ANNUAL REVIEWS

Annual Review of Public Health

Precision Medicine from a Public Health Perspective

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Annu. Rev. Public Health 2018. 39:153–68

First published as a Review in Advance on November 20, 2017

The *Annual Review of Public Health* is online at publhealth.annualreviews.org

https://doi.org/10.1146/annurev-publhealth-040617-014158

Keywords

personalized medicine, precision medicine, precision medicine initiative, moonshot program, health disparities

Abstract

Over the past decade, precision medicine (PM) approaches have received significant investment to create new therapies, learn more about disease processes, and potentially prevent diseases before they arise. However, in many ways, PM investments may come at the expense of existing public health measures that could have a greater impact on population health. As we tackle burgeoning public health concerns, such as obesity, and chronic diseases, such as cancer, it is not clear whether PM is aligned with public health or in conflict with its goals. We summarize the areas of promise demonstrated by PM, discuss the limitations of each of these areas from a population health perspective, and discuss how we can approach PM in a manner that is congruent with the core aims of public health.

1. INTRODUCTION

Although definitions of precision medicine (PM) vary, it is broadly understood to be the use of diagnostic tools and treatments targeted to the needs of the individual patient on the basis of genetic, biomarker, or psychosocial characteristics. In 2015, in his State of the Union Address, President Barack Obama hailed the virtues of the PM initiative, lauding priorities that included "delivering the right treatments, at the right time, every time to the right person" (95). There have been multibillion dollar investments in projects related to PM over the past decade. These investments inevitably come at the expense of other potential investments, occasioning concern in the public health community (9, 42). In particular, public health commentators have been skeptical of the wisdom of prioritizing individualized approaches that focus on diseased individuals rather than on population-based preventive programs that consider the behavioral, environmental, and social determinants of health (36).

In this review, we summarize the areas of promise demonstrated by PM, discuss the limitations of each of these areas from a population health perspective, highlight the potential shortcomings of the PM approach, and provide a perspective on the potential of PM that could be congruent with the core aims of public health.

2. DEFINITION AND EVOLUTION OF PRECISION MEDICINE

Personalized medicine is an older term that is often used interchangeably with PM. It seeks to utilize treatments or prevention strategies that are tailored to an individual's disease process or symptoms. This perspective emerged as a critique of medical practices characterized as employing reductionist and oversimplified methods of disease categorization (3, 26). Treatment methods adopted a one-size-fits-all framework wherein all individuals presenting with some constellation of symptoms receive a similar treatment. This practice has led to a desire, reasonably enough, for more precise forms of diagnosis and treatment, whereby more individualized care is available to patients with particular presentations. In many ways, the management of communicable diseases has long been consistent with the goals of PM by seeking to identify causative organisms and creating data repositories to direct specific treatment for infections. Over time, infectious disease management has also incorporated technology to gain greater knowledge about resistant organisms and to protect populations (14).

More than a century ago, Sir William Osler described the goals of medicine as being "to wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease—these are our ambitions" (68, p. 281). The accumulation of large quantities of health data may indeed bring us closer to the aspirations of Sir William Osler. DNA-sequencing methods, in particular, have contributed to an enormous increase in data availability that may lead to the prevention and cure of disease. The first human genome sequenced in 2001 cost $95 million. Since that time, costs have fallen with the automation of sequencing technologies, paralleling Moore's laws in electronics. The cost of whole exosome sequencing is now less than $1,000 and has encouraged rapid innovation that looks to harness these outputs to optimize health care delivery for individuals (29).

PM then seeks to incorporate technology into medicine to create a data ecosystem that can better identify, and treat, an individual patient's disease. This approach aims to seamlessly integrate clinical phenotypes and biological information, from imaging to laboratory tests (including -omics data) and health records. The rationale is to develop a "new taxonomy of human disease based on molecular biology" (65, p. 1). The National Research Council Report of 2011 implied that this

process would enhance the awareness of causes of disease and lead to more accurate diagnosis, treatment selection, and development of novel therapies (65).

