VIEWPOINT

Precision Treatment and Precision Prevention
Integrating "Below and Above the Skin"

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In 2015, President Obama unveiled "a new research effort to revolutionize how we improve health and treat disease," based on the premise that accounting for "individual differences in people's genes, environments, and lifestyles" will improve both disease prevention and treatment.[1,2] Most of the history and current application of these concepts, however, has focused on treatment over prevention. If the scientific community is not vigilant, emphasis on successful treatments for small subsets of patients may overshadow prevention efforts to improve the health of all Americans. We contend that integrating 2 paradigms of research, both of which aim to understand "what works, for whom, and under what circumstances," can lead to a sounder balance of treatment and prevention. Advances in precision can benefit both halves of this effort and ultimately have the potential to integrate them.

To date, precision medicine has focused on treating existing disease much more than preventing it in the first place; we call this *precision treatment*. At the risk of oversimplification, precision treatment is most concerned with finding the most efficacious and least harmful pharmaceutical treatments for avoiding high-frequency outcomes among patients with existing disease, such as relapse or death after a diagnosis of cancer. Using high-throughput technologies, precision treatment efforts typically interrogate individuals' "below the skin" networks of metabolism, epigenetics, and genetics to guide personalized therapy.[3] This approach characterizes the near-term goals of the new National Institutes of Health Precision Medicine Initiative.[4] To date, precision treatment frequently emphasizes the "what" (eg, the best drug for this patient), more than the "how" (eg, delivery system reform to accommodate the increased need for genetic counseling).

What we call *precision prevention*, on the other hand, has generally involved tailoring behavioral interventions to individuals' characteristics. Historically, it has operated "above the skin" to overcome psychosocial barriers, emphasize achievable goals, or adapt to families' differing economic or cultural circumstances. While precision prevention can aim to change individual behavior, it can also target "precise" groups or entire communities by modifying care delivery systems, optimizing transmission through social networks, or instituting targeted policy or macroenvironmental changes that are different from one community to the next.[5] Precision prevention often emphasizes the "how" (eg, the most cost-effective implementation approach) as much as the "what" (which behaviors to target) or the "why" (the biological mechanisms that mediate prevention effectiveness).

Despite these historical differences, we believe the nascent precision revolution can benefit both treatment and prevention alike. Three loci hold particular promise: mutual learning from each other's research paradigms, sharing study designs, and transdisciplinary integration through innovative data analysis and modeling.

First, taking lessons from across the "skin barrier" may increase effectiveness of both efforts. For precision treatment, this can mean invoking above-the-skin strategies for implementing and sustaining changes in practice, as is already beginning to happen. For example, a flood of 'omics information to clinicians will require increased capacity for counseling, necessitating additional training, space, and funding—purviews of health services research. Another example is finding the best ways to ensure improving adherence to medicines, which is crucial for effectiveness and is determined by a host of psychological, economic, and social factors. For precision prevention, recognition of how powerfully biology may act as a mediator of societal-level effects transcends the skin barrier. We often think of how biological mechanisms mediate individual behaviors, for example, how maternal diet during pregnancy could affect preterm birth via changes in metabolomics. Socially patterned above-the-skin factors like stress, however, may directly embed themselves within below-the-skin biology without invoking individuals' behavior.[6] Using 'omics technologies to understand the mechanisms by which stress alters health outcomes such as preterm birth could lead to a more specific understanding of how different types of stress affect different people. This understanding could translate into more precise prevention strategies both within and outside medical care, conceivably narrowing disparities in health outcomes.

A second locus revolves around sharing study designs and clinical epidemiologic principles. One of the stated promises of precision medicine is to distinguish individuals, either on prognosis or on potential response to intervention, often called prediction. This goal presents higher obstacles in precision prevention than treatment: the comparative infrequency of disease incidence in prevention renders positive predictive values relatively low for any index of personal characteristics. This is one reason why many prevention programs invoke broad environmental changes that affect large numbers of individuals rather than adopt interventions only for higher-risk people. To estimate the value of high-risk approaches, the precision prevention community must focus more on absolute than relative risks, a focus that already fits naturally in treatment paradigms. On the other hand, precision prevention has always relied on large population-based cohorts. Now, "big cohort data" derived from medical care encounters from conception to old age, informed by judicious use of patient-empowered information from biology, behavior, social networks, geography, and the macroenvironment, also have the potential to yield real-world answers to comparative effectiveness treatment questions.

Third, both prevention and treatment could gain precision via emerging analytic and modeling techniques specifically designed to address the inherent complexity of the multilevel, dynamic systems that govern health. Useful insights will likely derive from comparing below- and above-the-skin methodological approaches that may seem distinct but actually share common features. Consider, on the one hand, the use of systems biology to identify attributes of biological networks that pinpoint predictive signatures for cancer patients, and on the other, analysis of social systems to identify how to magnify efforts for obesity prevention. Systems biology includes newly available high-resolution measurements of 'omic modifications, and social systems analyses increasingly benefit from high-granularity data such as ecological momentary assessments. Systems biology uses integrative statistical and network modeling to identify drivers of tumorigenesis, and social systems analysis uses statistical and stochastic-actor modeling to identify patterns of behavior concentration within social networks or other environments. Systems biology has started to use computational modeling of heterogeneous and interacting populations (of cancer cells) to understand common mechanisms and predict dynamics; analysis of social systems can include computational modeling (of people) to gain insight into analogous mechanisms and dynamics.

On a deeper plane, crossing the skin barrier with a common approach may offer a true integration for the benefit of both precision treatment and precision prevention, especially where key dynamic pathways inherently connect across these levels. An example is the mesolimbic reward system in the brain, an important driver of health behaviors such as eating, exercising, and substance abuse. Sequences of environmental exposures to cues like food shape below-the-skin encoding of learned expected rewards, leading to "sticky" preferences that motivate reward-seeking behavior, which in turn shape further exposure via food choice, ultimately feeding back to reinforce the neurobiology.[7] Systems science modeling approaches such as agent-based modeling, a technique more often used in engineering, ecology, business, and social science, are particularly well suited for modeling these types of feedback dynamics across the skin barrier and hold promise for pinpointing best practices in both prevention and treatment. Application of these tools to communicable disease has already led to deeper understanding of core mechanisms, in silico testing of more effective interventions, and valuable policy application. Extension of these methods to common chronic diseases is not far behind.

These frontiers will require incentives to enhance partnerships across traditional disciplinary lines. For the precision revolution to reach its full potential to improve human health, such partnerships to integrate strategies that permeate above and below the skin, as well as bridge prevention and treatment, are essential.

ARTICLE INFORMATION

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