Appraising screening, making risk in/visible. The medical debate over Non-Rare Thrombophilia (NRT) testing before prescribing the pill

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ORIGINAL ARTICLE

Appraising screening, making risk in/visible. The medical debate over Non-Rare Thrombophilia (NRT) testing before prescribing the pill

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Abstract

Non-rare thrombophilia (NRT) are hereditary predispositions to thromboembolism, the most severe side effect of combined hormonal contraception. In the mid-1990s, the identification of NRT stirred up a controversy over the possibility of investigating these genetic variants in women wishing to use contraception. Through a review of literature, this article reconstructs the debate over whether and how this genetic test should be prescribed as a way to reconfigure the risk visibility on pharmacological contraception. The main arguments identified concern the epidemiological, social, economic and clinical aspects of the test. In a context where the overall thrombotic risk for hormonal contraception is largely invisible, the genetic tests turn to embody the thrombotic risk itself. Those who opt for selective screening argue that a better estimation of risk implies a test prescription embed in a global medical assessment of women's individual risk. To advocates of universal or 'extended' screening, the tests are valuable tools to inform women on the thrombotic risk and, as such, appraised as a moral/legal obligation, whatever their predictive power. Risk visibility thus appears as an insightful

Abbreviations: ADR, adverse drug reaction; AVEP, the French Association of Pulmonary Embolism and Stroke Victims associated with Hormonal Contraception; COC, combined oral contraceptive; FVL, factor V Leiden; HAS, Haute Autorité de Santé; NRT, non-rare thrombophilia; VTE, venous thromboembolism.

concept to analyse a complex setting associating clinical, political, social and cultural considerations that touches upon medical power, women's responsibility and drug safety.

KEYWORDS

adverse drug reactions, controversy, hormonal contraception, medical profession role, risk, screening, visibility

THE 'PILL CRISIS' IN FRANCE AND THE DEBATE AROUND THROMBOPHILIA SCREENING

At the age of 18, Marion Larat suffered a massive stroke attributed to the birth-control pill she was taking, Méliane. In December 2012, she decided to take to court both the pharmaceutical company Bayer, for having produced this oral contraceptive, and the French drug regulatory agency (*Agence Nationale de Sécurité des Médicaments*), for having authorized it. Her story attracted a lot of media attention and triggered a national 'pill crisis'. A collective sentiment of distrust started to spread among French women, and use of the pill decreased from 45% of the global average of contraception in 2010 to 36.6% in 2016 (Rahib et al., 2016). Larat pointed out, among other things, that she was a carrier of non-rare thrombophilia (NRT). NRT are hereditary predispositions to form blood clots within the veins' vessels, which can lead to venous thromboembolism (VTE). A molecular test could have identified this genetic susceptibility, thus alerting her to the increased thromboembolic risks associated with taking the pill. Larat was not an isolated case. The Association of Pulmonary Embolism and Stroke Victims associated with Hormonal Contraception (AVEP), critical about how the medical profession regulates contraceptive practices, campaigned for a specific measure: the setting of national universal thrombophilia screening (TS) before prescribing the pill for the first time. The AVEP argued that, in so doing, women at higher risk of having a thromboembolic accident would be identified and discouraged from taking hormonal contraception. The French health-care regulatory Agency (*Haute Autorité de Santé*, *HAS*) evaluated this proposal carefully. In 2015, the Agency released a long report that rejected the principle of universal screening by drawing on '(a)ll existing guidelines that have addressed this issue, based on expert opinion and economic modelling' (HAS, 2015).

What may at first glance appear to be a mere claim of the pill victims' association was in fact a new episode in a controversy that has enlivened and divided the medical-scientific community specialized in VTE since the day after the discovery of NRT in the mid-1990s. At that time, identification of NRT was regarded as an important step in understanding the pathophysiology of haemostasis and thrombosis at the molecular level. Yet, their predictive capacity proved to be relatively low—many people with NRT never developed VTE—and usage in clinical care became problematic. The tests are currently one of the most common genetic investigations in the Global North, but determining whom to test and how to use the results is still a matter of debate. In previous work on the subject (Turrini & Bourgain, 2020; Turrini et al., 2020), we showed that the dual nature of the tests, with both a molecular and a statistical meaning, their association with pharmacological treatments and their usage in different clinical contexts were key drivers of this unstable situation.

