PREDICTION OF VENOUS THROMBOEMBOLISM IN AVERAGE-RISK YOUNG CANDIDATES FOR ORAL CONTRACEPTIVE USE: TO GENOTYPE, OR NOT TO GENOTYPE, THAT IS THE QUESTION

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Dear Editor,

Lo Faro and colleagues propose the systematic use of a GWAS-based polygenic risk score (PRS) to identify women with an increased likelihood of venous thromboembolism (VTE) before prescribing combined oral contraceptives (COC).[1]

However, the genetic contribution to most common diseases, including cardiovascular events, is modest, and PRSs generally define only a limited proportion of the genetic component.[2,3] If the predictive power of the proposed PRS, modeled in a highly selected group of volunteers, were to be weaker than expected when implemented in the actual population, most VTE events would occur in patients not assigned to the highest risk category. Thus, the approach hypothesized by Lo Faro *et al*.[1] raises several questions.[2,3]

1. As monogenic and polygenic risks are largely independent, what proportion of young average-risk women has a PRS high enough to be considered equivalent to carrying a heterozygous factor V Leiden (FVL) or prothrombin factor II (PTM) mutation, and what would be the specific COC-associated VTE burden attributable to polygenic variants?

2. Because standard genome-wide genotyping arrays may not well genotype classic monogenic mutations, screening for at least FVL and PTM variants should be performed anyway to predict VTE risk accurately. This test combination would likely exceed the maximum threshold a decision-maker is willing to pay in most European countries. A health-economic assessment is needed to quantify the trade-offs between the utility costs and the magnitude of the potential benefits.[2] Would targeted, rather than systematic, genotyping based on the traditional risk factors be more cost-effective?

3. The notion that PRSs may improve risk prediction because they are largely independent of common risk factors has been questioned.[2,3] It seems unclear how many deaths would be prevented by adding the VTE-PRS to established algorithms based on medical history and clinical variables. Mortality from VTE in women aged 20 to 40 years age

is ~1%. Therefore, the use of COCs containing ethinylestradiol (EE) causes ~1 additional death per 100,000 women each year.[4] The maternal mortality rate in women with unintended pregnancies is ~12 per 100,000.[4] The prolonged use of COCs is associated with considerable and sustained reductions in the risk of ovarian, endometrial, and colon cancers.[4] Would the long-term calculation of comprehensive COC-associated mortality differ substantially, and in which direction, with the use versus non-use of the proposed VTE-PRS?

4. Multiple PRSs for different conditions can be estimated from a single genotyping array. While this may be considered advantageous, it also entails several unresolved ethical, psychological, clinical, legal, economic, and social issues.[2,3] Could unfavorable downstream consequences, including overdiagnosis, be anticipated once women and gynecologists are aware that the potential use of genotyping is not limited to VTE risk prediction?

5. In many countries, PRSs are the subject of research but are not provided by public health services. Implementation of PRSs requires knowledge of genetics, full awareness and understanding of the above issues, and risk communication skills. Suppose private companies will offer direct-to-consumer genetic testing to define VTE risk before COC use, bypassing an updating process that could be very costly and take years. Would more good or harm be done to women and could health disparity issues arise?

6. Finally, COCs are an effective, well-tolerated, and affordable therapy for disabling conditions such as endometriosis.[4] This may change the balance between the potential benefits and harms when COCs are used as a treatment with limited alternative options, and not "just" as a contraceptive method. Would this render VTE-PRS less relevant in specific patient subpopulations?

In our opinion, pilot studies and health economic analyses should be conducted to understand the long-term effectiveness and global costs of VTE-PRS before hypothesizing its clinical implementation.[2]

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