PM has also had implications for the treatment of noncommunicable disease. Notionally, PM approaches will help inform and improve disease taxonomy, leading to more specificity about the pathogenesis of complex conditions such as heart disease, cancer, and obesity and a paradigm shift in potential therapeutic interventions that maximize treatment of disease with minimal adverse events (21).

To facilitate drug discovery from PM-driven studies, investigators have developed new trial designs—such as basket or umbrella trials—which have been used in numerous precision oncology cancer studies (1, 11, 77). Those in the public health community have been concerned about the generalizability and validity of these outcomes (22). In particular, concern has arisen from PM's central focus on genomic advances, given the relatively small impact of genomic factors on overall health in contrast with behavioral or social factors that are frequently neglected in PM discussions (44).

With this backdrop, we more fully explore the potential role of PM in diagnosis and treatment to better consider the potential impact that PM can have on the health of populations.

3. PRECISION MEDICINE: DIAGNOSTIC METHODS

First we consider the impact of PM-led developments in diagnostic methods among individuals with disease, as well as those considered to be at high risk within the general population.

3.1. Individuals with Disease

Perhaps the clearest utility of PM approaches thus far has emerged from efforts to improve disease diagnosis with the promise of better treatment. PM approaches may improve the diagnosis of disease processes for both infectious and chronic diseases.

In certain communicable diseases, such as influenza, Ebola, and human immunodeficiency virus (HIV), PM approaches may provide a better understanding of the patterns that cause resistant strains of the disease. This knowledge may help guide physicians to effectively treat resistant pathogens. There are two uses of whole-genome sequencing in clinical microbiology. First is the identification of genotypes that can be used to predict phenotypes and direct therapeutic strategies. Second, genetic testing can have utility for the purposes of surveillance and identification of genetic relatedness in outbreaks. For example, in a study of extensively drug-resistant tuberculosis (XDR-TB), investigators from South Africa used targeted and whole-genome sequencing to account for the geographic distribution of XDR-TB strains (82). Tuberculosis strains were divided into those attributed to acquired resistance (because of inadequate treatment, poor treatment adherence, or subtherapeutic drug levels) or those attributed to transmitted resistance. This study showed with high prevalence that transmitted resistance, and not acquired resistance, was predominant in this area. Social network analysis identified person-to-person or hospital-based epidemiologic links for the 30% of study participants who spend substantial amounts of time in community areas such as churches, bars, and restaurants. Therefore, PM in combination with existing epidemiologic methods may enhance the disease mapping and guide health policy decisions.

Greater awareness of disease processes could lead to the identification of causes, thereby improving our capacity to treat disease. This view has been most readily apparent in cancer. For example, in the past, lung cancer was largely divided into its histological subtypes, on the basis of clinical phenotypes, i.e., non–small cell and small cell lung cancer. Patients with non–small cell lung cancer had further histological subdivisions; for example, adenocarcinomas are more

commonly seen among nonsmokers. Molecular testing has permitted further delineation of subtypes to describe abnormalities on the surface of the cancer cell such as epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations (69, 88). EGFR mutation tumors are in turn associated with a clinical phenotype. In one study of never smoking Asian women with adenocarcinoma of the lung, 80% of this group had mutations in EGFR (84). Such distinct entities within the larger phenotypic or histological group have led to the emergence of specific targeted therapies. Compared with standard chemotherapeutic agents, targeted therapies such as erlotinib and gefitinib have been shown to improve progression-free survival in patients with metastatic non–small cell lung cancer with EGFR mutations (53, 96). Molecular profiling has also been useful in other subtypes, such as breast and colorectal cancers, in providing prognostic information and directing treatment strategies (49, 85, 87).

In addition to providing new and more precise classification of disease, genetic sequencing of tumors can provide prognostic information to guide treatment decisions. For example, in the case of myelodysplastic syndromes, allogeneic stem cell transplantation (SCT) offers a cure. However, this strategy comes with a real and human cost. Patients may experience substantial transplant-related morbidity or mortality. In a recent study, patients had blood samples sequenced prior to SCT, and those who harbored mutations in the tumor suppressor gene p53 had poor outcomes irrespective of treatment with SCT (50). In patients with breast cancer, several tools are available for health providers to analyze and sequence individual tumor biology. This has led to the development of several prognostic kits, such as Oncotype DX, Mammostrat, and EndoPredict analyses, which stratify a patient's risk of future cancer recurrence (8, 16).