In this article, we analyse the debate this risk-assessing tool has been creating for more than twenty years in regard to oral contraceptives based on a combination of oestrogens and progesterone[1]. The increased risk of VTE associated with combined oral contraceptives was identified by the end of the

1960s. Starting in the mid-1990s, several epidemiological studies showed that the risk was not only higher among women with NRT, but also that the risk increase was more than a simple addition of the two risks. Combined oral contraceptives and NRT had an interactive effect. In spite of this, universal screening prior to prescribing oral contraceptive pills for the first time was not adopted. Guidelines opted broadly for selective screening of high-risk women identified by clinicians using personal or family history of thrombosis (HAS, 2015). However, the capacity of NRT tests to predict the most severe adverse reactions to hormonal contraceptives has made clinicians and public health researchers question *access* to NRT testing, that is offering it as either *general* or *selective screening* or, very rarely, *neither*. More recently, a fourth approach has emerged, *extended testing*, which involves informing women without assuming their participation.

This long controversy has been the subject of editorials and *ad-hoc* research, mainly epidemiological studies and cost-benefit analyses. This literary corpus is used here to analyse how a core group of specialists, practitioners and researchers has rationalized the routine use of this genetic test in respect to prescribing hormonal contraception. We are particularly interested in characterizing the implications of the controversy on the visibility of the thrombotic risk.

Brighenti (2010) has introduced the notion of 'visibility' in social sciences to combine the Foucauldian nexus between knowledge and power with an analysis of the relations, practices, contexts and technologies socially defining our perceptions. He uses this concept especially in processes of recognition by, and control and surveillance of, individuals and collectivities. This article intends to widen this notion to risk in order to explore political and epistemological implications of screening. How is a risk recognized and communicated? Which actors are involved in this publicization? How does control over risk shape its visibility? To what extent do the molecularization of risk and its incorporation into a technique impact its visibility?

The article begins by elaborating risk visibility as a concept and situating it in the case study of NRT screening and adverse effects of hormonal contraception. Then, it presents the methods and materials employed, and it continues by structuring the analyses in five sections: an introduction about the controversy on NRT screening, followed by an exploration of the four main arguments (epidemiological, social, economic and clinical) debated during this dispute.

SCREENING AND RISK VISIBILITY FOR HORMONAL CONTRACEPTION

Risk has been widely analysed through a Foucauldian framework as a turning point in governmentality. According to Castel (1991), the advent of risk marks the shift from disciplinary institutions, including hospitals, targeting deviants, to a methodical, systematic and automatic monitoring extended to normal populations. Armstrong (1995) singles out this phenomenon as the rise of 'surveillance medicine,' a fundamental remapping of the spaces of pathology in hospital medicine, or the 'Clinic' in Foucault's terms, where risk factor replaces symptoms as the pivotal tool of monitoring and intervention on illness. Differently from *symptom*, which has a static and causal relationship with the lesion, *risk factor* opens up a space of possibility by pointing to the hybrid space between the normal and the pathological. Clarke and colleagues (2003) consider preventive interventions based on biomarkers as a vector of 'biomedicalization', that is an expansive movement of the medical gaze. As opposed to previous forms of 'medicalization', biomedicalization does not necessarily imply an increase in medical prerogatives over health care, but rather their devolution towards more open and accountable forms of decision-making and a delegation to society of concerns and responsibility over health and wellness. In the case of biologically incorporated risk, Rose (2007) prefers to speak of susceptibility

in order to emphasize the belief that patients and healthy people could have the possibility to intervene on, and change, their own biology.

In contrast with this description of molecular risks associated with ineluctable dynamics, 'sociology of screening' has widely documented, through empirical case studies, the ways in which population-based preventive programmes are often surrounded by uncertainties and controversies (Armstrong & Eborall, 2012). Since the 1970s, screening has been called into question not only due to, primarily, its exorbitant costs, but also for its social acceptability, psychological impact, overdiagnosis and ability to effectively identify common diseases. Rather than disappearing, preventive prophylactic testing tends to be integrated into clinical practice and implemented in a selective and opportunistic way, that is on the basis of individual examinations. In this regard, risk visibility may provide a useful descriptive and interpretative tool to grasp the political and epistemological implications of the different components of screening (referral protocol, clinical consequences and economic costs) and to analyse the strategies of emerging actors participating in their definition.

