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Short communication

Towards precision prevention: Technologies for identifying healthy individuals with high risk of disease

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ABSTRACT

The rise of advanced technologies for characterizing human populations at the molecular level, from sequence to function, is shifting disease prevention paradigms toward personalized strategies. Because minimization of adverse outcomes is a key driver for treatment decisions for diseased populations, developing personalized therapy strategies represent an important dimension of both precision medicine and personalized prevention. In this commentary, we highlight recently developed enabling technologies in the field of DNA damage, DNA repair, and mutagenesis. We propose that omics approaches and functional assays can be integrated into population studies that fuse basic, translational and clinical research with commercial expertise in order to accelerate personalized prevention and treatment of cancer and other diseases linked to aberrant responses to DNA damage. This collaborative approach is generally applicable to efforts to develop data-driven, individualized prevention and treatment strategies for other diseases. We also recommend strategies for maximizing the use of biological samples for epidemiological studies, and for applying emerging technologies to clinical applications.

1. Introduction

The National Institute of Environmental Health Sciences (NIEHS) sponsored a workshop in June 2015 entitled “Workshop on New Approaches for Detecting DNA Damage and Mutation in Population Studies”. This commentary emerged from a consensus-building discussion that followed technology-focused presentations by attendees, including several of the authors. Attendees broadly agreed that the field of DNA damage, repair, and mutagenesis is uniquely positioned to take a leading role in developing strategies for personalized disease prevention. The purpose of this publication, therefore, is to propose a framework for promoting personalized prevention through collaborative population-based studies that engage cutting-edge technologies.

In the quarter century since the human genome project was launched it has become apparent that the molecular basis for inter-individual differences includes much more than just the DNA sequence. Environmental exposures and stochastic phenomena produce enormous complexity in biological response at the level of epigenetics, transcrip-

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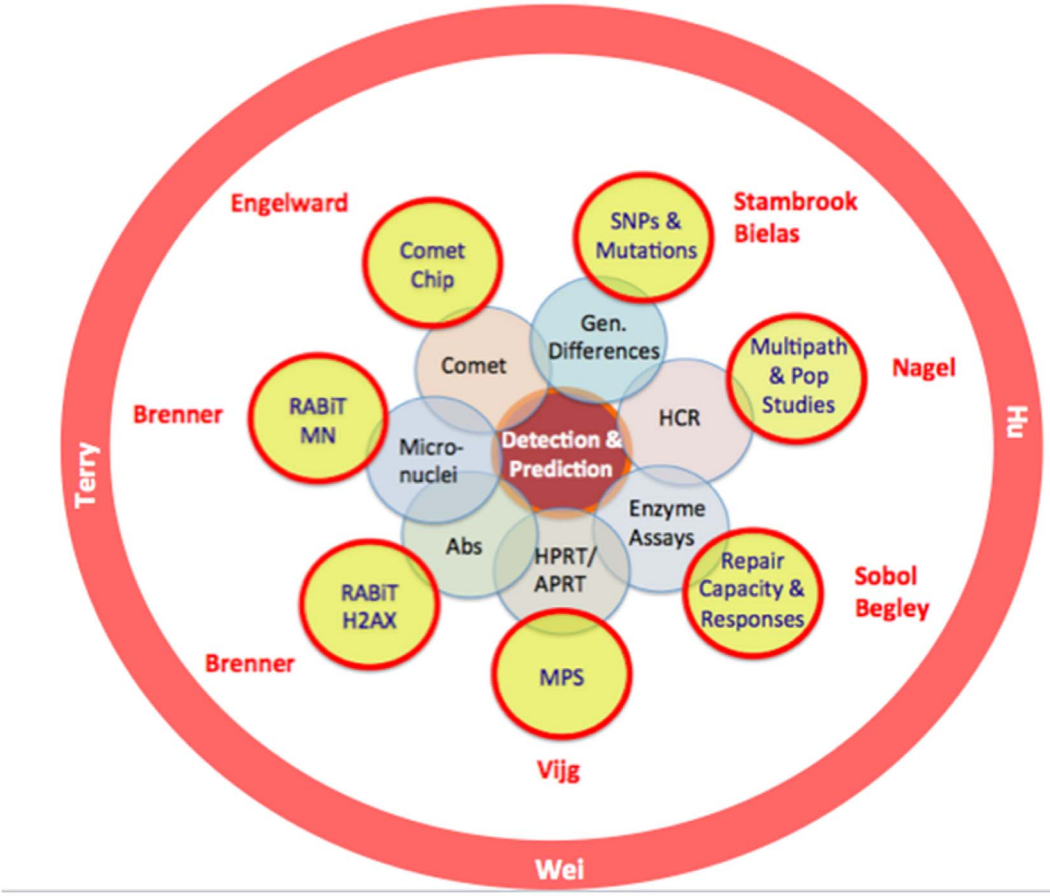