Studies on the value of gene-expression profiling tests have produced conflicting evidence. Systematic reviews reported limited evidence of the clinical utility of these technologies in predicting the effects of adjuvant chemotherapy for patients with early breast cancer (55). However, the MINDACT study, an international randomized controlled trial by Cardoso et al., compared clinical tumor phenotypes, and genetic information identified a large group of patients with early breast cancer (17). These patients had a theoretical recurrence risk that would not be affected by adjuvant chemotherapy and were randomized to treatment according to clinical and genomic risk. A 70-gene signature Mammaprint was used to assess the risk of recurrence at 5 years. The trial found that use of such genomic technology compared with traditional phenotypic assessment would reduce the need for chemotherapy in 14% of cases (17). Reducing the need for toxic therapy decreased individual patient costs and morbidity related to treatment. Such interventions could reduce the treatment-related burden of disease among individuals with disease in the general population. Though tools such as these may be validated in a large population, individual risks, preferences, and decisions need to be reviewed (35).

Developments in imaging, which is considered a part of the armamentarium of PM, have also improved the diagnosis of disease. Historically, patients who presented with certain symptoms or had suspected cancers underwent extensive surgeries, which may not provide additional benefit. Imaging modalities such as positron emission tomography highlight the metabolic activity of disease and in cases of Hodgkin's disease may guide the management plan and detect recurrence of cancer prior to the emergence of symptoms (41, 46).

Imaging is used in different aspects of population-based screening and the diagnosis of breast, lung, and prostate cancer. The interests of both PM and public health converge on the issue of population-based precision cancer screening. For example, existing mammography screening guidelines vary between populations, but recommendations on when to start screening are based largely on age rather than on breast density or environmental or genetic factors. In recent years, the adverse events attributed to mammography—such as the rates of overdiagnosis of breast cancer, which can result in unnecessary, invasive procedures in women (12, 94)—have become a

growing concern. Studies have highlighted predisposing genetic variants that can be used to create a polygenic risk score and identify those at high risk of breast cancer (59, 61). The combination of molecular testing with current approaches would allow providers to tailor screening specifically for high-risk patients. However, the utility of these methods is uncertain. Additionally, there is no consensus on how to evaluate the strength of precision screening methods (54). Population-based precision cancer screening may create different tiers of cancer screening risk, which may also lead to confusion among the general public and medical practitioners.

PM may also be useful in rare hereditary conditions such that clinical phenotypes may indicate one condition while molecular or genomic testing may reveal a specific mutation. In these instances of orphan diseases, options for diagnosis, treatment, and prevention are limited. Examples of this scenario include Wiskott-Aldrich syndrome and X-linked severe combined immunodeficiency, which is caused by one mutation (18, 40).

Therefore, PM applied in the diagnosis of disease assumes that molecular or genetic testing may improve the nosology of these conditions, which may lead to more precise treatment among those with disease. However, several issues need to be addressed with this point of view.

First, improving the classification of disease is beneficial principally if therapies are available. In the absence of treatment options, better description of pathogenic processes may yield little benefit to the patient even if it may benefit other patients in the future. For example, in patients with Huntington's disease (HD), genetic testing for this condition has been available since 1993 (79). The decision to test for the mutation is difficult for asymptomatic individuals with a family history because there are no treatments to prevent or delay HD and, over time, patients are offered symptomatic and supportive care (79). To improve the treatment of neurological conditions such as Parkinson's disease, some advocate for the use of PM methods to classify distinct subtypes, a blueprint similar to cancer (25). However, so far, this technique has not led to substantial progress in developing new therapies.

Second, these approaches are, of course, far from cost free. Even if a precise diagnosis leads to a single genetic or molecular aberration, which can be targeted, the cost and time to development and clinical use may be significant.

Third, more precise stratification of disease also introduces more financial burden and the potential for inefficiencies with little or no tangible clinical benefit. The challenge to population health is that using a disease process to improve individuals' treatment may have limited utility for the improvement of overall population health. Creating several molecular classifications of one disease entity may subsequently fragment the management of these conditions, which may in turn impose significant strains on existing health services that deliver health care on the basis of organ systems rather than molecular subtypes.

