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EDITORIAL COMMENT

O tempora, o mores

The Age We Live In, Machine Learning, Hypertension, and Primary Aldosteronism*

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Hypertension (HTN) is one of the leading causes of overall morbidity and mortality in the world.[1] Most patients are diagnosed with essential HTN, and secondary HTN accounts for up to 10% of the cases and is mainly due to kidney disease, vascular abnormalities, and metabolic disorders, such as diabetes.[2] Primary aldosteronism (PA) accounts for up to 6% of primary care patients with HTN and may be responsible for as much as 10% to 15% of referral cases with difficult to control HTN.[3] In the past 30 years, genetic causes of PA have been found from the chimeric *CYP11B1/CYP11B2* genes in glucocorticoid-remediable hyperaldosteronism, to pathogenic variants in the *KCNJ5*, *ATP1A1*, *ATP2B3*, *CACNA1D*, *CACNA1H*, *CLCN2*, and *CTNNB1* genes, rarely in the germline and mostly in the somatic state, within the aldosterone-producing adenoma (APA) tissue only.[4] Even for somatic mutations, genetics clearly plays a role in the development of PA, as recent studies in Black individuals in the United States showed.[5] The genetic cause of PA, germline, somatic, or simply predisposition, is important not only for counseling, medical treatment, or prognosis, respectively, but also to decide who among the patients might benefit from surgery. Yet, the latter requires either invasive procedures or it is impossible for some patients who may receive inadequate medical therapy for years.

The study by Chen et al[6] published in this issue of *JACC: Asia* uses machine learning models to identify APAs with *KCNJ5* mutations among patients with PA using baseline characteristics and routine blood and urine tests preoperatively. The study, the first of its kind, needs to be confirmed in a larger dataset and population, but it is characteristic of the changes we see happening now every day in the practice of medicine.

As Cicero said, "*O tempora, o mores! Nihil nimium vetus proferam,*" which roughly translates to "*What an age we live in! Yet I will speak of what is not very ancient history*!"[7]

Indeed, the story of *KCNJ5* in APAs is not that old: it is only 11 years since we published the first *KCNJ5* mutations in our patients,[8] new phenotypes associated with *KCNJ5* defects, including somatic mosaicism for defects of the same gene in a patient with PA and adrenocortical hyperplasia, and a novel *KCNJ5* variant associated with cyclical Cushing syndrome in childhood,[9-13] findings that we reviewed recently.[14]

In this short time, it became clear that new protocols were needed to identify patients with PA who would benefit most from surgical intervention, especially those with *KCNJ5* defects.[15] The first applications of machine learning in the diagnosis and management of PA were, as expected, where the data were more robust, such as in steroid profiling[16] and proteomics.[17] Since the publication of the first study to use machine learning and artificial intelligence in PA using common clinical and biochemical data,[18] there have been now almost a dozen such reports including the latest ones,[19,20] yet none that specifically accessed a particular genotype, such as the study by Chen et al.[6]

The study by Chen et al[6] is not only well done (as far as methods is concerned), but also pioneering in

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its concept: linking a particular genetic alteration to a specific phenotype that causes aldosterone excess and may be treated surgically. And, of course, there are many more genes involved and, thus, we are looking forward to what comes next almost certainly: using similar approaches to differentiate genetic defects and guide treatment and prognosis of patients with PA.

Applying machine learning to benefit patients with PA and HTN is a welcome development in a field that has seen extraordinary scientific advances in the past 2 decades, without clear clinical benefit: deciding who will benefit from surgery remains challenging to date. Almost certainly, similar methods (ie, artificial intelligence) will be used for the identification or the design of molecules that may be used therapeutically (instead of surgery) especially for those patients with PA harboring genetic defects in smaller lesions. Prediction models may be able to identify who has what pathogenic variants in the *KCNJ5*, *ATP1A1*, *ATP2B3*, *CACNA1D*, *CACNA1H*, *CLCN2*, or *CTNNB1* genes and provide the respective molecular therapy.

Indeed, "*what an age we live in!*" A marvelous age in medical discoveries and a true revolution in the practice of medicine!

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Dr Stratakis serves as a consultant to ELPEN, SteroTx, and Lundbeck pharmaceuticals; has received a research grant from Pfizer for the study and treatment of acromegaly; and holds patents on the defects and function of the PRKAR1A, PDE11A, and GPR101 genes.

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