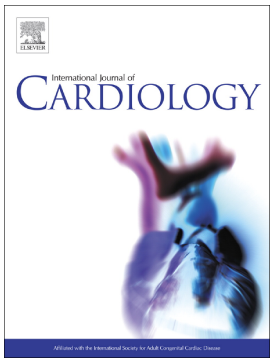

Refining ischemic stroke risk using combined polygenic scores. Are we ready for the clinical use?

Davide Ramoni, Amedeo Tirandi, Alessandro Scuricini, Federico Carbone, Fabrizio Montecucco, Luca Liberale

PII: S0167-5273(24)00628-4

DOI: https://doi.org/10.1016/j.ijcard.2024.132034

Reference: IJCA 132034

To appear in: *International Journal of Cardiology*

Received date: 2 April 2024

Revised date: 4 April 2024

Accepted date: 7 April 2024

Please cite this article as: D. Ramoni, A. Tirandi, A. Scuricini, et al., Refining ischemic stroke risk using combined polygenic scores. Are we ready for the clinical use?, *International Journal of Cardiology* (2023), https://doi.org/10.1016/j.ijcard.2024.132034

Refining ischemic stroke risk using combined polygenic scores. Are we ready for the clinical use?

Davide Ramoni[1], Amedeo Tirandi[1], Alessandro Scuricini[1], Federico Carbone[1,2], Fabrizio Montecucco[1,2] and Luca Liberale[1,2]

Affiliations:

[1] Department of Internal Medicine, University of Genoa, 6 viale Benedetto XV, 16132 Genoa, Italy.

[2] IRCCS Ospedale Policlinico San Martino Genoa - Italian Cardiovascular Network, Largo Rosanna Benzi 10, 16132, Genoa, Italy.

Corresponding author: Liberale Luca, MD, PhD, FESC. First Clinic of Internal Medicine, Department of Internal Medicine, University of Genoa, 6 viale Benedetto XV, 13132 Genova. Tel: +39 010 353 8694; Fax: +39 010 353 8638; E mail: luca.liberale@unige.it

Author contribution: Ramoni D., Scuricini A., and Tirandi A. wrote the full paper; Carbone F., Liberale L., and Montecucco F. supervised the entire work. All authors have read and approved the final manuscript.

Keywords: Ethical concerns; Ischemic stroke; Polygenic score; Population-wide screening; Risk assessment.

Running head: Polygenic score for risk assessment of ischemic ictus.

Abbreviation: IS, ischemic stroke; PGS, polygenic score.

This editorial comments on the manuscript by Huang S. and colleagues, recently published in the International Journal of Cardiology (1). We focus here on the still challenging application of polygenetic score for improved risk assessment of ischemic stroke (IS) in clinical practice, especially about its feasibility and ethical concerns.

IS is an age-related disease that continues to pose a significant burden of disability in our society. As our population ages, finding novel methods to prevent this condition become increasingly important. Over the past decades, genomic technologies have enabled the screening of various genetic polymorphisms. These polymorphisms can be utilized to stratify an individual's risk for specific diseases. In recent years, polygenic scores (PGSs) have demonstrated clinical utility in creating preventive intervention strategies across various disease categories (2,3). For example, polygenic risk scores have yielded intriguing findings related to the evaluation of type 2 diabetes mellitus, coronary heart disease (4) and venous thromboembolism (5). By incorporating patients into screening programs, early identification of potential future diseases becomes possible. This, in turn, facilitates the adoption of preventive measures and the initiation of targeted therapies at very early stage of the disease or even for preventing it. Regarding IS, the evaluation of PGSs has shown promising results (6). Thus, similar to what has been observed for cardiovascular disease, PGs might find application also for risk stratification in patients with IS (7).

Overview and outlook on polygenetic score for risk assessment of ischemic stroke.

In their study, Huang S. et al. provided novel insights regarding the theoretical feasibility of creating a risk score for IS using polygenic assessment (1). The study involved a large cohort of patients (479,576) from the UK Biobank, with no prior history of ischemic stroke at enrollment. During 12.5 years of follow-up, 8,374 patients experienced an ischemic stroke

event. The authors demonstrated that a combined model, integrating both clinical factors and PGSs related to IS and IS-associated diseases, significantly improved risk stratification, with an AUC of 0.725 and a p-value < 0.001. This study contributes valuable knowledge to the field of IS risk stratification and underscores the importance of integrating clinical evaluation with genetic risk assessment to potentially prevent the burden of ischemic stroke.

