Published in final edited form as:

JAMA. 2016 January 26; 315(4): 343–344. doi:10.1001/jama.2015.18359.

Ushering Hypertension Into a New Era of Precision Medicine

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Approximately 80 million US adults have hypertension, and hypertension remains a leading risk factor for stroke and cardiovascular disease.[1] In 2009–2010,48% of treated hypertensive patients in the United States were taking more than 1 drug, and blood pressure remained uncontrolled among 40% of those receiving drug treatment.[1] Current guidelines for prevention and treatment of hypertension are based on observational studies in populations and clinical trials in large groups of patients. Precision medicine and epigenetics are 2 emerging and complementary strategies that have the potential to alter clinical approaches to understanding and treating hypertension. Both approaches have the goal of more effective hypertension control by providing personalized targets for preventive and therapeutic interventions.

Precision Medicine

In 2011, the US National Research Council introduced a more expansive and comprehensive concept of precision medicine, based on the assumption that an individual's genomic and epigenomic determinants will enable the personalization of appropriate preventive and therapeutic interventions. Recently articulated by President Obama and endorsed by the National Institutes of Health (NIH), the Precision Medicine Initiative is intended to develop new approaches for detecting, measuring, and analyzing a wide range of biomedical information, including molecular, genomic, cellular, clinical, behavioral, physiological, and environmental parameters. NIH has recently announced new funding opportunities for precision medicine research initiatives.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Kotchen reports receipt of a stipend for serving as co-executive editor of the *American Journal of Hypertension*. The other authors report no disclosures.

Author Contributions: Drs Kotchen and Liang contributed equally to the preparation of this article.

Current efforts in precision medicine focus primarily, often exclusively, on genome sequences. This approach is likely to be productive for congenital disorders and diseases such as cancer, for which a small number of genome sequence variations appear to play a major role in individual patients. Oncology is currently a focus of the Precision Medicine Initiative because of the prevalence of cancer, the recognition of unique genomic signatures of an increasing number of cancers, and the potential benefit of genetically targeted therapies. Genome sequences alone, however, do not account for environmental and lifestyle factors that also contribute to common complex diseases such as hypertension, heart disease, and type 2 diabetes. In these disorders, the effects of genome sequence variations may be small, and the number of variations in any single individual may be large.[2]

Addressing all areas of health, including complex diseases, is a longer-term goal of the Precision Medicine Initiative. Relevant to this goal, epigenetic profiling, ie, analysis of epigenetic marks in individual patients, may be a complementary strategy to physiological profiling and DNA sequencing for targeting hypertension prevention and treatment strategies.

Epigenomics

Epigenomics is the study of epigenetic marks on a genome or near-genome scale. Epigenomes capture the biological influence of environmental and lifestyle factors in a quantifiable and analyzable molecular form. Epigenetic dysregulation has emerged as a hallmark of several complex pathologies, including hypertension, other cardiovascular disease risk factors (eg, smoking, diabetes, aging), cardiovascular disease, and all-cause mortality. Epigenetic modifications may influence changes in the protein products of genes and can be transmitted through mitosis or meiosis without altering the DNA sequence.[3] These modifications are orchestrated by several molecular processes, including the following[4]:

- Methylation at specific sites in DNA influences gene expression by directly interfering with transcriptional factor-binding complexes or by inducing histone modifications mediated by methyl CpG–binding proteins.
- Posttranslational histone modifications contribute to the regulation of gene expression through chromatin modifications.
- Noncoding RNAs also contribute to epigenetic regulation of gene expression. Micro-RNAs (miRNAs), for example, can regulate the expression of hundreds of genes.
- Three-dimensional conformation of chromatin, which may be in part determined by some or all of these factors, has an important role in the regulation of gene transcription including regulation by DNA elements located far from the gene or even on a different chromosome.

Epigenetic changes may be cell-type specific and reversible and can arise throughout life from early embryos to old age. In model organisms and to a lesser extent in humans, the consequences of environmental exposures and epigenetic variants can be transmitted for at least several generations.[5] Epigenomic features that involve covalent modifications, such as DNA methylation, may better reflect cumulative effects of environmental and lifestyle factors than expression profiles that are subject to transient changes.

Application to Hypertension

Hypertension is not a homogeneous disorder, and strategies to improve hypertension control may involve using specific therapies for individual patients. Hypertension-related mechanisms differ among subgroups of patients, and blood pressure responses to different classes of antihypertensive agents vary among individual patients. The concept of physiological profiling to guide the selection of specific classes of antihypertensive agents for individual patients has the potential to increase the effectiveness of the drugs. For example, in the 1970s, based on standardized measurements of plasma renin activity, Laragh et al proposed a vasoconstrictor volume analysis for understanding and treating hypertension.[6] Although acceptance of renin-guided treatment of hypertension is limited, the attempt to direct antihypertensive therapy to a physiological phenotype is an important concept for the treatment of hypertension. Other researchers have documented the value of noninvasive hemodynamic monitoring as a guide to selecting an initial antihypertensive drug. Analysis of the epigenomes of individual patients is a potential approach for building on these earlier efforts and possibly realizing the goals of precision medicine for hypertension.

Several challenges contribute to the difficulty of identifying the epigenetic determinants of hypertension and cardiovascular disease. Specific environmental exposures may be difficult to identify and quantify and may have small effects. There is also the potential for reverse causality. Because of its lability, blood pressure is a difficult phenotype to accurately assess. Further, hypertension may not be a discrete phenotype. Based on epidemiologic evidence and results of clinical trials, definitions of hypertension, prehypertension, and targets for blood pressure control have useful clinical relevance. However, as articulated by Pickering more than half a century ago: “…the practice of making a sharp division between normal and pathologically high pressure is entirely arbitrary and is in the nature of artifact. Essential hypertension represents the upper end of a distribution curve showing continuous variation, with no definite evidence of two populations.”[7]

Knowledge about the role of epigenetic modifications in hypertension and cardiovascular disease is fragmentary, inconsistent, and largely unexplored. Most studies of epigenetic associations of hypertension in humans have focused on gene-specific modifications.[8,9] However, the focus of cardiovascular epigenetics is shifting from candidate regions to epigenome-wide studies. To date, there are few analyses of genome-wide methylation studies in human hypertension. Results are conflicting and are based on cross-sectional studies in small numbers of study participants, thereby limiting causal inferences.

In summary, precision medicine that incorporates epigenetic analysis (Box) is a potentially powerful approach for evaluating the influence of environmental and lifestyle modifications on the heritability of hypertension and for personalizing patient care. In the long term, these approaches may lead to the development of new targets for the more effective prevention and treatment of hypertension. However, translation into the clinical arena is in its infancy. Clinical translation will require convergence, coordination, and integration among multidisciplinary teams with expertise in laboratory, clinical, and population-based research, as well as in computational and modeling methods.

Box

Integrated Strategies for Epigenetic Profiling

- Identification of epigenetic mechanisms that are sustained, transmitted across generations, and reversible
- RNA profiling to evaluate the influence of epigenetic changes on gene expression
- Integration of DNA sequence variation, epigenetic changes, and gene expression information
- Studies in animal models and in vitro studies with cell lines specific to the disease
- Clinical studies with detailed phenotyping and collection of tissues relevant to the disease
- Epidemiologic studies in large populations, cohort studies, and replication studies

Acknowledgments

Funding/Support: The authors acknowledge grant support from the American Heart Association (15SFRN23910002) and the National Institutes of Health (UL1TR001436 and HL-082798).

Role of the Funder/Sponsor: The funding sources had no role in the preparation, review, approval, or decision to submit the manuscript for publication.

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