Something is visible when somebody recognizes it as relevant. Visibility, thus, involves both a quantitative and a qualitative dimension. From a quantitative perspective, it depends on the number of people who attach significance to it. The distinction between universal and selective screening (Armstrong, 2019) exemplifies this perspective well. The former, addressing large populations, increases the risk visibility, while the latter that only targets smaller, at-risk individuals, reduces it. These two settings also correspond to two registers of professional uses for the tests, a public health register and a clinical register (Beaudevin et al., 2021), which affect risk visibility qualitatively. Selective settings, based on a clinical evaluation of specific individuals, are 'more local, less formal, more penetrating and less resistible' (Armstrong, 2012). Interactions take place within clinical encounters. Decisions are more likely to be considered as clinical choices. Turned into an ad-hoc type of symptoms, risk loses its specificity and visibility. In contrast, context, actors and practices of universal screening tend to reinforce the ambivalent status of risk factors, their uncertain nature, situated at the frontier of the normal and the pathological and, correlatively, to maintain their visibility.

We have shown elsewhere that all general professional guidelines for NRT testing call for a very restricted usage of the tests. As for other genetic risk factors, clinicians are encouraged to subordinate test prescriptions to thorough clinical investigations and identification of a familial history of disease (Turrini & Bourgain, 2020). Professional regulation thus favours a clinical register over a larger, public health register for test prescriptions.

Medical professionals are not the only actors shaping risk visibility. Screening programmes are as much social interventions as medical ones. Several lobby groups and patients' associations have asked for the extension of existing screening programmes (Löwy, 2010) or the establishment of new ones (Faulkner, 2012). In the same vein, private DTC companies promote the visibility genetic risk factors to foster a blooming market, despite strong critics from medical associations and regulatory agencies on their lack of medical rationality and assistance (Turrini, 2018). In fact, at the same time, health systems are no strangers to the imperative to deliver preventive information to patients and healthy people, in order to make them more responsible for their own health and wellness. Recently, a new approach to screening has emerged through a renewed centrality of informed consent and patient's choice. It gives impetus to the question about how to truly inform people about a detectable heath risk riddled with uncertainties, without necessarily expecting them to undergo a screening test (Armstrong, 2019).

Finally, analysing risks through the lens of visibility helps considering the relational dimension of risks. Risk proliferates in contemporary societies where it is an authoritative source of values and norms based on trust. The multiplicity of risk may lead to conflicting situations. Visibility helps in considering the interactions among different competing risks, in terms of an economy of attention:

casting light on something may obscure something else. In our case study, NRT screening revitalizes old questions around iatrogenic risks of hormonal contraception, how they should be communicated and how they could affect the perception of these pharmacological treatments.

The 'distribution system' of a drug—that is the standardized procedures of its provision—is designed to ensure its safety, by normalizing the adverse reactions it could provoke (Timmermans & Leiter, 2000). All risks may not be treated equally in this normalization process, and some may turn to be made less visible than others. Since the first clinical trials in Puerto Rico, adverse reactions to the pill have been downplayed in comparison with their benefits in terms of reduction in unintended pregnancies and unsafe abortions (Marks, 2001; Watkins, 1998). This is not to say that side effects have not been recognized. The exclusive prerogative of medical doctors on their prescription, despite initial reluctance, was legitimated as a form of supervision over any adverse reactions. Yet, in practice, the dominant medical risk model framed the women's contraceptive risk/benefit balance with a population control discourse, under which 'the risks of using a contraceptive method were compared with the risks of not using such a method', in a time where unsafe abortion was the primary cause of maternal mortality (van Kammen & Oudshoorn, 2002: 439). Consequently, measurements of risks tend to be higher than they would be if assessed in comparison with alternative contraceptives. Similarly, this 'pill-centric' approach (Roux, 2020) may bias the evaluation of efficacy, when the protection from dangers of unplanned pregnancies are evaluated against no protection rather than alternatives means (Marks, 2001). Since the late 1960s and early 1970s, the U.S. Women's Health Movement contested this dominant position (Watkins, 1998), but it was not until the 1990s that new risk models were established that emphasized women's contraceptive choice and included an assessment of the quality of care and, more generally, of the general reproductive health of women (van Kammen & Oudshoorn, 2002).