3.2. High Risk and the General Population

Improvement of population health will require that PM approaches identify high-risk individuals in the general population, offering some promise of improving chances for disease prevention in specific groups. PM approaches may hold some benefit for disease identification in this context. Molecular testing and genetic sequencing can identify persons who are at high risk of developing a disease. Biomarkers may be more reliable in predicting disease than are clinical markers and may be useful among individuals with a family history of cancer, heart disease, or sudden death.

By way of illustration, hereditary forms of breast and ovarian cancers have been noted in certain ethnic groups such as the Ashkenazi Jewish populations, yet a clear predictive marker had not been described in the past. The association between breast cancer and germline mutations in the *BRCA1* and *BRCA2* tumor suppressor genes has allowed investigators to quantify lifetime risk

of developing cancer. Studies have shown that among women who inherit the *BRCA1* mutation, 55–65% will develop breast cancer by the age of 70 years. Forty-five percent of women who inherit the *BRCA2* mutation will develop breast cancer by 70 years of age (6, 20), as compared with 12% of women in the general population who will develop breast cancer in their lifetime (34). *BRCA* mutations and molecular diagnosis of other familial cancer syndromes such as multiple endocrine neoplasia type 2 have led to treatment options that can reduce one's risk of developing cancers (38).

Genetic profiling can improve diagnosis among family members and spare unaffected individuals from unnecessary routine surveillance or screening procedures that may be associated with harm. Patients with a high risk of cardiovascular disease due to familial hyperlipidemia or those with a family history of cardiac arrhythmias have also harnessed the accuracy of genetic sequencing to improve diagnosis in high-risk individuals (32, 93). One particular study has highlighted the cost-effectiveness of cascade testing of relatives of patients with definite and probable familial hypercholesterolemia using a combination of genetic testing for known family mutations and standard serum low-density lipoprotein (LDL) cholesterol levels when such mutations cannot be found (67).

There remain, however, substantial challenges to the wide-scale applicability of this approach to the health of populations. First, it is unclear whether individuals who test positive for genetic predisposition to a condition alter high-risk behaviors or adopt lifestyle changes when they are identified as part of a high-risk population. Marteau and colleagues found that in an analysis of 341 families with a history of hypercholesterolemia who were randomized to receive risk information about the condition with or without genetic confirmation of a familial hypercholesterolemia mutation, the evidence showed no difference in diet, physical activity, smoking, or medication use between these groups at six months (57). In cases where individuals were positive for the FH (fumarate hydratase) mutation, this mutation may lead to reliance on biological interventions rather than behavioral changes (i.e., low-fat diet or exercise) (58). Genetic risk information may also create a sense of fatalism among those who are positive for a mutation that increases their risk for a disease or for addiction (56, 81), which may be due to the belief that these biological risks are indelible and cannot be changed by behavioral modification. Therefore, even in the presence of precise information on the underlying cause of disease, instituting preventive policies may not be feasible on an individual or population level.

Second, there currently remains substantial disparity in access to modern technology and novel therapeutics, which may be due to the cost of these services to minority groups. Compared with non-white Hispanic individuals, African Americans are less likely to be covered by private or employment-based health insurance plans (89). PM will likely widen the gap between those who can afford such technology and those who do not have insurance to cover additional genetic sequencing. Several studies have also shown that ethnic minorities express mistrust of genetic services, which may limit the ability of this approach to manage patients with clinical features of high-risk disease (7, 71, 89). In addition, even among those in minority groups who can access genetic services, information within these registries may not be diverse, resulting in an inability to classify benign processes from pathological variants among minority groups. In 2009, an analysis of genome-wide association studies revealed that 96% of participants were of European descent (66). Since this time there has been an effort to include participants from diverse backgrounds within these studies. As of 2016, 19% of participants were non-European, but only a small proportion included those with African ancestry (73). The lack of diversity in existing genomic data repositories may lead to misclassification of disease processes in minority groups, thereby leading to poor prevention strategies among those with high risk of disease.