Fig. 1. From traditional assays (center) to today's tools for population studies (outer circle). The impact of new technologies emerges through their integration into population studies (orange circle).

tional and translational regulation, and posttranslational modifications of proteins. Furthermore, every individual possesses a mosaic of heterogeneous cells. This staggering variability leads to a unique set of risks and vulnerabilities for each individual and calls into question the standard approach that has dominated preventive medicine since its inception.

An increasing focus on "Precision Medicine" [1] at the national level reflects the growing recognition that, because no two individuals are exactly alike, a tailored approach to treatment based on either germline genetics and/or tumor-specific genetics is likely to provide the largest benefit to patients and to best uphold the principle of *primum non nocere*. Here, we discuss the role that DNA repair phenotype assays and new DNA sequencing approaches can play in improving precision medicine and cancer prevention. As precision medicine methods apply to tertiary prevention, we extend these principles to secondary (screening) and primary prevention under a general framework of "Precision prevention" and its importance in exposure biology. The same principles of targeted therapy apply, at likely much higher benefit given the lower cost of treatment to patients when interventions are made further upstream. Thus, rather than waiting for a potentially incurable disease to manifest, one can instead address the specific needs of individuals through disease-preventing interventions, or detection and treatment at the earliest possible stage. Precision prevention focuses on being able to predict who is at high risk for a given disease and thereby target screening frequency and onset as well as primary prevention interventions earlier in life to alter disease susceptibility. Individualized prediction is derived from the integrated impact of individual inherent factors (the individual's genome and epigenome), individual physiological factors (e.g., inflammation and comorbidities) as well as individual biomarkers and response to environmental factors (e.g., individual responses to exposure to air, water, soil, and food). For example, while almost everybody may be exposed to certain pollutants in the environment, such as polycyclic aromatic hydrocarbons (PAH), some individuals may be more susceptible to their health effects based on having deficient DNA repair capacity (DRC). Thus, in this example, measuring DRC in combination with measures of individual PAH metabolites can help in terms of risk stratification and risk assessment. In general, information about inter-individual differences in the ability to respond to environmental exposures and physiological stress are potentially useful for personalized prevention of any disease for which risk is governed by gene-environment interactions.

Precision prevention requires screening tools that enable stratification to identify groups that would most benefit from interventions. Furthermore, fine-tuned tools are needed to prevent ineffective focus on individuals who would not benefit greatly from primary and secondary prevention interventions. Precision prevention promises to identify at-risk individuals, empowering educated decisions on prevention. Importantly, the concept of precision prevention applies not only to the identification of risk-prone individuals, but is also relevant to the evaluation of risk-associated exposures. For example, with the advent of robust analytical tools, we are now poised to break down complex mixtures so that effort(s) can be made toward mitigating the effects of key harmful constituents. Importantly, precision prevention will certainly reduce health care costs over time, because small advances in disease prevention among many add up to a significant reduction in the socioeconomic burden of disease.

This review focuses on emerging methods for developing better predictors for disease risk in populations exposed to known or unknown agents that can induce DNA damage or alter the ability to repair DNA damage. DNA damage can lead to mutations and cell death; inefficient