

Genetic testing to identify women at risk of venous thromboembolism with contraceptive pills: evidence- or hope-based tool?

A position paper endorsed by the Working Party on Haemostasis of the Swiss Society of Haematology

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Summary

Combined oestrogen-progestin oral contraceptives cause venous thromboembolism in women of reproductive age. Healthcare providers typically rely on women's characteristics, medical history and family history to select the most appropriate contraceptives, in an effort to reduce risks of venous thromboembolism. This position paper discusses the use of a new prediction tool (Pill Protect[®]), available in Switzerland, which adds genetic profiling to clinical characteristics with the aim of predicting individual contraceptive-related thrombotic risks and individualising contraceptive prescription. After reviewing the available data regarding this tool, we believe that its development and validation process may be incomplete and that it is uncertain whether the use of Pill Protect[®] would lead to better health outcomes. Until we understand the necessarily rigorous scientific validation of this tool, we urge caution to physicians and women who may want to use it.

In Switzerland, about 400 000 women use a combined oestrogen-progestin oral contraceptive (COC). On top of their very efficient contraception, COCs may result in many noncontraceptive benefits, such as predictable menstruation of decreased volume and duration, relief of dysmenorrhoea or endometriosis symptoms, and reduction in risks of endometrial and ovarian cancers [1].

However, the use of COCs also results in well-characterised prothrombotic modifications such as decreased levels of protein S and tissue factor pathway inhibitor, and an acquired resistance to activated protein C [2]. This prothrombotic modification has direct consequences for users of COCs, with a two- to six-fold increased risk of incident pulmonary embolism and deep vein thrombosis, together known as venous thromboembolism (VTE). It can be es-

timated that 60–80% of the 200–480 VTE events occurring in the 400 000 Swiss COC users annually are imputable to the COC [3]. Efforts to promote a better identification of women at high-risk of COC-related VTE are invaluable, as they may lead to more adequate prescription of contraception with less or no thrombogenic influence and perhaps a decrease of these preventable VTE events.

Currently, healthcare providers can modulate the prescription of contraception on the basis of documented VTE risk factors. Recommendations of the Swiss Society of Gynaecology and Obstetrics, similarly to many other guidelines, advise withholding a COC from women with, among other contra-indications, a personal history of VTE, documented thrombophilia or several of the following minor risk factors: family history of VTE, current smoking, >35 years of age, obesity or potential vascular problems (hypertension, diabetes, systemic lupus erythematosus, migraine) [4]. Screening for thrombophilia such as factor V Leiden or G20210A prothrombin mutations is suggested only in the presence of a positive family history for VTE, if the mutation is present in the index case [4]. It must be remembered that, since these mutations are common (prevalence of 5% and 2% among Caucasians of European ancestry), the vast majority of carriers will never develop VTE. Screening may therefore lead to the unnecessary denial of possibly beneficial drugs such as COCs, incremental anxiety for patients and healthcare providers and a negative cost-effectiveness balance. Similarly to Swiss guidelines, the Faculty of Sexual & Reproductive Healthcare (Royal College of Obstetricians and Gynaecologists, United Kingdom), the Haute Autorité de Santé (France) and the Centers for Disease Control and Prevention (USA) do not recommend routine thrombophilia screening before prescribing a COC [5–7].

The type of contraceptive must be tailored to the individual risk of VTE. In individuals with a high risk of COC-related VTE such as those with a personal history of VTE, con-

traceptive methods with no incremental thrombotic risk should be prescribed (progestin-only pills or intrauterine devices). One could even argue that, for women not at high risk of VTE, preference should still be given to these contraceptives or to a COC with a low thrombogenic profile. The progestin part of COCs plays an important role here. A COC with a second-generation progestin (such as levonorgestrel), which has less thrombotic potential than more recent progestins [8], should be the preferred COC for most women.

Recently, we have received mailed marketing information and have attended an oral presentation on Pill Protect[®], presented as a clinically validated test for identifying women at risk of developing deep vein thrombosis under contraceptive pills. As we understand it, Pill Protect[®] uses information from ≈10 common genetic polymorphisms measured in DNA from a saliva sample, and from risk factors for COC-related VTE (body mass index, current smoking, age and family history of VTE), in order to predict absolute risks of VTE associated with various COC preparations in an individual woman. Such predictions are meant to provide women and their physicians with a better understanding of the risks of COC use and may enhance a highly desirable shared decision-making process in this setting.

Excellent performance of this prediction tool is reported, with a positive predictive value (PPV) of 88% and a specificity of 97% at a high-score threshold. In marketing information from Gene Predictis[®] [9], Pill Protect[®] is referred to as a “fantastic breakthrough in women’s care”, “amongst the most welcome tests a gynecologist may dream of” and allows “the prescription of the safest contraception method for each woman”. With such arguments, and given that Pill Protect[®] appears to be reimbursed by Swiss health insurers, it is unlikely that any COC prescribers or any potential oral contraceptive user would want to ignore this promised valuable information.

However, we do not know if the promises of Pill Protect[®] are based on a sound scientific background, and whether its use may lead to better COC prescription and better clinical outcomes. We would like to emphasise several potential limitations of this test and its development:

- Very little scientific information is available on the development and validation of the Pill Protect[®]. Given that no peer-reviewed publication has been made available on this prediction model, it closely resembles a black box, whose results may or may not be rigorous.
- To our understanding, the derivation and validation of this complex tool arise mainly from a secondary analysis from the PILGRIM study (Prof. PE Morange, personal communication) [10]. This retrospective case-control study was conducted in a tertiary centre with expertise in VTE research in Marseille. Cases were consecutive women using a COC with a first documented episode of VTE. Controls were consecutive women using a COC without VTE, but who were referred for thrombophilia screening because of a family history of VTE. Because of this design the associations of environmental risk factors with the risk of VTE were as expected, but those of genetic risk factors were not. For example, obese women and current smokers were at

greater risk of VTE, but women carrying the factor V Leiden or the G20210A prothrombin polymorphisms were not. This paradox is logically explained by the oversampling of women with such minor thrombophilic traits in controls, owing to their family history of VTE. As acknowledged by the authors of the original PILGRIM publication, the findings from the PILGRIM study cannot be extrapolated to the general population, where most women do not have a family history of VTE [10].