Third, PM purports greater accuracy with ever decreasing technology costs, yet it is not clear whether results derived from PM methods are accurate and sufficiently cost beneficial compared with existing methods. Using family history as a risk assessment is an inexpensive tool and may

be purposeful and more accurate compared with genomic screening. This proposal is illustrated by Heald and colleagues where the concordance of hereditary cancer risk assessment between a family history–based risk assessment with personal genome screening was assessed in a study of 44 participants (31). They found discordance between family history–based and genome risk assessments for hereditary cancer risks, whereby the genome screening was unable to pick up individuals at risk of hereditary or highest risk of common cancers. This lack of data creates concern about the widespread implementation of PM for the diagnosis of high-risk individuals in the population.

Fourth, the general population utility of PM approaches rests in no small part on the predictive capacity of PM approaches. It is, however, unclear that genetic or molecular approaches will ever approach such predictive utility within populations with environmental factors that are also causal. This notion is supported by a study by Keyes and colleagues, which highlights the limitations of using germline genetic variants to predict health outcomes in the presence of other genes and environmental factors (43). By way of illustration, in a study, Belsky and colleagues analyzed how creating a genetic risk score using single-nucleotide polymorphisms from genome-wide association studies (GWAS) related to the developmental and biological characteristics of asthma in a population-based running cohort (10). They found that those who had a higher genetic risk developed asthma earlier in life than did those who had a lower genetic risk. Individuals with a higher genetic risk also had the possibility of developing life-course-persistent asthma symptoms. There was, however, no overlap in the genetic risk score between individuals with asthma and those without; half of the healthy individuals had between 14 and 25 asthma risk alleles without being affected by asthma by 38 years of age, which was the follow-up period at the time of the study (24). This result illustrates elegantly that genetic risk of asthma at an individual level cannot be predicted by genetic information alone, which highlights the difficulty in extrapolating data from such studies to the prevention of disease among individuals and populations (39).

4. PRECISION MEDICINE AND NOVEL THERAPIES

Next we consider the impact of PM-led therapies among individuals with disease and among those considered to be at high risk within the general population.

4.1. Individuals with Disease

As we have noted, the promise of PM rests in large part on the notion that it can identify novel therapies that can treat diseases that previously were not treatable. The definition of precision has changed over time in cancer therapy. The term was initially used to describe the design of targeted therapy against tumor characteristics defined by organ type. The shift from organ type to molecular identification has led to the development of therapies such as erlotinib or gefitinib for lung cancer that overexpresses EGFR mutation, which have offered an alternative to chemotherapy regimens (52, 83). Another example of a drug developed with rational drug design has been imatinib, which is used for chronic myeloid leukemia (CML). The predominant cause of this condition is the Philadelphia chromosome mutation, which leads to hyperactive Breakpoint cluster region–Abelson (Bcr-abl) fusion protein. Imatinib is a tyrosine kinase inhibitor that binds specifically to the hyperactive protein. Prior to 2001, one-third of patients with CML survived 5 years past their initial diagnosis. Following clinical trials of imatinib in CML, recent studies showed that the estimated 6-year overall survival rate was 83% (33).

The promise of PM has recently been highlighted by the possibility of directing treatment programs that are related to data generated about the patient's individual characteristics and tumor biology irrespective of the organ from which the cancer originated. For patients expressing

the *BRCA* mutation, specific drugs such as olaparib have been approved for use in certain cases (91). Identifying drugs that specifically target driver mutations on cancer cells, which prolong survival, has been the central goal of precision oncology. Anecdotal reports indicate that some patients have had genetic sequencing of their tumors and responded to targeted therapies that have been found as a result of tumor characteristics (80).

Gene therapy and gene editing techniques specifically use techniques that target the mutated gene and have evolved to become a therapeutic option for patients with certain rare conditions such as hemophilia B. In a phase I study investigating gene therapy, affected patients were intravenously administered cells with an adeno-associated virus serotype 8 (AAV8) vector that infiltrated the liver and increased levels of the absent clotting factor IX (63). For patients who require frequent clotting infusions, this approach may be a longstanding solution that reduces costs and medical complications and may reduce both morbidity and mortality.