However, the clinical utility of PGSs remains limited at present. Population-wide screening has the potential to enable personalized prevention and early detection of high-risk individuals for IS prior to symptom onset. However, technical limitations and ethical dilemmas still need to be addressed. Ideally, the most effective use of PGS would require a large-scale genetic study conducted on patients before they actually experience an ischemic stroke. Firstly, an economic evaluation must be considered. Although the cost of a single genome analysis for PGS calculation appears to be less than $100, screening a large population could represent quite a demanding task in terms of benefit-to-cost analysis, given the substantial portion of screenable individuals, as an example the working-age population, which globally stood at 65% in 2022 (8). The resulting overall expense bears accessibility and equity challenges for genetic tests, impacting both insurance-based and universal healthcare systems. Large-scale screening for risk stratification presupposes, ideally, the availability of preventive measures. Therefore, it is imperative to ensure accessibility to these interventions for the entire population before implementing genetic screening and disclosing genetic information to individuals. Moreover, many diseases related to IS, such as diabetes mellitus and hypertension, are typically chronic conditions. Managing these pathologies presents challenges in preventing their complications, as treatment responses can vary significantly among patients – likely influenced by genetic, environmental, and lifestyle factors. Furthermore, possible concerns may arise from the potential discovery of unexpected

or incidental findings during genome screening, posing ethical dilemmas for both patients and physicians (9). Actually, even if a genetic predisposition is found, there is currently no precise method to predict the exact timing of disease onset or even its inevitability. Environmental factors interact with genetic risk, contributing to the manifestation of specific diseases. Consequently, genetically screened individuals may experience a psychological burden upon learning about their risk for a certain disease in the future. Considering the potential risks, it is crucial to deliberate whether genetic test results should be disclosed to third parties, such as family members, to prevent discrimination and other adverse consequences. Therefore, adequate genetic counseling is essential for the ethical validity of genetic tests (10). To address these complexities, we propose a clinical flowchart that explores the use of polygenic approaches for risk assessment in routine practice as showed in *Figure 1*.

In conclusion, overcoming the abovementioned ethical and practical issues is crucial in order to benefits from the use of PGS in clinical practice. In fact, a rational knowledge of genetic predisposition can favor the development of a more precise and tailored medicine, paving the way toward an amelioration of life years in both quantity and quality. The work by Huang S. et al. represents a step in the future of clinical disease prevention, although further studies are needed to explore clinical utility, guided by established standards and regulation to prevent unethical misconduct. Using joint clinical/PGS scores alongside newer and hopefully more efficient treatments may represent the future of clinical medicine.

Declaration of interests

LL is coinventor on the International Patent (WO/2020/226993) filed in April 2020 and relating to the use of antibodies which specifically bind IL-1α to reduce various sequelae of

ischemia–reperfusion injury to the central nervous system. LL has received speaker fees outside of this work from Daichi-Sankyo. The other authors have no conflict to disclose.

References:

1. Huang S, Joshi A, Shi Z, Wei J, Tran H, Zheng SL, et al. Combined polygenic scores for ischemic stroke risk factors aid risk assessment of ischemic stroke. Int J Cardiol. 21 March 2024;131990.

2. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nat Rev Genet. September 2018;19(9):581–90.

3. Truong B, Hull LE, Ruan Y, Huang QQ, Hornsby W, Martin H, et al. Integrative polygenic risk score improves the prediction accuracy of complex traits and diseases. Cell Genom. 12 March 2024;100523.

4. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet. September 2018;50(9):1219–24.

5. Ghouse J, Tragante V, Ahlberg G, Rand SA, Jespersen JB, Leinøe EB, et al. Genome-wide meta-analysis identifies 93 risk loci and enables risk prediction equivalent to monogenic forms of venous thromboembolism. Nat Genet. March 2023;55(3):399–409.

6. Hachiya T, Kamatani Y, Takahashi A, Hata J, Furukawa R, Shiwa Y, et al. Genetic Predisposition to Ischemic Stroke: A Polygenic Risk Score. Stroke. February 2017;48(2):253–8.

7. Abraham G, Rutten-Jacobs L, Inouye M. Risk Prediction Using Polygenic Risk Scores for Prevention of Stroke and Other Cardiovascular Diseases. Stroke. August 2021;52(9):2983–91.

8. Gerland P, Hertog S, Wheldon M, Kantorova V, Gu D, Gonnella G, et al. World Population Prospects 2022: Summary of results. United Nations. Department of Economic and Social Affairs. Population Division. 2022.

9. Christenhusz GM, Devriendt K, Dierickx K. To tell or not to tell? A systematic review of ethical reflections on incidental findings arising in genetics contexts. Eur J Hum Genet. March 2013;21(3):248–55.

