EDITORIAL

Questions, Behavior, and Responsibility in Precision Medicine

We are living in a unique time in history as the scientific community undergoes changes in behavior and technology to enable impactful discoveries from large data sets and clinical trials that include precision medicine. Impactful discoveries may arise from asking the most fundamental question through the eyes of a patient and choosing a new method of analysis. In this issue of Circulation, 2 new studies asked fundamental questions: “How does one use precise genetic information about an individual to predict a stroke?” and “How does one use precise genetic information about an individual to predict drug-induced long QT syndrome?”

These 2 studies illustrate how behavioral changes in our community embracing data sharing and precision medicine clinical trials help solve these questions. Importantly, behavioral change is fundamental to opening the gates and delivering individuals precise knowledge about their health and precise solutions to prevent or cure a cardiovascular event or stroke.

Atrial fibrillation affects 33.5 million individuals globally. The heritability of lone atrial fibrillation has been well established in the literature. Individuals with atrial fibrillation are at a significantly increased risk of stroke. However, many individuals with atrial fibrillation choose to avoid oral anticoagulation for reasons of healthcare costs, time, or uncertainty. These individuals may not connect atrial fibrillation with the significantly increased risk of stroke and may not recognize the importance of starting treatment to decrease the risk of stroke.

From a healthcare perspective, identifying individuals at risk of stroke and providing preventive care has been challenging. In this issue of Circulation, Lubitz and a team of cross-disciplinary investigators sought to determine whether an individual’s genetic risk for atrial fibrillation could help predict the risk of cardioembolic stroke.

Lubitz and colleagues included just over 18,000 individuals of self-reported European ancestry ranging from 58 to 75 years of age with the proportion of women ranging from 47% to 52% from all included cohorts. During 5 years of follow-up, 5.5% of the individuals developed incident atrial fibrillation. The atrial fibrillation genetic risk score for each individual was calculated by summing the dosage of each atrial fibrillation risk allele carried (ranging from 0–2) weighted by the natural algorithm of the relative risk for each single-nucleotide polymorphism (SNP). The 719 SNPs used in the study were derived from the pruning of 2.2 million HapMap variants included in a prior independent meta-analysis of genome-wide association studies for atrial fibrillation from the AFGen consortium (Atrial Fibrillation Consortium) and then further narrowed. The genetic risk score was tested on 5 prospective studies. The association between AF genetic risk and stroke was also examined in MGH-GASROS (Massachusetts General Hospital Genes Associated With Stroke and Outcomes Study) and referent individuals from the Myocardial Infarction Genetics Consortium.
Lubitz and coworkers\textsuperscript{1} found that the genetic risk score for atrial fibrillation was associated with 5-year risks of new-onset atrial fibrillation after adjustment for clinical risk factors. However, the added benefit of the genetic risk score after adjustment for clinical risk factors was low.\textsuperscript{1} This finding is in agreement with previous work.\textsuperscript{5–8} Lubitz and colleagues also provide evidence suggesting that the genetic risk score for atrial fibrillation is associated with risk for cardioembolic stroke. This study, together with previous work, suggests that the SNPs in the DNA associated with atrial fibrillation may help to identify the underlying mechanisms of stroke. In other words, mutations in genes or proteins that are currently associated with atrial fibrillation may also alter molecular signaling pathways that affect risk of stroke. Overall, the inclusion of multiple cohorts, inclusion of all analyses, and ability to bring cross-disciplinary communities together are strengths. Limitations are noted by the authors and are the barriers of the cohorts themselves (European ancestry only) and the lack of other biomarkers besides DNA.

In the second study in this issue of \textit{Circulation}, healthy individuals in the community agreed to participate in genetic testing and a randomized, double-blind, crossover trial that included 3 QT-prolonging drugs to test whether underlying genetics predict response to drug-induced long QT syndrome.\textsuperscript{2} In the study from Strauss and colleagues,\textsuperscript{2} healthy individuals consented to a study to help understand the impact of underlying genetics on the risk of developing drug-induced long-QT syndrome. The participant/researcher partnership is critical for the success of these new clinical trials in the era of precision medicine.