In other rare diseases, such as cystic fibrosis, new therapies directed at cystic fibrosis transmembrane conductance regulator gene (*CFTR*), ivacaftor and lumacaftor, have been approved. These treatments can be used in combination for patients with specific CFTR mutations and have been shown to improve respiratory function (92).

Challenges to the utility of PM approaches in this manner also abound. First, it is not at all clear that these approaches yield large-scale utility. Cancer trials designed to specifically test the use of genetic mutations to direct therapy as defined by PM have not led to benefit for patients (74). The SHIVA trial assigned patients with metastatic cancer to therapies based on mutations or treatments selected by their physicians (47). When comparing these groups, the progression-free survival rate was less than three months in both groups. Additionally, use of progression-free survival as a surrogate for overall survival may not represent the full impact of therapy on people with these conditions. It is also unclear whether drugs such as lumacaftor help improve outcomes in patients with cystic fibrosis. Because such drug developments affect only a small subset of patients, overall survival benefits in cystic fibrosis may be due to management guidelines that prioritize treatment of infections and appropriate nutritional replacement.

Second, although PM approaches develop predictive and prognostic biomarkers in tandem that can help physicians direct targeted treatment for a patient's condition or avoid harmful therapies (70), they may also be used to create new therapies. However, these biomarkers are often difficult to collect and validate in both the trial and clinical settings (51). These biomarker discoveries will likely suffer the same fate as that of many existing serological markers, such as tumor markers; there is a lack of agreement on their utility and validity in diagnosing certain cancers (5). Therefore, despite the specificity and sensitivity of biomarkers derived from PM, there may be resistance to the use of these biomarkers in clinical practice owing to a lack of generalizability.

Third, there has been substantial federal and private-sector investment in PM directed at individuals with disease. For example, the Cancer Moonshot initiative, which aims to provide patients with therapies, has directed $125 million to develop a cancer immunotherapy center (30). Such initiatives have been criticized for focusing on one area of therapy with a lack of appreciation for the heterogeneity of causes of cancer.

Beyond racial differences in drug metabolism or excretion, PM may provide accurate characterization of genetic variations that increase drug-related adverse events (13). The relevance of pharmacogenomics is seen among common drugs such as clopidogrel in coronary artery disease (86). More than 100 drugs are listed under a genomic label by the US Food and Drug Administration, which recommends genomic assessment prior to use. However, pharmacogenomic assessments rarely have a functional place in routine clinical care (90).

Among antidepressant drugs, which are commonly prescribed, PM may also provide methods to categorize genetic variants of drug-metabolizing enzymes into those that are poor metabolizers

or those that are extensive metabolizers. Certain cardiac toxicities were not dose dependent but instead were associated with rates of CYPC219 metabolism. To harness PM in the prescription of antidepressants, the Clinical Pharmacogenetics Implementation Consortium considered an algorithm based on medical literature, which considers the use of such tests in helping physicians choose specific antidepressant drugs (62). The study authors do caution against routine genetic testing because clinical utility and validity remain theoretical.

It is not clear whether using such pharmacogenomics provides a cost-effective option to existing public health measures. Use of pharmocogenomic biomarkers to direct personalized smoking cessation programs encouraged proponents of PM. Investigators identified smokers on the basis of a genetically informed biomarker based on CYP2A6, and participants were divided into those who were slow metabolisers of nicotine and those who were normal metabolisers (48). The study concluded that normal metabolisers should be treated with varenicline to increase smoking abstinence rates and slow metabolisers should be administered the nicotine patch. A cost-effective analysis was not done as part of the study. These pharmacogenomic biomarkers have identified a small subset of the population in which these interventions benefit. Studies such as these highlight the tension between PM and existing public health objectives that cater to a larger proportion of the population.

