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Genetic Screening for the Predisposition to Venous Thromboembolism: A Cost-Utility Analysis of Clinical Practice in the Italian Health Care System

Amelia Compagni, PhD[1,2,*], *Alessia Melegaro, PhD*[2,3], *Rosanna Tarricone, PhD*[1,2]

[1]*Department of Policy Analysis and Public Management;* [2]*Centre for Research in Health and Social Care Management (CeRGAS);* [3]*Dondena Center for Research on Social Dynamics, Bocconi University, Milan, Italy*

ABSTRACT

Objectives: In the Italian health care system, genetic tests for factor V Leiden and factor II are routinely prescribed to assess the predisposition to venous thromboembolism (VTE) of women who request oral contraception. With specific reference to two subpopulations of women already at risk (i.e., familial history or previous event of VTE), the study aimed to assess whether current screening practices in Italy are cost-effective. **Methods:** Two decisional models accrued costs and quality-adjusted life-years (QALY) annually from the perspective of the National Health Service. The two models were derived from a decision analysis exercise concerning testing practices and consequent prescribing behavior for oral contraception conducted with 250 Italian gynecologists. Health care costs were compiled on the basis of 10-year hospital discharge records and the activities of a thrombosis center. Whenever possible, input data were based on the Italian context; otherwise, the data were taken from the international literature. **Results:** Current testing practices on women with a familial history of VTE generate an incremental cost-effectiveness ratio of €72,412/QALY, which is well above the acceptable threshold of cost-effectiveness of €40,000 to €50,000/QALY. In the case of women with a previous event of VTE, the most frequently used testing strategy is cost-ineffective and leads to an overall loss of QALY. **Conclusions:** This study represents the first attempt to conduct a cost-utility analysis of genetic screening practices for the predisposition to VTE in the Italian setting. The results indicate that there is an urgent need to better monitor the indications for which tests for factor V Leiden and factor II are prescribed.

Keywords: cost-utility analysis, genetic testing, Italy, venous thromboembolism.

Introduction

Genetic testing is progressively entering clinical practice and screening programs. It is estimated that genetic tests are available for more than 1300 diseases, including those detecting predispositions to common multifactorial diseases or such conditions as cancer, diabetes, hypertension, psychological disorders, and defective drug metabolism [1]. Health policymakers in several industrialized countries have recognized that the rapid technological progress in this field and the rising interest of people in genetic information necessitate more strategic planning and a better assessment of the real benefits brought by genomic medicine [2].

There is a general consensus that most genetic tests introduced in health care systems since the late 1990s were "riding a wave of enthusiasm rather than evidence" [3]. These tests' uncontrolled spread might be due to a combination of reasons. Producers of in vitro diagnostics are subject to a loose regulatory regime, both in the United States and in Europe, which allows tests to be marketed without having to prove their clinical validity or utility in randomized controlled trials [4,5]. Furthermore, so-called home brews are rather common. These tests are optimized by hospitals and laboratories for research purposes; however, because of the lack of quality control programs for most genetic tests, the tests end up being used for medical applications with poor monitoring of their actual utilization [6]. Finally, genetic tests can be directly advertised to consumers through the Internet, and, as such, they are more prone to be introduced on the basis of a commercial rather than scientific or medical basis [7]. Given these dynamics, genetic tests might be able to diffuse easily into health care systems with little chance for policymakers to actually predict their impact and control that tests are actually used on those who can benefit the most from their predictive power.

In this scenario, evaluation frameworks for the assessment of genetic tests are still scarce. The so-called ACCE [8] and

Note: Amelia Compagni and Alessia Melgaro equally contributed to this article.

Address correspondence to: Amelia Compagni, Department of Policy Analysis and Public Management, Bocconi University, Via Roentgen 1, 20136 Milan, Italy.

E-mail: amelia.compagni@unibocconi.it.

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Evaluation of Genomic Applications in Practice and Prevention [9] are the most well-established, though still rarely used, frameworks. These frameworks propose that both the analytical and clinical validity and the clinical utility of genetic tests should be clearly established before introducing a new test or deciding its reimbursement by third-party payers. Moreover, the ACCE framework indicates the need to include economic evaluations to support this type of decision. Despite the economic evidence accumulating in the literature regarding genetic testing [10–12], it is argued that economic analyses, besides presenting several methodological challenges [13], have had little impact to date in informing policies and reimbursement practices concerning genetic testing [3]. The analyses are of highly variable quality, and, particularly for cost-utility studies that would allow an easy comparison of genetic testing with other health care interventions, are rather uncommon [10].

Given the challenges in assessing diagnostics and devices through experimental studies, such as randomized controlled trials [13], in this study, we start from the perspective that economic analyses and health technology assessments should aim at informing current clinical practice and optimizing the utilization of genetic tests, rather than attempting to curb their initial introduction. The viewpoint is consistent with the broader recommendations of the HTAi Policy Forum in 2009 [14] and with more recent work by the ISPOR Good Research Practices Task Force on Observational Studies that has highlighted the relevance —and good practice—of using real-world data to inform decision makers [15–18]. As such, to provide valid information to prescribing clinicians and policymakers, economic evaluations should be based on the best available knowledge of how and why genetic tests are prescribed and used in current practice.

