EDITORIAL

Envirotyping: The Next Leap Forward in the Practice of Precision Medicine?

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IN HIS 2015 STATE OF THE UNION ADDRESS, PRESIDENT Barack Obama announced the launch of the Precision Medicine Initiative, a bold research effort to revolutionize health care delivery. Precision medicine – prevention and treatment strategies that account for individual variability in genes, environment, and lifestyle – is not a new idea, but recent technological improvements in both patient characterization and in computational tools for analyzing large data sets have made it a short-term medical frontier.[1] Deep-learning approaches, which utilizes artificial neural network and extensive computing powers to extract representative features from large data sets, are also increasingly being used to investigate the social and environmental determinants of health, which have received resurgent attention over the last decade.[2] We propose that a reorientation toward envirotyping – the computation of a high-resolution, individualized exposure profile that is potentially the socio-environmental analog to genotyping – could facilitate our next leap forward in the practice of precision medicine.

Barely a century ago, most diseases were described in primarily observational terms, and phenotypic descriptions led to rudimentary (and often inaccurate) explanations of disease mechanisms. Treatment strategies, usually based on anecdotal reports, generally produced little or no effect. Between the mid-1800s and the early 1900s, the works of Czech naturalist Gregor Mendel and Danish botanist Wilhelm Johannsen on plant genetics introduced genotyping as a new branch of pathophysiology. Genotyping has since matured from observing Mendelian inheritance patterns to highly specialized molecular genetics testing, and is now a standard component of disease characterization. However, the functional impact of genetic variation on disorders with complex inheritance remains largely obscure, as even identical genetic mutations often yield discordant disease phenotypes. For example, a recent large-scale trial of targeted therapies for specific gene mutations in cancer treatment resulted in lower-than-expected efficacy rates,[3] illustrating the insufficiency of current genotyping alone as a precision medicine strategy in oncology.

We have long known that the environment influences disease expression, and have attributed most cases of genotype-phenotype discordance to the amorphous "gene-environment interaction." For years, social scientists have studied environmental drivers of health, collectively known as "neighborhood effects." Most effect sizes have been small, and most studies are limited by simplistic designs and nebulous definitions of neighborhood.[4] Ideally, precision medicine will obviate many of these limitations by pairing genomic and biometric data with high-resolution data describing an individual's spatiotemporal life path, e.g. a quantitative description of an individual's physical whereabouts over a time period. We are currently witnessing a surge in the availability of such data via the growing popularity and affordability of early-generation wearable technologies and related mobile apps. Through these technologies, real-time biometric data, such as heart rate, respiratory rate, oxygen saturation, body temperature, blood pressure and blood alcohol content, are collected along with geo-environmental data both static (e.g. physical location, including altitude when inside a multi-level building) and dynamic (e.g. distance and velocity of travel when inside a moving vehicle). Scientists are busy exploring new ways to pair these data with high-resolution, global databases of environmental characteristics (such as weather and climate or land cover change), and with local or regional data on everyday experiences (such as air and water quality or traffic and noise). Envirotyping could integrate theoretically robust, multi-scalar data sets of physical and social exposures encountered by an individual in his/her daily path, which may allow us to characterize potential epigenetic factors associated with one's envirotype. The interaction of genotype, phenotype, and envirotype data is likely dynamic and reciprocal. Envirotype data may steer genotype-phenotype investigation strategies by providing socio-environmental (geodemographic) clues of genetic isolation, bottlenecks, or ancestral clusters and may prompt the search for novel

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gene mutations. Such envirotyping will be facilitated by the rapid growth in computational approaches to integrate geospatial health and exposure data along the life path, and by the rise of sensor-rich "smart cities" that characterize urban environments at increasingly finer scales. This notion of "precision public health"[5] is expected to yield new insights about how different conceptualizations of environment shape our health.

The field of ophthalmology presents opportunities for envirotyping to enhance current precision medicine efforts. Recently, three separate genome-wide studies showed significant association of certain alleles of *LOXL1* (chromosome 15q24.1) with exfoliation glaucoma (XFG), with odds ratio ranging from 2- to 10-fold on average per-copy of the risk allele.[6–8] Despite this robust genetic association, the XFG burden amongst pathogenic allele carriers varies with the latitude of residence, with higher disease burden positively correlated with the patient's distance from the equator.[9,10] This implies that the pathogenic *LOXL1* alleles contribute to the development of, but are not sufficient to cause, XFG, while the environmental factors related to residential latitude (e.g. ambient light, average temperature, etc.) may significantly modify the carrier phenotype and may in turn be moderated by additional socio-environmental factors. Likewise, location analysis, a technique for discovering, assessing and specifying locations as a variable in complex systems modeling, has been considered in medical genetics evaluation. In a report of a pair of dysmorphic siblings with normal cytogenetic microarray and two long, contiguous segments of allelic homozygosity of unclear significance, the residential history of the parents' families demonstrated longstanding non-migration, which raised the possibility of occult consanguinity. This led to the targeted analyses of recessive disorder genes and eventually the discovery of a novel, homozygous variant of *SH3PXD2B* with a frameshift mutation in both siblings.[11] Somatic mutations, epigenetic changes and personal environment affect the transcriptome and proteome, which manifest as the disease phenotype, that is, its diagnosis, natural history, treatment response, and prognosis. The high-resolution, individualized, geospatially-referenced exposure profiles envisioned through envirotyping will likely provide a powerful tool for precision medicine.

The fledgling field of envirotyping faces several challenges. It is difficult to reconstruct historical life paths at any meaningful level of resolution, a confound that has plagued efforts to infer causality in retrospective environmental exposure studies, and much work is needed before the utility of envirotyping justifies the potential costs. As with genotyping, there will also always be concerns over data privacy and equity for marginalized populations. The scientific community also lacks clear consensus on the details of data ownership and informed consent procedures for future, unanticipated studies using data that is inherently filled with personal identifiers. Nevertheless, envirotyping has the potential to enhance current precision medicine efforts by integrating robust environmental profiles with individual genotypes, thus further connecting the dots between genotype and phenotype. We hypothesize that genotype/envirotype modeling of diseases will outperform the traditional genotype alone in predicting disease phenotype and management outcome. As the American public increasingly embraces wearable technology and our environmental sensing capabilities inch closer to providing real-time data, it behooves us to work across disciplines to accelerate realizing the promise of precision medicine.

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