4.2. High Risk and the General Population

Utility for PM approaches for the improvement of the population's health rests on the adaptability of these approaches to whole populations and ideally to the prevention of disease. There is some promise in this regard. For example, identification of genetic aberrations associated with familial cancer syndromes has led to therapeutic options to reduce the risk of cancer development. Among patients who test positive for multiple endocrine neoplasia 2, a total thyroidectomy is the only method to prevent medullary thyroid cancer (76). In the case of patients with BRCA mutations, prophylactic bilateral mastectomy and salpingo-oophorectomy are options to reduce breast and ovarian cancer risk, respectively. Bilateral prophylactic mastectomy reduces the risk of breast cancer by at least 95% among women with a deleterious mutation in the *BRCA1* or *BRCA2* gene (23, 60). A noninvasive method of cancer prevention includes regular screening or tamoxifen as antiestrogen therapy. The latter has shown to be beneficial among women with BRCA2 mutations specifically and reduced breast cancer risk by 62% (45). Other chemoprevention therapies in familial cancer syndromes include the use of 600 mg per day of aspirin to reduce the risk of colorectal cancer in Lynch syndrome carriers (15).

However, these approaches are also limited in multiple ways when applied to whole populations. First, these cancer risk reduction methods can be used only among the 5–10% of breast cancer patients who harbor the *BRCA* mutation (27); therefore, this approach may not help reduce the risk in the majority of patients. In addition, these interventions affect only a small proportion of the general population. An estimated 15–20% of cancers worldwide are linked to infectious etiology (72). Vaccination programs to prevent hepatitis B or human papilloma virus (HPV) have not used PM methods. The quadrivalent HPV vaccine and cervical cancer screening have been efficacious and have played a role in reducing cervical cancer incidence (4, 19).

Second, PM approaches and genetic testing may lead to intervention, which could be harmful to individuals if the underlying tests are not sufficiently verified. A case report highlights the unintended consequences of PM (2). Following the sudden death of a young patient, which was attributed to a cardiac cause, family members underwent genetic testing. Results suggested that a genetic variant was present, indicative of long QT syndrome in family members. The deceased patient's brother had an implantable cardiac defibrillator (ICD) inserted as a preventive measure.

When the family presented for further evaluation, it became evident that the initial evaluation was inaccurate. The preventive intervention of ICD implantation was an inappropriate and invasive intervention that caused some harm to an asymptomatic individual. The authors of the report highlight the importance of using clinical data such as electrocardiograms, which ruled out long QT syndrome, rather than relying on the results of genetic tests alone to guide management. This case highlights the need for education of medical professionals in the interpretation of the genetic test results. PM and its results need to be robust and valid to ensure that any resulting interventions do not cause harm to the population.

5. INTEGRATING PUBLIC HEALTH AND PRECISION MEDICINE

In this review, we have summarized both the promise and the challenges facing PM approaches aiming to improve health, on the dimensions of both disease diagnosis and disease treatment. The ability to measure, store, and share health-related data has reached newfound heights in the last 20 years. In addition to the abundance of genetic testing tools available, wearable devices also identify biological data. Smartphones and watches can record social networks and capture behaviors. Electronic health records provide an overview of health outcomes at various stages of life. Together these data points may be able to convey health risks in individuals and improve health outcomes. While these approaches yield some degree of promise at the level of individual treatment and diagnosis, they are much more problematic when targeted at the population level, aiming to identify or improve the health of large-scale high-risk persons.

It becomes clear then that efforts to navigate PM from individual characteristics toward maintaining the health of the general population are still in their early stages of development at best. The challenge from a population health perspective comes about from the fundamental fissure that characterizes the competing world views of PM, focused as it is on clinical interventions, and public health, which is centered on population-wide concerns. There is no question that clinical care can contribute to well-being at the population level and that the inequitable distribution of health care services takes a toll that can be measured in terms of morbidity and mortality. But careful analyses for more than a century have demonstrated that social inequities, poverty, and racism have profound impacts on suffering and on life expectancy.

