The brave new world envisioned by proponents of personalized medicine has attracted considerable interest and investment during the past decade or so. The excitement is understandable because personalized medicine promises to drastically improve individual health and make more efficient use of existing resources, changing both health care and public health for the better. Improved use of resources is becoming particularly important, as many national healthcare schemes are straining to maintain affordable health care of acceptable quality under the combined pressures of rising costs, an aging population and the increasing prevalence of many chronic and common diseases. Although not a panacea for all these problems, personalized medicine could theoretically reduce healthcare costs, as an individual’s genetic or other biological information could be used to make better or earlier diagnoses of disease, apply cheaper, preventive measures to decrease disease risk, and make more efficient use of therapeutic options. However, there remains a considerable gap between theory and reality, and we think that the prevailing focus on an individual’s genes and biology insufficiently incorporates the important role of environmental factors in disease etiology and health. Including these factors in our approach to personalized medicine and population health should bring that theory closer to reality. However, it will require a fundamental change to the current research agenda and public health policies to emphasize the role of the social and physical environments and related epigenetic changes.

\[\text{. . . the prevailing focus on an individual’s genes and biology insufficiently incorporates the important role of environmental factors in disease etiology and health.}\]

Despite various calls for a more holistic view of personalized medicine, this term—or, alternatively, ‘precision medicine’—remains a proxy for the application of genetics to individualized therapies. This is apparent in the enthusiasm of clinicians, researchers and the pharmaceutical and gene-technology industries for pharmacogenomics and therapies based on this approach. It can also be shown quantitatively: searching PubMed for ‘personalized medicine’ yielded 12,677 citations in September 2013. A random sampling of 100 of those citations revealed only one abstract that included ‘environment’ or ‘exposure’ within the central premise of the work [1]. This corroborates our concern that a narrow, DNA-focused view of personalized medicine has become pervasive and, at the same time, isolated from other factors that could dramatically improve any personalized approach to medicine.

A particular drawback to the prevailing approach to personalized medicine is its primary focus on technology-driven therapies and diagnostics rather than on preventive public health measures [2], despite abundant evidence that reducing personal or collective exposure typically increases general health much more efficiently than treatment of disease [3]. Pharmacogenomics has achieved some impressive successes [4] and more are sure to follow, but these represent, by definition, the outcomes of a reactive approach. The ‘P4’—predictive, personalized, preventive and participatory—vision of medicine that National Institutes of Health (NIH) Director Francis Collins, Leroy Hood and others have advocated is a step in the right direction, but it does not go far enough to explicitly recognize the role of the environment, or to stress that gene-neutral population-level changes are often more powerful, cost-effective and equitable than efforts tailored to individuals [5]. One might have thought that the evolution to ‘P5’—adding population—[6] would have strengthened prevention, but instead it seems only to have

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risk and progression of common, non-communicable diseases, such as asthma, diabetes, cancer or cardiovascular diseases, crucially depend on environmental and behavioral factors rather than genetic ones. Genome-wide association studies (GWAS) have already effectively highlighted the very small contribution of specific genes to these complex diseases [8]. Though combinations of risk-conferring genes may increase the extent to which genes predict disease, the ‘elephant in the room’ of personalized medicine is the fact that genetic effects in isolation are insufficient to identify the risk in the most prevalent diseases. For effective risk identification, we will actually need to integrate genetic and epigenetic effects with environmental exposures.

A broader understanding of disease that includes gene-environment interactions would enable individuals and healthcare providers to realistically see genetics as just one of a suite of personalized tools to achieve healthier living, rather than an all-powerful method to reliably predict future disease. One clear application of genetics would involve the prospective genetic screening of newborn children to make recommendations, based upon the child’s genotype, about the possible effects of environmental exposures. By way of example, pediatricians could advise parents on the potential risks and benefits of having pets in the household. Given the effect of variants of the CD14 gene on the response to Gram-negative bacteria, the risk of dog ownership for a child’s developing allergic disease may be dependent on the genotype of the child [9] (Fig 1). In the future, a physician might therefore recommend that one set of parents get a puppy as soon as their child is born to protect against childhood allergies, but advise other parents not to have a dog in the home, as doing so would increase their child’s risk of allergic disease—with the difference between the two cases being the genotype of the child. Pet ownership is a modifiable exposure, and parents might be more likely to comply with a physician’s recommendation if they know that it is based on their child’s genetic profile. Personalized interventions and lifestyle recommendations in infancy based on genotype could become a cost-efficient public health intervention—one that current approaches, focused primarily on adult populations, miss. The emerging science of the microbiota and its interaction with the genome might provide another avenue by which to make personalized recommendations early in life.

