3.5 Clinical Utility

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3.5.1 INTRODUCTION

Clinical utility, in the context of the framework developed by the U.S. Task Force on Genetic Testing is considered as the balance of benefits to risks, and, thus, the Task Force recommended: “before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from both positive and negative results” (40). Originally, the Task Force contemplated as an aspect of the clinical utility also the assessment of the social and psychological benefits or harms of the genetic information, or, in other words, the ethical, legal and social implications of the genetic tests. However, this interpretation of the clinical utility was not accepted unanimously and successively it was proposed to list the psychosocial outcomes of testing in a different category called ELSI (Ethical, Legal and Social Implications) (41). The concept of clinical utility was subsequently developed by the major framework for the evaluation of genetic tests: the ACCE model. In this framework the clinical utility focuses specifically on the health outcomes (both positive and negative) associated with testing, taking into account the natural history of the clinical disorder and the availability and the effectiveness of interventions aimed at avoiding adverse clinical consequences (if no effective interventions are available, for example, testing may not be warranted) (42). A critical question to be answered before the introduction of a new DNA test is if there is an effective remedy, an acceptable action, or other measurable benefit. If the disorder of interest cannot be either treated or avoided, it is unlikely that justification can be made for routinely identifying it. Having an effective intervention to prevent or avoid the morbidity or mortality associated with the disorder (including risk-reducing behavior) is essential to address the decisions about the use of a test for population screening.

The standard framework of the ACCE model was used to assess the clinical utility of predictive genetic testing for venous thromboembolism (VTE) (Factor V Leiden, G20210A and MTHFR). Thus the natural history of the clinical disorder was analyzed and the impact of the results on the treatment and the effective preventive intervention in case of positive test was assessed. To fulfill these aims a systematic review and a quality assessment of the existing clinical guidelines about prevention and treatment of VTE in case of positive test was performed. Finally, we reported the assessment of the clinical utility of genetic testing predictive of VTE in the specific population of women taking oral contraceptives (OC).

3.5.2 RISK FACTORS AND CLINICAL EVOLUTION OF VTE

Pregnancy and oral contraceptive (OC) use are also recognized factors associated to VTE (for other risk factors see Chapter 1). The incidence of pregnancy-associated venous thromboembolism has been estimated to be one or two per 1 000 pregnancies (43). Pulmonary embolism occurs in approximately 16% of patients with untreated deep-vein thrombosis (DVT), and is the most common cause of maternal death (44). Also association between oral contraceptive (OC) use and VTE has long been recognized (45). The only meta-analysis comparing the risk of VTE in OC users versus non-users, published in 1995, found that the use of oral contraceptives is associated with a three-fold increase in VTE risk (46). Successively, other two meta-analyses showed that third generation OCs increase VTE risk more than second generation preparations (47, 48).

The extent of the health burden attributed to VTE in terms of the total number of incident and recurrent non-fatal DVT and PE clinical events, and VTE-related deaths per year has been calculated in six EU countries (France, Germany, Italy, Spain, Sweden, UK) (49). The results of the study indicate that VTE is a major public-health problem in these countries, with a predicted total number of DVT events just under half a million and almost a third of a million PE events per year. Furthermore, a third of a million deaths occur per year due to sudden PE or following undiagnosed and untreated VTE.

The major complications of venous thromboembolism are the post-thrombotic syndrome, which can manifest as venous ulcer, and the chronic thromboembolic pulmonary
hypertension (CTEPH). The post-thrombotic syndrome is a result of the venous hypertension due to outflow obstruction and damage to the venous valves, and it develops in 20-50% of subjects (50), even when optimal anticoagulant therapy is used to treat DVT. Clinical characteristics are leg pain, skin changes and swelling. The incidence of the CTEPH is difficult to assess and it is actually underestimated. Early autopsy studies showed a prevalence of CTEPH of about 0.1-0.5%, while recent longitudinal studies indicate an incidence of approximately 4% (51). Physicians need to be more aware of complications of VTE, even in patients with no clinically obvious symptoms.