Thirty years following the introduction of the National Health Service, the landmark Black Report in England released in 1980 concluded that a marked social gradient in health characterized the British population and social inequalities in health were pervasive (28). Disparities in the United States are, if anything, starker and have been growing. A report from the National Academy of Sciences, *The Growing Gap in Life Expectancy by Income*, found that when viewed from the perspective of income quantiles those born in 1930 witnessed a gap of 5.1 years in life expectancy between those at the bottom and those at the top. For males born in 1960, the projected gap had widened to 12.7 years. The case was similar for women; the gap had widened from 4 years to 13.6 years (64). A 2013 National Research Council/IOM Report, *U.S. Health in International Perspective: Shorter Lives, Poorer Health*, uncovered an American disadvantage (37). When compared with 17 peer nations, the United States had higher rates of adverse birth outcomes, heart disease, injuries from motor vehicle crashes and violence, sexually acquired diseases, and chronic lung disease (37). For those who are skeptical of the promises made by advocates for PM, these findings have made clear that a focus on individual vulnerabilities, the hallmark of PM, will have a tough time aligning with the core concerns of the public health population, well-being and social inequalities.

On the level of preventive interventions, those whose perspectives are shaped by public health have equal reason to be skeptical about what PM has to offer. Two pertinent examples illustrate this issue. Beginning in the 1960s, the devastating impact of cigarette smoking on the lives of

men and women became the subject of ongoing public health concern. At that time, more than one-half of men and one-third of women smoked. Over the next decades, in the face of industry resistance, public health measures were adopted: Cigarette package warning labels that sought first to inform and then to raise alarm were mandated; taxes were increased to ever higher levels, aiming to make the purchase of cigarettes ever more burdensome; smoking was prohibited in enclosed public settings and ultimately in open public spaces; and collective campaigns that sought to denormalize a formerly common social behavior were launched. The consequence of these efforts has been a striking reduction in the prevalence of cigarette smoking among US adults to less than approximately 18%. These results, of course, had nothing to do with the perspective of PM, and whatever role PM may play in developing targeted nicotine-based therapies is likely to be of marginal importance.

A second domain where public health measures are bound to play a role that overshadows what PM may contribute is that posed by obesity. Although there may be a genetic component to this critical problem, the development of obesity in the past decades cannot be the consequence of genetic changes over time, but rather a result of the radical modification of the American diet and the marketing of food products. Which measures will effectively confront pathogenic food consumption? Which industry regulations will be necessary? What role may taxes play? These remain open questions. However, from a public health perspective, the clinical focus of PM may not make a significant contribution.

These challenges have not gone unnoticed by the proponents of PM. A key part of the Precision Medicine Initiative is a 1-million-person cohort, known as the All of Us^{SM} Research Program, which serves to record lifestyle habits, health information, and environmental exposures from a diverse group of volunteers in the United States (75). The recruitment phase of this project began in 2017. The goal of this program is to integrate personal health data to deliver precise preventive care and medical treatment to an individual. Whether these data will indeed yield benefit remains to be seen.

These limitations also highlight the need for all PM approaches to emphasize the incorporation of data at multiple levels, including both biological and environmental data that can illuminate some of the core concerns of public health. A symbiotic relationship between public health and PM may exist where risks to the individual and the population are identified prior to their onset; this approach will be possible only with the integration of data across levels of influence and analytic wisdom in using these data toward better identification of disease risk. Rose highlighted the paradox of addressing simultaneous preventive measures in the individual and in the general population (78). PM may address Rose's prevention paradox by gathering information at the levels of both the individual and the population. In the future, biological data from individuals can be analyzed with environmental data to determine the drivers of health and well-being. PM has the potential to identify accurate biomarkers associated with changes in health states that may help provide prevention strategies for the individual and the community. Over time, with these rapid, cost-effective tools, this combined approach may improve population health in the long term provided that environmental and socioeconomic factors are incorporated. It will also require the adoption of methods that address the complexity of disease production by extending the typical tools that have been used predominantly with the end goal of improving the health of populations.

6. CONCLUSION

We cannot ignore the potential that PM holds for medical progress. However, PM has been disproportionately focused on drug development and strategies for those who have a disease with an intention to improve outcomes, leaving behind the concerns of whole population health.

The core public health concern is whether the new enthusiasm for targeted clinical intervention represents a profound distraction from population-level challenges that demand resources and sustained scientific attention. It does not necessarily have to be this way. The principles of PM and efforts to approaching the right health issues in a timely manner can be applied to population health. Doing so will, however, require a careful view and concerted effort to maintain the needs of population health at the forefront of all PM discussions and investments.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors are grateful to Laura Sampson and Shui Yu for editorial assistance on this manuscript.

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