10. Godino L, Turchetti D, Jackson L, Hennessy C, Skirton H. Impact of presymptomatic genetic testing on young adults: a systematic review. Eur J Hum Genet. April 2016;24(4):496–503.

Figure Legend

Figure 1. Flow-chart for clinical use of polygenic score for ischemic stroke risk stratification

Potential clinical application of polygenic score in patients before the onset of ischemic stroke starting from a background analysis to an eventual specific intervention and follow-up. IS: ischemic stroke.

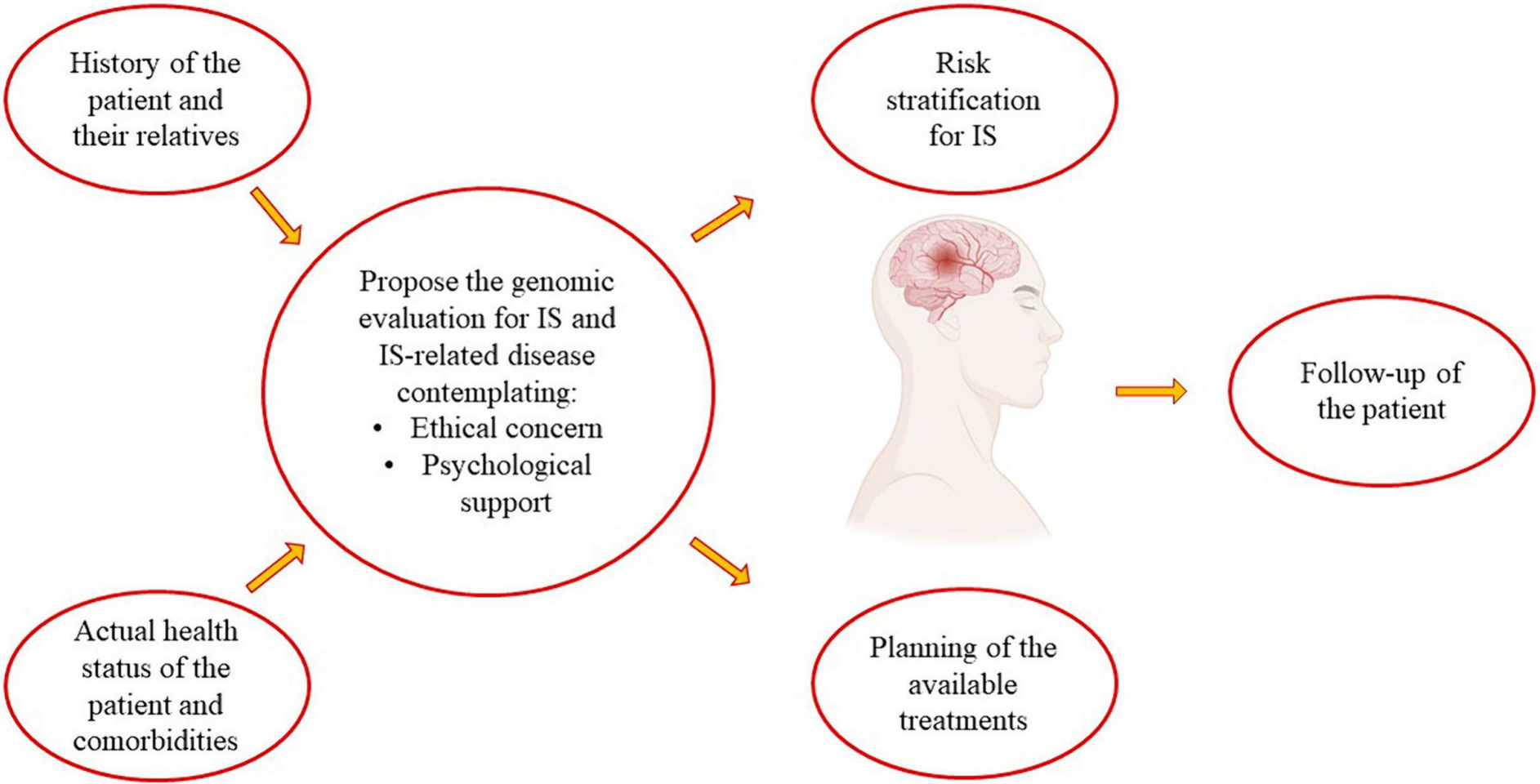
History of the patient and their relatives
Actual health status of the patient and comorbidities
Propose the genomic evaluation for IS and IS-related disease contemplating:
• Ethical concern
• Psychological support
Risk stratification for IS
Planning of the available treatments
Follow-up of the patient

Figure 1