However, this change had little impact on dominant medical discourse and practices. A recent study on English-speaking gynaecology manuals showed how medical knowledge frames hormonal contraception efficacy as certain and risks as doubtful and contentious (Bertotti & Miner, 2019). The scandal of so-called 3rd and 4th generation pills is an illustration of this trend. The new contraceptive drugs were largely presented as innovations because of their positive auxiliary effects on the skin, mood, etc., despite higher thrombotic risk than traditional pills (Watkins, 2012). When, in response to the scandal, U.S. and Canadian professional associations and regulatory bodies released reports between 2010 and 2014, these secondary health effects of the drugs were minimized by comparing them with thrombotic risk related to pregnancy and postpartum (Geampana, 2016).

To conclude, debates about screening are concerned with the recognition and management of certain specific risk factors as part of population-based preventive strategies. The prescription context situated between a clinical and a public health approach struggles for recognition of some screening investigations, commercialization of laboratory investigations, the style of communication adopted and the impact of testing on other risk factors and on the distribution system of drugs are all factors having a relevant influence on risk visibility.

MATERIALS AND METHODS

This article reconstructs the controversy surrounding the regulation of NRT testing before prescribing the pill as it has been discussed in biomedical literature. Specifically, the articles have been selected from two bibliographic searches done on PubMed, combining categories such as 'oral contraceptives', 'thromboembolism' and 'thrombophilia screening'[2]. The resulting articles (respectively, 83 and 103)

were all published after the discovery of the first genetic non-rare thrombophilia in 1993 (with the exception of two articles published in the 1980s) and with a rather steady distribution over time.

Following an inductive method typical of qualitative research, the publications were selected through a circular relationship with the analysis of the material itself. First, we considered the first studies published in the mid-1990s that stirred up the controversy over NRT testing and contraception. From analysis of this first corpus, we identified the main 'fracture lines' along which this dispute has developed. Second, through a reading of the titles and abstracts, we selected the articles that addressed these issues. We gave precedence to the opinions and editorials about screening for thrombogenic variants prior to using oral contraceptives, literature reviews and meta-analysis about the risk assessment of hormonal contraceptives and economic evaluations of the cost-benefit ratio of universal and selective NRT testing programmes. We examined 21 articles coming from these searches. Finally, we conducted independent manual searches of literature reviews and references from the studies found and obtained 7 additional articles. This study is part of a larger socio-ethnographic enquiry on the history, the practices and the professional regulation of NRT tests.

ORIGIN AND END OF THE CONTROVERSY IN THE AFTERMATH OF THE DISCOVERY OF NRT

In 1992, the Swedish biochemist Bjorn Dahlbäck came to identify a phenomenon of blood hypercoagulation, that was called resistance to the activated protein C, whose molecular description would subsequently be used to define NRT. One of the first potential applications Dahlbäck explored empirically was its association with pregnancy and oral contraception. Along with two clinicians, they described a remarkable increase in thrombosis among pill users who were 'resistant to the activated protein C' and suggested that a mass screening of the anomaly should be offered to all women before both pregnancy and prescription of oral contraceptives (Dahlbäck, 1996; Hellgren et al., 1995). Some physicians shared this position. Bridey et al., (1995), for example discussing the case of a fatal cerebral thrombosis in a 25-year-old woman who was a carrier of NRT, advocated for the same solution.

In 1994, an interdisciplinary team from the University Clinic of Leiden identified the genetic variant that underlies the resistance of activated protein C (hence named Factor V Leiden, FVL), and later, another variant with similar hyper-coagulant effect (prothrombotin). Taken together, these two variants define NRT. Characterizing an in-home cohort of thrombotic patients, the team demonstrated, in a statistically solid way, that the pill and NRT were not only two risk factors for VTE, but that also their combination was synergistic, meaning that the risk of their combined action was greater than the sum of the single risk factors acting independently.