### 3.5.3 Bibliographic Search of the Existing Guidelines

The existing guidelines concerning health interventions to reduce morbidity of VTE in subjects with genetic risk of thromboembolism has been identified through a systematic search of scientific electronic databases such as MEDLINE and EMBASE and through a hand search of the retrieved literature. Web sites of all main national and international agencies and medical specialty societies involved in the production of guidelines were explored. Practice guidelines were included if the following inclusion criteria were met: a) the guidelines must contain systematically developed recommendations, strategies or other information to assist health care decision making in specific circumstances; b) the guidelines must have been produced under the auspices of a relevant professional organization; c) the guideline development process must have included a verifiable, systematic literature search and review of existing evidence; d) the guideline must have been developed or revised within the last 7 years.

The quality evaluation of the guidelines on genetic tests has been performed using the quality assessment tool developed by AGREE (Appraisal of Guidelines Research and Evaluation), a checklist proposed by a European collaboration aimed at developing a common instrument for the quality assessment of guidelines of medical practice (52). AGREE consists of 23 key items organised in six domains. Each domain is intended to capture a separate dimension of guideline quality: scope and purpose; stakeholder involvement; rigour of development; clarity and presentation; applicability; editorial independence. Each item is rated on a four-point scale and a following overall assessment is provided by the appraiser on a four-point scale indicating the grade of recommendation from “unsure” to “strongly recommended”.

Of the fourteen guidelines retrieved, four were excluded because were not produced under the auspices of a relevant professional organization. Further two guidelines were excluded after a closer analysis because did not report strategies or other information to assist health care decision making in specific circumstances. Eight guidelines fulfilled the inclusion criteria (Table 3.3) and have consequently been included in the study (53-60). Three of these are from USA (55, 56, 59), two from UK (53, 60), one from Australia (57), one under the auspices of WHO (58) and one from the association of the most important European foundations in the field of thrombophilia (54). All the included guidelines have been produced or updated from 2003 to 2010. Five guidelines are strongly recommended (55, 57-60), according to the grading of the AGREE system. Three guidelines are recommended with provisos or alteration (53, 54, 56), in particular because of the absence of criteria for including or excluding evidence identified by the search and the absence of description of the methods used to formulate the recommendations; the lack of externally review before the publication; the absence of a described procedure for updating the guideline; and finally because the potential organisational barriers in applying the recommendations have not been discussed.

The retrieved guidelines (Figure 3.5), particularly those more recent and of higher methodological quality, were used to get the evidence on the effectiveness and the safety of available interventions in case of a positivity to a genetic predictive test for VTE. Original primary studies and important meta-analyses were also taken into consideration, although they were not systematically searched and reviewed.

### 3.5.4 Impact of Positive or Negative Test on Patient Treatment and Effective Preventive Interventions in Case of Positive Test

The objective of the evaluation of clinical utility in the specific context of predictive genetic testing for venous thromboembolism is to evaluate, on the base of the scientific evidence, whether there is an effective remedy, an acceptable medical intervention, or other measurable benefit in the
event of a positive test. If the disease in question can not be treated or prevented, it is very unlikely that use of routine testing is justified. Having an effective intervention to prevent or avoid the morbidity or mortality (including behavioural changes involving a reduction in risk) is the crucial point to decide how to use a genetic test for the screening of populations or groups of individuals.

The clinical utility can be investigated in four levels that describe the objectives of the questions provided by the ACCE model: 1) the diagnostic thinking, which is the value of information in relation to diagnosis and prognosis; 2) the choice of therapy, namely the use of test results in the clinical management of the patient; 3) the assessment of patient outcomes that is the impact on survival or quality of life of the subject; 4) the social impact, including the cost-effectiveness analysis (41). Even if each of these points can influence the ultimate impact of using the test in clinical practice, however, from the clinical perspective, diagnostic thinking and therapeutic choice may constitute the basis of clinical utility, even in absence of data on health outcomes or cost-effectiveness.

In the collection of clinical recommendations evaluated (Table 3.3), there is no indication to a primary preventive approach for subjects with positive genetic tests predictive of VTE without a positive clinical history for VTE or other risk factors. In this situation, the knowledge of the information given by the test result does not change from a prognostic point of view because there is no prophylaxis and treatment protocol to follow in case of positivity. By contrast, the value of information changes in presence of intercurrent events which might endanger the health and survival of the subjects with a positive genetic test result.

