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# A Public Health Perspective on a National Precision Medicine Cohort:

## Balancing Long-term Knowledge Generation With Early Health Benefit

**Muin J. Khoury, MD, PhD** and

Office of Public Health Genomics, Centers for Disease Control and Prevention, Atlanta, Georgia

**James P. Evans, MD, PhD**

Department of Genetics, University of North Carolina, Chapel Hill; and Department of Medicine, University of North Carolina, Chapel Hill

The new US precision medicine initiative[1] has been made possible by improvement and price reduction in genome sequencing, as well as advances in multiple sectors of biotechnology. The initiative includes 2 components: a focus on cancer intended to spur development of new targeted cancer treatments, and a proposal for establishing a national cohort of at least 1 million people to explore genetic and environmental determinants of health and disease. The success of this initiative requires a public health perspective to help ensure generalizability, assess methods of implementation, focus on prevention, and provide an appropriate balance between generation of long-term knowledge and short-term health gains.

Although precision medicine focuses on individualized care, it is impossible to infer causality by working from individual observations. Data from large numbers of people are required to identify characteristics, including genetic markers predictive of treatment response. Moreover, from a public health perspective, collecting information from large numbers of people is far more informative when these people reflect the diversity of the underlying population. Using convenience samples—ie, collected without regard to important factors such as race and ethnicity, age, and sex—can lead to substantial biases and nongeneralizable predictions. This is especially true in genomics because different ancestry may result in differing genomic architecture of health and disease states.

> The concept of precision prevention may therefore be valuable for efficiently targeting preventive strategies to the specific subsets of a population that will derive maximal benefit.

Precision medicine currently focuses largely on treatment, but decades of successful public health interventions suggest prevention warrants a robust focus. Although treatment can

**Corresponding Author:** Muin J. Khoury, MD, PhD, Office of Public Health Genomics, Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA 30333, (muk1@cdc.gov).

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reduce morbidity and improve quality of life for sick individuals, disease prevention is important for the entire population. Risks for various diseases vary among people based on genetic and environmental factors. The concept of precision prevention may therefore be valuable for efficiently targeting preventive strategies to the specific subsets of a population that will derive maximal benefit. For example, improving access to smoking cessation assistance is a component of the highly successful public health efforts that have resulted in reductions in smoking over the past few decades. Recent data suggest that using genetically informed biomarkers of the speed with which people metabolize nicotine[2] could lead to personalized smoking cessation. Another example of precision prevention is changes in recommended screening schedules for people at increased risk of cancer, identified either by acquisition of family health history or through detection of those individuals who carry pathogenic mutations in high-risk cancer genes.

The proposed long-term investment in precision medicine comes at a time of increasing fiscal restraint and widespread recognition that the US health care system underperforms in terms of health outcomes. Therefore, in addition to long-term knowledge acquisition, it is imperative that this investment also generates early measurable health benefits such as those that could be derived from the million-person cohort. At a recent National Institutes of Health workshop about the proposed national cohort,[3] early success was described using a hypothetical 50-year-old woman with type 2 diabetes and suboptimal glucose control. The patient had her genome sequenced and she had a tiny chip implanted to track her glucose level. Using these data, she changed her diet and her medicine dose schedule. Based on novel findings from the cohort, her physician switched her to a new molecularly targeted drug.

However, to realize improved diabetes control based on precision approaches, researchers will not only have to make new discoveries but would also need to conduct follow-up studies including randomized trials. A more realistic scenario for near-term health benefit derived from this large cohort is to assess implementation of already proven interventions, especially if the cohort adequately represents various populations including minority racial and ethnic groups and underserved populations. Using the example of the woman with type 2 diabetes, finding and enrolling people with prediabetes into diabetes prevention programs could help prevent the onset of overt disease. Potentially, millions of people in the United States could benefit from such interventions but do not know they have prediabetes. The cohort could assess how to identify thousands of persons with prediabetes (through standard non genomic tests) and connect them with available interventions.

A unique feature of the proposed cohort is whole-genome sequencing of the participants.[4, 5] Although this will inevitably lead to numerous discoveries and possible interventions, it will take time to yield dividends. In the meantime, there is a real opportunity for near-term benefit by focusing on conditions for which evidence-based applications are already available. The Centers for Disease Control and Prevention has created a 3-tier classification schema of genomic applications based on the methods of evidence-based medicine.[5] Similarly, a “binning” strategy for the human genome was proposed based on clinical validity and utility of genes and genomic variants.[6] Tier 1 (bin 1) genes and their variants are those with sufficient evidence for clinical validity and clinical utility to provide

meaningful and actionable information to consumers and health care practitioners. Tier 2 (bin 2) genes and their variants are those with established evidence of validity but insufficient evidence of utility to support a recommendation for medical action. Tier 3 (bin 3) genes and their variants are those with either sufficient evidence for a lack of utility or presence of clear risk of harm, or those with insufficient evidence for both validity and utility.

Adoption of tier 1 applications in the proposed million-person cohort could provide a path toward obtaining immediate benefits for thousands of participants and their families. Examples of tier 1 conditions for which preventive interventions are already available among persons with a predisposing mutation include hereditary breast and ovarian cancer syndrome (*BRCA* mutations), Lynch syndrome (associated with increased risk of colorectal cancer), and familial hypercholesterolemia. An estimated 2 million people in the United States have one of these conditions and most are not aware of their risk for cancer or heart disease. Once these individuals are identified, evidence-based interventions are available that can reduce their risk of adverse health outcomes. The challenges include how to best obtain consent, educate, identify, and deliver results to such individuals in the population because the implementation of any public health measure also carries risks and costs, as well as potential benefits. For example, although most would agree that identifying individuals at high risk of a preventable condition is desirable, important questions, such as the true penetrance of these conditions when ascertained via a population-based approach, remain to be answered.

This cohort of a million or more people would be expected to include many thousands of undiagnosed, unrecognized patients with a high risk for breast/ovarian cancer, colorectal cancer, or coronary heart disease, identified through genomic sequencing. If identified and properly educated, these individuals and their relatives could leverage established interventions to reduce their risk—an immediate potential benefit from this endeavor. Just as important, the cohort could inform many critical questions that need to be answered before implementing genomics at the population level. Other potential targets may include a carefully selected subset of highly actionable genes that the American College of Medical Genetics and Genomics[7] has recommended be analyzed when individuals undergo genome-scale sequencing for other reasons.

Important ingredients for optimal success of a large-scale cohort include engaging and educating the public, policy makers, and patients about precision medicine; ensuring access to validated discoveries; and measuring and addressing disparities. Other key components include linking health care and public health systems (eg, using state-based cancer registries to identify cases of cancers with specific genetic mutations) and developing population-level metrics for monitoring (eg, National Precision Medicine Objectives, similar to the US Healthy People 2020 objectives used to track progress in health care and prevention for decades).[8]

In summary, a large, diverse and inclusive, precision medicine cohort could eventually allow the United States to reap long-term benefits from a better understanding of human disease. Additionally, in the short term, there exists an immediate opportunity to deploy genomic

information for prevention and health care services, conduct applied research in communication and behavioral sciences, and pursue rigorous outcome research that could potentially benefit patients, families, and communities. A continued dialogue among initiative stakeholders will be necessary to balance such near-term potentials with the long-term goal of knowledge generation.

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