impact the work of public health professionals. Below we explore the conceptual and practical impact of PM on public health. Finally, we discuss these implications in the context of diabetes prevention and care.

PRECISION PUBLIC HEALTH IN THEORY

If PM is defined as optimizing care for well-characterized individual patients, then precision public health is characterized by discovering, validating, and optimizing care strategies for well-characterized population strata. How does precision public health differ from traditional public health? The difference is illustrated in Fig. 1. This figure applies to precision public health in the domains of both validating new clinical interventions and monitoring the efficacy of existing health maintenance and disease prevention programs. The center panel describes how public health and clinical scientists search for and verify interventions that, on the whole, produce better population-level health (e.g., more people with low fasting glucose) than is achieved through nonintervention or some other control condition. The left panel visualizes traditional public health efforts that have used that knowledge to increase the number of people in the population benefiting from the intervention (illustrated here by a single drug and diet) and decrease the number who could be but are not benefiting. Visually, this effort is represented as reshaping the distributions of the treated and nontreated/control groups. But note the idealized, typical distribution of treated individuals: there is a wide range and variable response when the intervention is applied to the entire population. In contrast, the right panel represents the futuristic approach of public health interventions informed by PM. While we retain the goal of traditional public health, we add to that the goal of reshaping the distribution in another dimension: by precisely targeting population strata that most benefit from the intervention (illustrated here by the use of omics, including pharmacogenomics) and withholding the intervention from those strata that would not benefit, we minimize the spread in the tails of the distribution. In short, precision public health seeks to get the right treatment or intervention to the right population with the aid of detailed genomic, environmental, lifestyle, and other data.

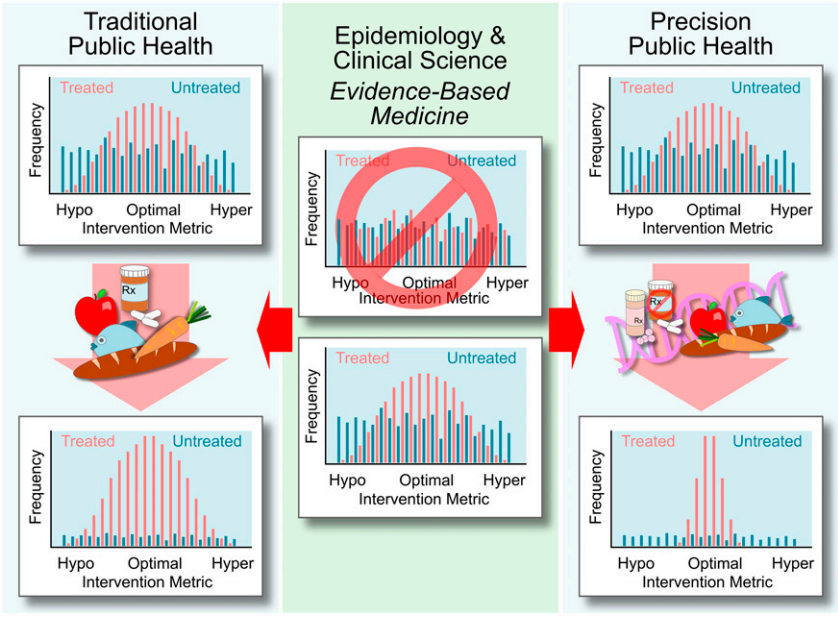

Figure 1—Differences between traditional public health and precision public health. Hypo and Hyper signify extremes of response to the intervention.

PRECISION PUBLIC HEALTH IN PRACTICE

Models such as that illustrated in Fig. 1 are useful for conceptual orientation, but how will public and population health practitioners contribute in the era of PM? Below we discuss three domains of public health practice that have played and will continue to play a role in the development of PM.

