Polygenic risk scores in the clinic: a case for stroke survivors

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Genome-wide association studies (GWAS) have provided evidence for a polygenic architecture of most common disorders[1]. By accumulating power with increasing sample sizes and increasing representation across ancestries, GWASs have detected thousands of loci across the genome associated with complex vascular diseases including stroke[2]. Polygenic risk scores (PRS) aggregate this information at an individual level by adding the number of genetic risk variants a person carries, weighted by the effect sizes from GWASs. Since their first description, PRSs were considered a means toward the clinical implementation of GWAS-derived data by consolidating complicated genomic data into a simple numerical biomarker representing an individual's genetic risk for a disease[3]. Similar to other complex traits, PRSs for ischemic stroke and intracerebral hemorrhage are strongly associated with risk of incident events in population-based settings and independently of clinical risk factors, such as hypertension.[2,4] However, despite innovations in PRS construction and improvements in their predictive ability, there has been to-date no strong evidentiary support for their use in clinical and public health practice.[5]

Whereas PRSs have been extensively studied in population-based research settings, covering this translational gap would require testing PRSs in prospective clinical studies and randomized trials. In an article published in this issue of *Neurology*, Acosta et al take a key step in this direction by exploring the added value of a PRS in a setting familiar to routine neurological practice[6]. Stroke survivors represent a unique patient group with great potential for implementing preventive approaches due to the established high absolute risk for stroke recurrence, disability, dementia, and acute coronary events. Lowering blood pressure (BP) is one of the key goals for secondary stroke prevention, but despite the best of our efforts, 37% of stroke survivors do not achieve appropriate BP control[7]. A PRS for hypertension is associated with cardiovascular risk independently of measured BP, bolstering the case for identifying high-risk individuals in the general population[8].

Here, the authors explore whether a PRS associated with elevated BP is associated with uncontrolled BP among stroke survivors. They analyzed a dataset of 5,490 ischemic and hemorrhagic stroke survivors from the population-based UK Biobank study (mean age 61 years, 41% females) and constructed PRSs for systolic and diastolic BP based on an existing GWAS, comprised of 732 variants. They found that genetic predisposition to high BP is associated with uncontrolled (systolic BP above 140 mmHg or diastolic BP > 90 mmHg at enrollment) and resistant hypertension (defined as systolic BP above 140 mmHg or diastolic BP >90 mmHg despite being on 3 BP medications of different classes, or four or more BP lowering medications of different classes regardless of BP levels) in models adjusted for age, sex, and vascular risk factors. The authors replicated their results in 1,750 individuals from the Vitamin Intervention for Stroke Prevention (VISP) trial.

The study covers a grey area between the development of a PRS in general population cohorts, and their implementation in clinically relevant populations with higher baseline absolute risk. The proportion of individuals at the low versus high quantile of the PRS with uncontrolled hypertension was 42.8% versus 57.2% and with resistant hypertension 3.9% versus 11%, respectively. This could be a clinically relevant difference. As such, assessing the PRS for hypertension at a clinical setting following diagnosis of a stroke could augment identifying individuals that would benefit from more aggressive antihypertensive treatment despite normal BP values.

Similar applications of PRSs in clinically relevant scenarios are becoming more common in stroke research (**Figure**). O'Sullivan et al showed that among patients with atrial fibrillation, an integrated tool of clinical risk factors and a PRS could improve prediction of ischemic stroke, when compared to the currently recommended risk tool (CHA2DS2-VASc).[9] Similarly, in a recent analysis, we provided evidence that a PRS can improve prediction of intracerebral

hemorrhage among individuals on anticoagulant medications. Adding a point of high genetic risk to a modified version of the HAS-BLED score led to a score that achieved better risk stratification. This is a clinically relevant population where weighting the benefits of anticoagulation for preventing ischemic events against bleeding risk is very important.[10]

Specific methodological limitations should be noted. First, the study was nested with the UK Biobank and stroke cases were ascertained either through self-report or electronic health records long after they suffered a stroke. As such, this population may not be comparable to a population of stroke survivors, who in most occasions are screened for vascular risk factors shortly after the stroke event. Second, BP was only assessed once in both the UK Biobank and VISP and as such, there might be some ascertainment error in the definitions of uncontrolled and resistant hypertension. Third, the study is restricted to individuals of European ancestry. Increasing the generalizability of genetic findings to other ancestries will require better representation not only in studies of genomic discovery, but also in studies of clinical validation.