Compared with women who did not use oral contraceptives and were not carriers of the mutation, the risk of thrombosis among those with both risk factors was increased more than 30-fold (Vandenbroucke et al., 1994: 1453).

Yet, the Leiden team excluded a systematic screening prior to prescribing the pill by considering the following epidemiological, social, economic and clinical points.

- First, these authors consider that the absolute risk of these 'profound tragedies that will be due to the combination of the pill and the mutation' (Vandenbroucke et al., 1996: 1127) is low—more specifically equal to 28.5 per 10,000 women per year.
- Second, 'about 20,000 women positive for factor V Leiden should be denied the use of oral contraceptives during 1 year to prevent one death' (ibid: 1128). Mass screening, while only preventing a

small number of deaths due to VTE, would exclude many women from accessing effective contraception and consequently increase the number of unwanted pregnancies.
- Third, *economically*, mass screening before prescribing the pill is calculated as cost-*in*effective.
- The fourth point concerns the *clinical arrangement* of the test. The authors argue that systematic screening would produce massive uncertainty and require intensive individualized work in clinical encounters to interpret the genetic results.

This article had a decisive influence on medical practice and further debate. As mentioned, to our knowledge, no health-care system has adopted a systematic screening for NRT before a first prescription for the pill. The decision on whom to test, how to present it to the patient and what to do of results was left to the clinician's choice, with an emphasis on individualized evaluation of thrombotic risk for each woman before testing. In the second half of the 2000s, the first guidelines published by medical societies and health-care agencies generally endorsed these views.

Still, each of the four points raised by the Leiden team met with criticism, and they remained the subject of discussion and clinical research. This dispute intertwined with the emergence of a new contraceptive risk that broke out in the same period. In 1995, the Leiden team demonstrated that new hormonal contraceptive compounds, the 3rd and 4th generation pills, were associated with a higher risk of VTE than older progesterone-only pills (Bloemenkamp et al., 1995). The finding resulted in the first wave of a 'pill scare', which started in the United Kingdom in 1995. More than ten years later, in France and other western societies, a new pill crisis began following confirmation of this increased risk by new epidemiological studies in the second half of 2000.

What follows is an analysis of each of the four arguments. The order in which they are presented seeks to capture the theoretical and diachronic development of this dispute. While the first two have gone rather uncontested, the last two have been the subject of dissenting voices.

Representing risk: measures and perceptions of danger

The way to express and measure risk may appear to be a pure technicality. In fact, it is a crucial element of the risk-benefit balance that underlies the dominant medical discourse on contraception. Its influence on the perception and communication of risk is decisive, especially among people without a solid statistical education, like most patients and doctors who prescribe the pill (mostly generalists and gynaecologists). The dispute over NRT screening sets an important difference between the *absolute* risk, the number of events occurring per time unit and the *relative* risk, which is the ratio between two absolute risks.

Practically, whereas the relative risk may sound alarming, the absolute risk looks more reassuring. The very first publication presenting this variant in women taking contraceptives mitigates the result of a 30-fold increase in relative risk by presenting the same risk in absolute terms as an incidence of 28.5 per 10,000 women-years, and adding that '[t]he absolute risk of deep venous thrombosis is low even among young women that have both risk factors' (Vandenbroucke et al., 1994: 1456). If a relative risk for increase in an event refers to a very low baseline, the argument follows, the event is still very unlikely. As thrombotic risk is very low among young women at a fertile age, it is also the case for those who take the pill and have a genetic susceptibility. More than ten years later, a systematic review expresses this argument very clearly:

Thrombophilia is associated with a substantial increase in relative risk of VTE, in particular among women on combined oral contraceptives… However, in view of the prevalence of thrombophilia, the

absolute risk remains low. Therefore, the absolute numbers of expected events and the estimated number of prevented events in these groups are low. (Wu et al., 2006, 62).