The expanded framework for personalized medicine being proposed here would also be applicable beyond the individual for population- or community-level interventions. For example, we might imagine a situation in which a city plans to build a new school in close proximity to a high-traffic road. It turns out that some of the children destined to attend this school are known— from screening in infancy—to have a higher risk of asthma owing to family history or variants in risk-conferring genes, such as glutathione-s-transferase [10]. The parents therefore might pressure the city to build the school elsewhere. The result would be that, although the evaluation of the genetic risk—that is, that some of the children are highly likely to develop asthma if the school is built in a polluted environment—is made on an individual basis, the prevention and/or remediation of the problem—to build the school elsewhere—is realized collectively and benefits all the children who attend the school, whether their risk of asthma is high or not (Fig 1). Of course, building schools a safe distance from major roadways is a sensible decision regardless of genomic risk, but integrating genomics might significantly influence policymakers and planners if it could be shown that vulnerable sub-populations have higher relative risks. The US Environmental Protection Agency has, for example, interpreted the Clean Air Act’s 1990 Amendment, which states that ‘The Administrator shall publish and make available […] information on measures which may be employed to reduce the impact on public health or protect the health of sensitive or susceptible individuals or groups’, such that one of its objectives is to identify genes involved with increased susceptibility to air pollution [11].

Epigenomics merits special emphasis in this context because it has been largely ignored in the ‘personalized medicine’ framework, even in its latest iterations. Yet it may represent the most exciting application of genomics, because a better understanding of the relationship between environmental exposure and the epigenome might lead to more efficient preventive measures [12].

Those responsible for research funding—whether they decide on funding priorities at higher levels or evaluate specific proposals—should encourage and support novel investigations that seek to demonstrate how personalizing data on gene-environment interactions lead to meaningful health outcomes. They also should explore social, psychological and economic factors: Would such a new framework of personalized medicine overcome a general tendency to prefer prescribing a simple pill over encouraging long-term changes to personal behavior or advocating for strong public health measures? Personalized and population-level medicine based on genome–epigenome–environment interactions could provide the additional and convincing arguments needed for such sweeping public health policies. In this way, harnessing environmental and genetic data could better translate genomics into personal and public health benefits.

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Those are several key messages to be taken from our argument for a greater appreciation of genetic and environmental factors and their effects on the epigenome and disease risk. First, the ongoing emphasis on narrowly defined, genetics-based, ‘personalized’ approaches to novel therapies and diagnostics is anachronistic, given the
complexity of most chronic diseases. Second, the popular focus on ‘personalized medicine’, as most commonly formulated, over-emphasizes genomics relative to the roles of environmental and social determinants of health. Third, a more efficient personalized approach would focus on health, rather than health care, by integrating the social and physical environments. Fourth, ‘personalized’ approaches to health would benefit from an explicitly integrative emphasis on education, research and policy. Fifth, to fully
realize the potential of personalized medicine, advocates need to adopt a long-term perspective that attends to early as well as later stages of life; the current personalized medicine approach favors the application of ‘quick fixes’ to conditions that were set in motion many years before diagnosis. Finally, epigenetics represents a key emerging opportunity, because the epigenome both reflects the history of past exposure and represents a potentially modifiable factor, allowing one to decrease disease risk through prevention or lifestyle.

... embracing the impact of the environment on health will require a new framework to guide both research and its application, and to steer public investment and research efforts toward more truly cost-efficient approaches to personalized health, health care and quality of life.

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Conflict of interest
The authors declare that they have no conflict of interest.

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