According to the guidelines evaluated, intercurrent events play an important role in increasing the risk in patients with an established presence of genetic thrombophilic mutations. These events include: recurrent VTE, pregnancy, use of oral contraceptives, surgery and travels that provide a period of prolonged immobilization (> 8h). In these cases, the recommendations of the guidelines are indications for prophylaxis with a preventive treatment.

We talk about recurrent VTE when there is a new confirmed venous thrombotic complication after a first episode of VTE. One-third of patients develop a new event of thromboembolism within about 8 years after a first episode (61), and some authors described an increased risk of recurrent VTE due to a genetic thrombophilic mutation (62). As reported in several studies, the homozygous and the double heterozygotes carriers for factor V Leiden, prothrombin G20210A and MTHFR mutations, have a stronger association to the risk than

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**FIG. 3.5**

**FLOW-CHART OF THE RETRIEVED GUIDELINES**

14 GUIDELINES RETRIEVED CONCERNING HEALTH INTERVENTIONS TO REDUCE MORBIDITY OF VTE IN SUBJECTS WITH GENETIC RISK OF THROMBOEMBOLISM, THROUGH BIBLIOGRAPHIC SEARCHING

- 14 GUIDELINES SCREENED
- 10 GUIDELINES ASSESSED FOR ELIGIBILITY
- 8 GUIDELINES INCLUDED IN THIS STUDY

4 GUIDELINES EXCLUDED BECAUSE WERE NOT PRODUCED UNDER THE AUSPICES OF A RELEVANT PROFESSIONAL ORGANIZATION

2 GUIDELINES EXCLUDED BECAUSE DID NOT REPORT STRATEGIES OR OTHER INFORMATION TO ASSIST HEALTH CARE DECISION MAKING IN SPECIFIC CIRCUMSTANCES
heterozygotes (63, 64); however, the choice of the therapy recommended in all patients with genetic thrombophilic mutations, regardless of the strength of association, is the same. The prophylaxis recommended by European and American guidelines is to assume anticoagulants for an extended period of time, at least 6 months (long-term treatment), or a lifelong treatment with a vitamin K antagonist in selected patients with added risk factors, although the decision to undertake this type of therapeutic approach is controversial. As a matter of fact, this long-term decision should be based on balancing the long-term mortality risk from recurrent VTE, largely preventable with oral anticoagulant therapy, against the long-term mortality risk of major bleeding, the most frequent complication of oral anticoagulant therapy (65). Dose and duration of the treatment are unaffected by the carrier status, and are based, as with non-carriers, on the determination of standard parameters commonly used (specifically the International Normalised Ratio, a derived measure of prothrombin time) (54, 66).

As already stated, the association between venous thromboembolism and pregnancy in women with genetic mutations has been well documented and about 60% of cases of gestational thromboembolism is associated with the state of carriers of genetic thrombophilic mutations (56). According to several studies, women with Factor V Leiden or Factor G20210A homozygosis, or combined heterozygosis for Factor V Leiden and Factor G20210A, are
considered to be at high risk and should be treated more aggressively compared to women with heterozygous Factor V Leiden or Factor G20210A mutations that are considered to be at moderate risk (54). In both cases prophylaxis could be recommended: first of all, women bearing genetic factors that increase the risk of VTE must be informed about the correlation of pregnancy with the potential development of VTE to promptly implement a program of prophylaxis. During pregnancy, prophylaxis should be implemented with low molecular weight heparin at prophylactic (4 000-5 000 U/die), intermediate (10 000 U/die) or adjusted dose (weight-adjusted, 200 U/kg) for high-risk groups (Factor V Leiden or Factor G20210A homozygosis, or combined heterozygosis for Factor V Leiden and Factor G20210A) regardless of the presence of a positive clinical history for VTE. For women with moderate risk (Factor V Leiden or Factor G20210A heterozygous) prophylaxis with heparin at prophylactic dose would be appropriate if they have more risk factors such as family history of VTE, age, immobilization, etc. or if they experienced previous episodes of VTE. Immediately after pregnancy, for both groups (high risk and moderate risk), prophylaxis should be continued with low molecular weight heparin or oral anticoagulants together with the use of elastic stockings for 6 weeks is recommended (67). In case of history of VTE, the recommendations include also a duplex ultrasound scan to serve as a reference and the use of elastic stockings. The women under long-term or lifelong therapy for VTE, during the pregnancy, must shift from oral anticoagulants, because of their teratogenic effects, to subcutaneous injections of low molecular weight heparin, resuming anticoagulants only at the end of pregnancy (68).