The difference between relative and absolute risk affects the way in which risk is communicated. In the context of the 'pill scare', the British gynaecologist Angela Mills devotes an article to the importance of reassuring women about the safety of hormonal contraception. On the one hand, she recognizes the need to speak about the increased risk associated with new generation pills or with NRT, as the lack of this communication may result in medical litigation. On the other, she suggests the use of specific methods of risk communication based on translating epidemiological findings into absolute risk in order to reassure women.

Medical journals need to be conscious that they will contribute to scaremongering newspaper headlines if they do not request authors to quantify ADR into best estimates of absolute numbers. (Mills, 1999, p. 650).

Her emphasis on absolute risk is further complemented by a balance of the benefits against the risk, following the dominant medical model of risk on contraception, discussed in the next section.

A new medical risk model between individual choice and public health

Commenting on the previously mentioned clinical case of a young woman affected by a pill-related stroke (Bridey et al., 1996), the leader of the Leiden team, Frits Rosendaal, insists on the importance of adopting a global view on NRT testing, as its generalization could potentially undermine the diffusion of pharmacological contraception:

Withholding oral contraceptives has other effects than decreasing the number of thromboses: withholding the most effective mode of contraception will lead to more pregnancies, and, in addition, associating prescription of oral contraceptives to a blood test may prevent some, probably mainly the youngest, women of consulting their GP for contraception. (Rosendaal, 1996: 524).

Inspired by population control, the risk model that underlies this view—the social risk of unwanted pregnancies should be prioritized over the pill's health side effects—embodies the medical discourse on hormonal contraception, much criticized but notably resilient since the 1980s. Rosendaal's argument usually goes along with the previous one on absolute risk. Those who argue that mass screening for NRT is a threat to the current model of fertility control advocate for information on NRT and thrombotic risk that should not discourage women from taking the pill.

Interestingly, development of the controversy has made the evaluation of the risk balance between hormonal contraception and unwanted pregnancy more intricate. In 2011, a retrospective family cohort study of thrombophilic women compared the risk of NRT associated with hormonal contraception with that associated with pregnancy/postpartum, and concluded that:

Although in the women with [NRT], the absolute risk of VTE increased during COC [combined oral contraceptive, that is the 3rd and 4th generation pills] use, this risk was importantly lower than the absolute risk observed during the pregnancy-postpartum period. These data provide evidence that the policy to contraindicate COC use in these women needs reconsideration. (Van Vlijmen et al., 2011: 2060).

The thrombotic side effects of combined hormonal contraceptives should not only be weighted against unwanted pregnancy as a social issue, but also against the thrombotic side effects that these unwanted pregnancies would entail. Similarly, in a clinical review, the internist Ángeles Blanco-Molina (2012) contends that the choice of birth-control method should depend on a balance between different types of thrombotic risks inherent to: genetic predispositions, the contraceptive method, and eventual unintended pregnancy resulting from contraceptive failure. Altogether, she argues that the use of oral

contraception to control pregnancies would be the most efficient way to reduce the global VTE burden in fertile women. This evolving argument is interesting in what it reveals of the constructivist nature of the risk/benefit balance, the potential emergence of new competing risks and the possibility of having a social risk (i.e. unwanted pregnancy) partly rewritten in biological terms (increased thrombotic risk associated with unwanted pregnancies).

This argument draws on the well-established tendency to medicalize pregnancy by focusing on and prioritizing the dangers that may occur in this period. NRT are no exception. In France, for example, the first recommendations about thrombophilia risk management were published in 1999 by the French College of gynaecology and obstetrics and they only concern pregnancy (Verspyck et al., 1999). Some years later, the French National Agency for Health Accreditation and Evaluation organized a consensus conference on the subject (ANAES, 2003), and two national score systems are available for VTE risk in pregnancy that includes NRT testing (Chauleur et al., 2010; Dargaud et al., 2009). On the contrary, NRT testing before contraception is only discussed in 2009, in the very last section of very general national guidelines (Pernod et al., 2009)[3].

In a field such as prenatal medicine, thrombotic risk is taken into account, as part and parcel of the web of potential dangers which the medical discourse used to monitor pregnancy. In contrast, in the context of contraception, NRT are isolated risk factors and, so, results too 'generic' to be clinically informative on an individual basis. The duty of clinicians is, consequently, to resist the screening imperative (Faulkner, 2012) and to restrict NRT usage to clinically controlled contexts. There, the thrombotic risk and its balance with other risks can be properly assessed.