In conclusion, this study highlights the potential of transitioning PRSs from primary risk assessment tools in population-based settings to useful risk stratification tools in clinically relevant scenarios. Extensive evidence now suggests that PRSs can provide useful risk information on top of variables typically collected in clinical practice. As such, clinical researchers should embrace PRSs as potentially useful biomarkers and study their properties in diverse settings. Necessary next steps include testing associations of such genetic scores not only with intermediate endpoints, such as uncontrolled and resistant hypertension, but also with clinical outcomes, such as stroke recurrence, disability, dementia, and death. Ultimately, the ability of PRSs to influence decision-making would require their implementation in clinical trials, which would test personalized secondary preventive approaches according to individual

background genetic risk. Insights from such trials could guide the development of focused preventive strategies for ameliorating the risk of adverse outcomes among stroke survivors.

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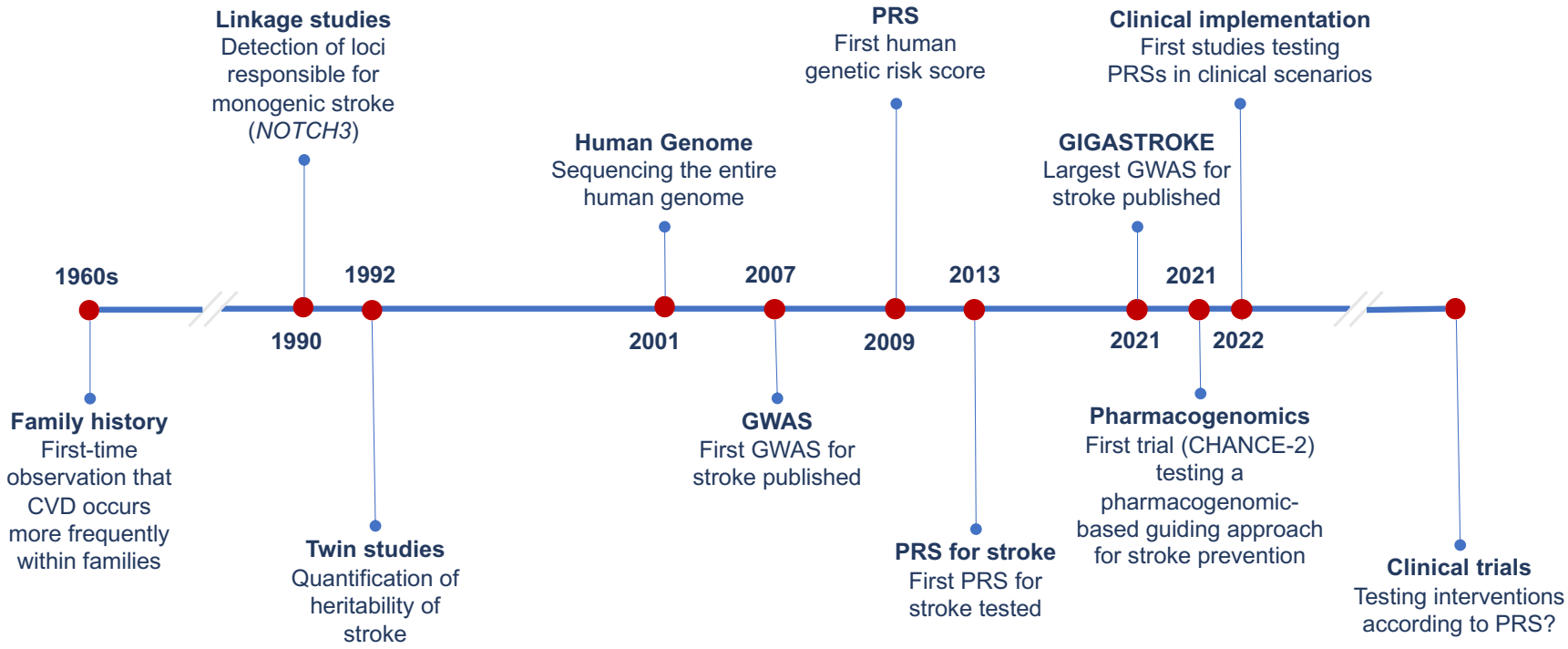

Figure. Milestones in the history of discoveries in stroke genetics up to the development and implementation of polygenic risk scores.