- The statistical handling of the derivation and validation of the Pill Protect[®] test may reflect suboptimal methodology. Clinicians and patients are most interested in absolute risks and positive and negative predictive values (PPV: the proportion of participants with the disease among those with a positive test; NPV: the proportion of participants without the disease among those with a negative test). By definition, absolute risks, PPV and NPV cannot be directly calculated from case-control studies, as these depend on the prevalence of disease in the population [11]. We therefore question the validity of the reported PPV of 88% for a score of 20, which would correspond to an unreasonably strong association of the test with the risk of VTE at an accepted annual incidence of VTE among oral contraceptive users of 0.1%, without confidence intervals to inform on the precision of the estimate.
- Based on the available information, we would not agree that Pill Protect[®] is a clinically validated test, as stated by its manufacturer. Risk prediction models have optimistically good performances in their initial derivation cohort [12]. An internal validation using a bootstrapping technique cannot completely address this problem, and a true validation of the Pill Protect[®] requires its testing in an independent sample to confirm its performance (sensitivity and specificity) [13]. We are not aware that such an external validation has been undertaken for Pill Protect[®].
- Of utmost importance, clinicians and patients anticipate that the use Pill Protect[®] would bring incremental value to the standard of care, but there is no evidence to support this, in the absence of any comparative management study.

In view of these possible limitations, in particular the absence of a peer-reviewed publication describing in details the Pill Protect[®] model and the possible lack of replication in an independent cohort, we feel uncomfortable using this test or interpreting its results with our patients.

This position paper is in no way a critique of the effort to implement personalised medicine for the prescription of COCs. In other settings, personalised medicine through genomic measurements has shown promise [14]. This is particularly true in oncology, where biologics may be targeted to tumours carrying specific genetic markers. However, VTE is a complex disease with interactions between multiple genetic factors (thought to explain about half of its variance), of which a minority are known, and acquired/environmental factors. Although genetic testing approaches may in the future produce reliable prediction tools [15], it is known that population-based genetic risk factors may not translate into effective predictive variables in individu-

als [16] and, so far, genetic prediction rules for VTE have been somewhat disappointing. Previous rigorous scientific work has shown that genetic testing improves the risk prediction of first venous thrombosis, with a score combining polymorphisms of factor V (Factor V Leiden), factor II (G20210A), ABO (blood group), fibrinogen and factor XI [17]. Whereas the diagnostic AUC significantly increased with the use of the genetic score in addition to a clinical score, compared with the clinical score only (0.81 vs 0.73 among women using oral contraceptives), the authors acknowledge that the usefulness of this score, if any, is likely restricted to high-risk populations. This is not the case for individual women of reproductive age, who suffer from a low absolute VTE risk (2/10 000 woman-years).

In cardiovascular medicine, other promises of genetic prediction were disappointing at the stage of implementation. Two examples include the use of genetic variants to predict the dosage requirement of warfarin in first users and genetic variants to identify patients treated with clopidogrel at risk for major cardiovascular events. For vitamin K antagonists (VKA), two polymorphisms explain more than 30% of the variance associated with stable therapeutic doses warfarin: *VKORC1* (encoding the vitamin K epoxide reductase enzyme producing the active form of vitamin K) and *CYP2C9* (encoding an enzyme metabolising warfarin). While prediction models using both clinical and genotyping markers have better predictability of biological outcomes (prothrombin time international normalised ratio) than clinical models alone, the implementation of genetic testing has not resulted in better clinical outcomes so far [18]. Similarly, *CYP2C19* loss-of-function variant *2 (rs4244285) has been linked both to a poor pharmacodynamic response to clopidogrel and to an increased risk of recurrent cardiovascular events [19]. The reported association between loss-of-function alleles and poor cardiovascular outcomes was found to suffer from bias due to small-study effects, with no risk increase being found in a pooled analysis of studies involving more than 500 patients [20]. These examples demonstrate the complexity of implementing prediction models in the real world, and the need for thorough scientific assessments before observing clinical benefits to patients.

Prediction tools may also raise new questions, which need to be addressed. Women who have a presumed high VTE risk in the Pill Protect[®] or with other genetic-based assays such as the Kailos[®] test may become pregnant in the future, with much uncertainty regarding their best care during the ante-natal or post-natal periods. Also, one could imagine that high scores may affect the ability to agree insurance contracts, by making perfectly healthy women somewhat less healthy.

In summary, it seems unknown whether Pill Protect[®] accurately identifies women at risk of COC-related VTE in the general population and whether the use of Pill Protect[®] decreases the risk of VTE, compared with the current clinical practice. In this setting, we would argue that the clinical use of Pill Protect[®] in Switzerland may be too precipitate. Until we understand the necessarily rigorous scientific validation of this tool, we urge caution to physicians who may want to use this prediction tool for their patients. Individual assessment of VTE risk factors, giving dedicated

information to patients on COC-related VTE risks and the consequent preferential prescription of contraceptives with low or no thrombogenic profiles remain, in our opinion, the best current strategy for physicians who prescribe contraceptives.

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