Discover and Validate New Markers of Health and Disease

Discovery-based research by epidemiologists has identified associations and generated testable hypotheses concerning genomic, environmental, and lifestyle factors influencing health and disease. For example, to date, 87 type 2 diabetes genome-wide association studies (which can assay millions of genetic variants in an individual DNA sample) have reported 640 disease phenotype–genetic variant associations (3). Such discovery efforts must increase in the era of PM. The million-person cohort proposed by the PMI alone will offer unprecedented opportunities for discovery. The practical impact of these discoveries will be the increased stratification of populations and the shrinking of subgroups available for subsequent hypothesis testing and validation. In some cases, this may pose significant challenges in terms of achieving sufficient statistical power and avoiding selection bias. For example, assuming a rough 10% prevalence of type 2 diabetes in the million-person cohort, a rare variant's minor allele (1%) can be expected in only 1,000 affected individuals in the entire sample. If a type 2 diabetes disease subtype stratum were the object of study, this number would be considerably lower. Although daunting, these are familiar challenges to population health researchers and professionals, and successful incorporation of PM into clinical practice will be feasible only with the assistance of public health experts who will help to validate the clinical validity and utility of newly identified PM markers.

Monitor Population Health

The emerging tools of PM will also be brought to bear on public health surveillance efforts. Changes will be seen in two dimensions of surveillance: the metrics being tracked and the methods used to gather data. Genomic data—both sequence genetics and epigenetic profiling—is

anticipated to add much to our understanding of disease risk; with decreasing costs, collection of population-level genomic data becomes increasingly possible. Already large cohort genetic and epigenetic studies have contributed to public health recommendations and strategies intended to reduce the burden of diabetes (4). Wider genomic surveillance may prove even more impactful. A major component of the PMI is the collection and interpretation of environmental and lifestyle data. These measures may offer new surveillance metrics or improve upon more traditional self-report data. Mobile (e.g., internet- and cellular phone–based) technologies may make possible the collection of vast amounts of environmental and lifestyle data. Already these technologies have been incorporated into diabetes self-monitoring (diet, activity, glucose) programs (5,6), although their patient acceptability has not been established (5). Whether the use of mobile technologies will be acceptable to participants in surveillance programs also remains an open question, but the ability to accurately detect population-level changes in health behaviors and environmental exposures remains an enticing possibility. Electronic health records (EHR) represent another possible source of population-level data. Despite the daunting technological hurdles and unresolved ethical issues, largely related to patient privacy, posed by PM's potential surveillance measures, the U.S. Centers for Disease Control and Prevention (CDC) 2014 surveillance strategy proposes to "accelerate the utilization of emerging tools and approaches" (7). To this end, the CDC appointed two senior-level officers to develop effective health information technology policies; the agency is also working with outside developers to create advanced surveillance technologies and tools (7).

Prevent Disease and Maintain Health

PM's principle of targeted intervention applies equally well to programs designed to maintain health and prevent disease. These objectives fall soundly into the public health professional's purview. Precision health maintenance and disease prevention will find ways to use the emerging technologies and tools of PM to efficiently target strategies to those population strata that will reap the greatest benefit. These programs may take a number of forms. For example, there is much hope that widespread genomic profiling will enable the identification of individuals at elevated risk for disease. The CDC Office of Public Health Genomics currently provides a Genomic Applications Toolkit for public health departments that includes a list of genomic tests that have potential public health utility (8). These "genomic applications" are scrutinized by panels of experts and rated according to the application's level of analytical and clinical validity, clinical utility, potential benefits versus harms, and whether the application has an evidence-based recommendation (8). Three "tier 1" (i.e., highest level of validity, utility, and evidence) genomic applications have been deemed ready for pilot or demonstration population-level programs (9), although none apply yet to diabetes. For example, ~2–7% of breast cancers and ~10–15% of ovarian cancers are linked to mutations in *BRCA1* and *BRCA2* (10) (resulting in ~10,000 and ~2,700 cases of breast and ovarian cancer, respectively, per year, according to a 2012 estimate [11]). Women with clinically important *BRCA1* and *BRCA2* mutations have a 35–84% chance of developing breast cancer and a 10–50% chance of developing ovarian cancer by age 70 years (12). The U.S. Preventive Services Task Force currently recommends *BRCA1* and *BRCA2* genetic counseling for women with a family history of breast or ovarian cancer (12). Public health interventions (education, increased screening) targeting those with elevated *BRCA1* and/or *BRCA2* risk may provide measurable population-level benefit (9).