To address this issue, the present work explores the specific instance of genetic tests for the predisposition to venous thromboembolism (VTE). VTE is a multifactorial disease caused by a strong interplay between environmental and genetic factors [19], with an incidence ranging from 7 to 18 per 10,000 person-years according to the geographic area [20–24]. VTE consists of a milder form, deep-vein thrombosis (DVT), and a more severe condition, pulmonary embolism (PE), which has been shown to account for 10% of hospital deaths [25–27]. Three genetic defects have been proven to predispose patients to VTE: factor V Leiden (FVL; Arg506Gln substitution), factor II/prothrombin (FII; G20210A polymorphism), and methylenetetrahydrofolate reductase (C677T polymorphism) [28]. The likelihood of developing VTE is further augmented in such situations as pregnancy, oral contraception use, forced immobilization (e.g., long-distance flight), and major surgery.

Since the late 1990s, the tests detecting the above-mentioned three most important genetic alterations have been among the first to enter clinical practice. Italy is no exception to this trend, and, overall, more than 60,000 tests —approximately a quarter of all molecular ones—are conducted every year in the country to screen for predisposition to VTE [29,30]. The expenditure for these tests can be estimated to be approximately €18 million per annum; still, a rather limited amount of money. The main concern, though, derives from the sharp increase in the number of tests over recent years (e.g., there was a 50% increase between 2004 and 2007) [30]. This information is particularly relevant, given that all tests for thrombophilia are reimbursed by the Italian National Health Service (NHS) and that to date, national and international medical associations have produced notably cautious recommendations concerning the use of these tests [e.g., 31–33].

Economic analyses in this field are rather rare but have provided evidence that universal screening for the predisposition to VTE is not a worthwhile investment of public resources [34–36]. For instance, Wu et al. [36] showed that screening for this predisposition in all women administered oral contraceptives would impose an additional cost of £200,000 to avoid one VTE event. Even considering more targeted populations, such as those at high risk of VTE because of a family or personal history of the condition, the results are not always consistent nor do they show clear cost-effectiveness, if compared with the cost-effectiveness threshold of €40,000/quality-adjusted life-year (QALY).

In the present study, we considered the application of genetic testing for the predisposition to VTE of broad relevance for public health, namely, that for women already at risk who are seeking oral contraception. We adopted the perspective of the third-party payer (i.e., the Italian NHS) and attempted to answer the following questions: what are the costs and the benefits of the current screening practice in the Italian setting? On what aspects could policymakers and clinicians leverage to improve the effectiveness of the current testing practice and reduce the associated costs?

Methods

A cost-utility model was developed to compare costs and utilities associated with different practices of genetic screening for 15- to 45-year-old women at high risk of VTE who visit a gynecologist for a prescription for the oral contraceptive pill (OCP). To identify current genetic screening practices in Italy, a questionnaire was designed in collaboration with a group of three gynecologists. The questionnaire presented two different scenarios (scenario 1: familial history; scenario 2: previous event of VTE) and recorded the decisions normally made by gynecologists when facing these clinical cases. Unlike the study by Wu et al. [36], the two scenarios were kept separate because they might be associated with a different perception of risk by clinicians. In both scenarios, the questionnaire referred to "idiopathic VTE," which is an event that had arisen spontaneously and was not induced, for instance, by a surgical operation.

The questionnaire was first validated by eight gynecologists, modified, and converted into an electronic platform. The questionnaire was subsequently disseminated by e-mail through the Italian Society of Gynecologists and Obstetricians (Società Italiana di Ginecologia e Ostetricia [SIGO]). Invitations to respond to the survey were sent to 1000 randomly selected SIGO members and contained a unique personal link to the questionnaire. In total, 250 gynecologists completed the questionnaire for a response rate of 25%. The respondents were homogeneously distributed across the country (northern Italy: 32%; central Italy: 30%; southern Italy: 38%).

In the attempt to reproduce as closely as possible the Italian clinical practice, the model structure and parameters were derived from survey results. First, two different courses of action were reported, depending on the scenario (i.e., whether the woman had a familial history of VTE or had experienced a VTE event herself). More specifically, in the case of familial history of VTE (scenario 1), the great majority of gynecologists prescribed a battery of biochemical and genetic tests (69.3%), while the rest were equally split between those who prescribed biochemical tests only (13.4%) or genetic tests only (13.4%). In contrast, when facing a case of previous VTE event (scenario 2), gynecologists mostly tended either to prescribe a battery of biochemical and genetic tests (65.1%) or not to conduct any screening and avoid OCP prescription altogether (24.1%). The strategies to be included and compared in the two models (i.e., for scenario 1 and for scenario 2) were derived from these results (see the following section for a more detailed description of the models' structure).

Second, the probabilities of subsequent therapeutic choices by gynecologists (i.e., to prescribe or not OCP) in face of positive biochemical and/or genetic test results were also derived from the survey results (see details in the Appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.05.003). The findings showed that gynecologists consistently perceived the case of a previous VTE event to be riskier compared with a familial history of VTE, even if the scientific evidence suggests