Drug-induced long-QT syndrome experienced by some individuals is associated with torsade de pointes. Identifying individuals at risk for drug-induced long-QT syndrome or torsade de pointes has been challenging. The incidence of torsade de pointes is low, and only a fraction of individuals who develop torsade de pointes have preceding drug-induced long-QT syndrome. However, the number of different drugs (ie, antiarrhythmics, antibiotics, antiemetics, calcium channel blockers, antihistamines) listed as being associated with either torsade de pointes or drug-induced long-QT syndrome continues to grow (http://www.torsades.org).

Strauss and colleagues\textsuperscript{2} enrolled 22 healthy individuals (17 self-described whites, 4 blacks, and 1 Asian) to assess the role of underlying genetics in active response to drug-induced long-QT syndrome. The individuals in the study were 18 to 35 years of age, had no evidence of cardiovascular disease or unexplained sudden cardiac death in their family history, had a baseline QT of <450 milliseconds (if male) and <470 milliseconds (if female), and exhibited <12 ventricular ectopic beats during a 3-hour continuous recording. Each subject received a single dose of 3 different drug treatments (dofetilide 500 \(\mu\)g, quinidine sulfate 400 mg, and ranolazine 1500 mg, and verapamil hydrochloride 120 mg) with a 7-day washout period between each. (Verapamil did not prolong QTc at the dose administered and was not included in the analysis.) Continuous ECGs were recorded over 24 hours after dose.

The genetic QT score was derived from 61 SNPs chosen from a previous expanded meta-analysis performed by the QT Interval–International GWAS Consortium in ≈76000 individuals of European ancestry.\textsuperscript{9} The large consortium of European ancestry is a potential strength of the study from the standpoint of deriving the genetic QT score for the 17 self-described white individuals in the study by Strauss et al. The genetic QT score lacks the same strength for the black population given that only 15% of the SNPs used in the genetic QT score were replicated in a much smaller cohort (13105 individuals of African ancestry in the CARE-COGEN consortium (Candidate-Gene Association Resource Consortium and Continental Origins and Genetic Epidemiology Network)).\textsuperscript{9,10} Combined with the fact that only 4 blacks and 1 Asian were enrolled in the Strauss et al study, the data in these 2 minority populations are preliminary at best. The authors themselves note this fact.

In the 17 white individuals (8 men and 9 women), the genetic score explained \(\approx\)27% of the variability in baseline QTc \((P=0.03)\). Twenty-seven percent is high compared with the previous study from which these 61 SNPs originated\textsuperscript{9} and a second heritability analysis.\textsuperscript{11} The reasons for this are not entirely clear. Baseline QTc did not predict drug-induced QTc prolongation for any of the drugs in the 17 white subjects. However, the European genetic score explained between 23% and 30% of the variability in response to dofetilide, quinidine, and ranolazine. The genetic QT score significantly predicted drug-induced torsade de pointes in a second independent sample of 216 cases and 771 controls \((P=1\times10^{-7})\). These findings suggest that underlying genetics may be a valuable addition to predicting drug-induced QT prolongation. Future studies in larger sample sizes are needed to replicate these findings.

The randomized clinical trial design chosen by Strauss et al to assess the role of underlying genetics in active response to drug-induced long-QT syndrome is a step in the right direction as we look toward the future. One could argue that the young, healthy subjects are not representative of the population. However, alternative study designs to begin to test this hypothesis may put subjects at unnecessary risk and complicate the interpretation of the analysis. Studies such as these are important first steps in actively testing the role of underlying genetics in drug-induced long-QT syndrome. Moreover, deepening our understanding of how genetic mutations lead to QT prolongation provides keys to unlocking new therapies.
In conclusion, both studies exemplify our global responsibility as members of the scientific community. The first study provides an example of how consortia building and a commitment to open science and working together provide the greatest impact for science. The second study provides an example of how a focus on participants and their willingness to participate in clinical trials such as this with a precision medicine component will be one of the new approaches from which we will learn and advance science. The American Heart Association is proud to work in partnership with many scientists, clinicians, institutions, and partners around the globe to support global and social responsibility to excellence.

DISCLOSURES
None.

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FOOTNOTES

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