Owning genetic thrombophilic mutations is one of the risk factors for the development of VTE during long distance travels, with the increased risk persisting for about 8 weeks after the travel. Given the conflicting views about the use of thromboprophylaxis in travellers, there is insufficient evidence to support the routine use of active thromboprophylaxis measures in any group of travelers. However, it is reasonable to advise passengers to reduce venous stasis and to avoid dehydration, although these measures have also not been assessed in clinical trials (69).

3.5.5 RESULTS OF A SYSTEMATIC REVIEW AND META-ANALYSIS TO EVALUATE THE CLINICAL UTILITY OF THREE GENETIC TESTS FOR VTE IN WOMEN ASSUMING ORAL CONTRACEPTIVES

Given the large number of formulations, dosages and characteristics of studies, a meta-analysis was carried out to summarize the existing evidence on the association between VTE and OC use and to investigate how such association may vary according to several OC, users and study characteristics. The final goal of the study was to find the formulations which are associated to the lower risk of VTE. The methodology and the results of the meta-analysis are described in detail elsewhere (70); here only the main findings are reported.

Relevant cohort or case-control studies were searched in Medline and other electronic databases up to May 2010, with no language restriction. Data were combined using a generic inverse variance approach. Overall, the results of 55 observational studies were included. The risk of developing venous thromboembolism was significantly higher in women who use OC.
odds ratio (OR) obtained by combining all 32 studies that reported data on the comparison between the use and non-use of OC was equal to 3.41 (95% Confidence Interval [CI]: 2.98-3.92, p <0.001). This value corresponds, approximately, to a higher risk of VTE of 3-4 times for OC users. Overall, the risk of VTE appeared slightly lower in cohort studies (OR=2.91; 95%CI: 2.33-3.62) than in case-control studies (OR=3.60; 95%CI: 3.01-4.31). Besides study design, the risk of VTE for OC users was lower in population-based studies than hospital-based studies (OR=3.31 [p<0.001] vs OR=4.19 [p<0.001]), in studies evaluating all VTE rather than idiopathic VTE only (OR=3.09 [p<0.001] vs 4.94 [p<0.001], respectively), in studies co-sponsored by one or more pharmaceutical companies (OR=2.70 [p<0.001] vs 4.14 [p<0.001]), and in non-smokers samples (OR=2.00 [p=0.2] vs OR=5.04 [p<0.001]).

Third-generation OCs (desogestrel and gestodene) are associated with an increased risk of VTE compared to second generation (primarily levonorgestrel) (OR=1.57; 95%CI: 1.24-1.98). When the newest OCs containing drospirenone were compared to other preparations (except those containing levonorgestrel only), VTE risk did not significantly increase (OR=1.13; 95%CI: 0.94-1.35). Differences in VTE risk were also observed according to oestrogen dose: users of OC at doses ≥50 mcg show an higher risk of VTE compared to users of OC at doses <50mcg (OR=1.42; 95%CI: 1.15-1.76).

The pooled OR of the studies that have examined the risk of VTE in women with only G20210A mutation taking OC, compared to women with the same mutation but not taking OC, is equal to 1.63 (95%CI: 1.01-2.65). The overall OR of VTE for women taking OC in the population of women with FVL mutation was 1.80 (95%CI: 1.20-2.71). Women with the MTHFR mutation OC users showed a higher risk of VTE compared with non-users (OR=2.73; 95%CI 0.78-9.56), but this increase was not significant.

Based on the results of 55 observational datasets, this meta-analysis confirms that OC use is associated with a significant increase in VTE risk. The strength of this association, however, varies according to OC generation, outcome definition, presence of a genetic mutation and eventually smoking status, with relative risks varying from 3 to 5 for OC users. When compared with other available OC preparations (except those containing levonorgestrel only), the newest OCs containing drospirenone did not show a significant increase in VTE risk. As regards outcome definition, the development of methodological standards for studies on VTE is strongly warranted to reduce the variation in the estimates of singles studies, or at least to prevent misinterpretation of the strength of the association between VTE and OC use. Concerning genetic mutations, the further increase in VTE risk among the carriers of G20210A and FVL mutations prompts further evaluations of the potential implications of genetic testing.

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