It is feasible that PMI environmental and lifestyle data collected via mobile technologies could be incorporated into health maintenance and disease prevention programs. For example, mobile technologies could be used to collect diet and activity data to identify at-risk individuals and to mediate an intervention program. Small-scale intervention trials have been promising (13).

PRECISION PUBLIC HEALTH IN DIABETES PREVENTION AND CARE

Currently, our genomic understanding of type 1 diabetes outpaces that of many other diseases: up to 50% of genetic risk for type 1 diabetes can be attributed to *HLA-DQA1*, *HLA-DQB1*, and *HLA-DRB1* alleles (14). Alleles in *PTPN22*, *UBASH3A*, *PTPN2*, *INS*, and other genes have been found to be associated with type 1 diabetes risk (15). Already these findings are being incorporated into population-level research. Since 2004, The Environmental Determinants of Diabetes in the Young (TEDDY) study has used newborn *HLA* screening to identify children with high genetic risk of type 1 diabetes. TEDDY investigators are following over 6,000 children until age 15 years. Follow-up has discovered 225 children with type 1 diabetes. Within the TEDDY cohort, nested case-control studies are analyzing gene expression, microbiomes, viromes, metabolomics, and dietary biomarkers. The TEDDY study has already published important findings regarding islet autoimmunity, celiac disease, and disease risk and progression. In addition to this critical discovery research, the TEDDY study is providing important insights into the potential of population-level screening (16).

Although many genetic variants are associated with type 2 diabetes risk, the amount of disease risk accounted for by these variants is low (~10%), and the mechanisms and pathways by which these genes exert their influence is yet unclear (17). Some have reported considerable heterogeneity in variants associated with type 2 diabetes among different ethnic groups. This may significantly complicate translating discoveries in this disease domain into meaningful public health efforts (18). Type 2 diabetes is itself a heterogeneous disease, and while the designation has proven clinically useful, type 2 diabetes is likely a "broad umbrella" used to refer to a constellation of physiological diseases (19). This fact may, however, prove instrumental to precision public health. Studies of type 2 diabetes susceptibility variants have pointed to mechanistic heterogeneity (20). A recent study used EHR data-mining techniques in combination with genetic data from over 11,000 patients to identify three distinct type 2 diabetes subtypes characterized by distinct comorbidities (21). This opens the possibility that genomic information could be used to characterize type 2 diabetes subtypes. Ultimately, understanding the pathology of these subtypes may lead to subtype-specific interventions that could be used to target genetically identified treatment strata.

To date, there are no "tier 1" genomic applications recommended for either

type 1 diabetes or type 2 diabetes, although there are several lower-tier applications for variants with evidence of validity but insufficient evidence of utility to recommend use (8). A review of evidence by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found that genetic profiling (using 28 predictive variants) used to assess risk for type 2 diabetes in the general population provided virtually no net benefit alone or in combination with traditional risk factors (22). As discovery research continues in this area (23), we expect more novel omics discoveries in the diabetes domain.

Finally, EHR have been used in nascent diabetes precision public health studies. One study of EHR in three U.S. counties identified small geographic areas within the counties with the least effective control of diabetes. Wider EHR surveillance may pinpoint areas for neighborhood-level interventions (24).

CONCLUSIONS

We have alluded to some of the scientific challenges faced by those seeking to make the idea of precision public health a reality. There are other challenges: translating omics into practice and ensuring that these novel interventions do not serve only the highest socioeconomic stratum and lead to a new form of health care disparities. While the PMI evidence base is growing, we must challenge ourselves to identify and translate into action what we already know about the determinants and interventions to halt the dramatic rise of diabetes around the world.

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