Progestogen-only preparations may for instance be a good alternative for contraception among women whose oestrogen use is contra-indicated [i.e. NRT carriers or at-risk women such as smokers and the obese] (…) [and are] recommended in the guidelines as a safe birth-control method in women with thrombophilic defects (Blanco-Molina, 2012, S18).

Here, clinicians are encouraged to use NRT testing as a tool to optimize and personalize the choice of the right pill among the many available. After conducting a thoroughly contextualized assessment of the patient's thrombotic risk, the latter can rightfully decide on their contraception prescription choice. This approach has been particularly advocated after the 'pill crisis' and litigation against the prescription of the 3rd and 4th generation pills. In France, for example, new generation pills are usually suggested as a second-line option and are not reimbursed by the national health-care system anymore.

To conclude, the medical framework dominating the regulation of NRT tests in the context of hormonal contraception considers that universal measurements of thrombotic risk are negligible as compared to the risks associated with unwanted pregnancies. Only individualized measurements of risks, evaluated in the context of clinical encounters, can pretend to be informative enough to usefully influence prescription of hormonal contraception. While the materialization of the thrombotic risk in a genetic test could have been expected to increase its visibility, its management under the sole responsibility of clinicians has paradoxically made it largely invisible. Consequently, this thrombotic risk of a biological nature continues to be supplanted by a broader risk of a more social nature (unwanted pregnancies), although the latter has recently been partly reframed in biological terms as an overload of pregnancy-associated thrombosis, in order to make it bolder. In this context, the decision to arbitrate between risks is in the clinician's hands. At best, the NRT test is perceived as a decision-support tool to help the clinician in his contraception prescription, but not as a materialization of risk.

The economics of testing between illness ontologies and medical models of risk

The cost of a screening programme is often an insurmountable obstacle to its implementation. Many studies committed to cost-benefit analyses confirmed the intuition of the Leiden team, according to which universal NRT screening is economically unsustainable. If anything, testing should be offered selectively, to women with a family or personal history of VTE. According to Creinin et al., (1999), the prevention of one death from pill-related VTE would require screening more than 92,000 women, for a total cost of more than $300 million. The cost of each year of life saved amounts to several million dollars, much higher than other screening programmes, such as mammography for breast cancer. None of the 11 studies analysed in the systematic review of Ademi et al., (2017) considered universal NRT screening as cost effective.

This literature, despite its unanimous conclusions, met with sharp criticism from two recent meta-analyses (Ademi et al., 2017; Vernon et al., 2017). These studies, the meta-analyses argue, lack general rigor in the construction of their economic models. Underlying assumptions are not standardized with regard to the type of molecular examinations considered (NRT only or NRT and other rarer or even acquired hereditary thrombophilia); the consequences of a thromboembolic accident, which are too often limited to death; and, finally, the costs, which often do not include the treatments required after thrombotic accidents. The meta-analyses introduce a more general epistemological and ontological reflection on risk, which reveals its multiple, conventional and socio-cultural character, in particular concerning the implicit temporality embedded in the models.

Most studies underestimated the benefits of thrombophilia screening by comparing one-time costs of genetic screening against benefits per person-year, thus implicitly assuming a 1-year duration of COC use, neglecting the long-term implications of VTE and/or neglecting the lifetime benefits of awareness of inherited thrombophilia (Vernon et al., 2017).

As emphasized in this quotation, the study points to three major temporal flaws. First, the economic models consider the beneficial consequences produced in just 1 year for pill users, although evidence shows that average use is much longer than 1 year. Given the accumulation of risks over time, the benefits of screening are systematically underestimated. Secondly, most models only consider death caused by thromboembolic accident. They do not include the wide range of possible sequelae that VTE may cause, including thrombotic recurrences, bleeding, stroke and post-thrombotic syndrome, just to name a few. Finally, the models do not incorporate 'additional lifetime benefits of knowledge of inherited thrombophilia for other situations characterized by elevated thrombotic risk or excluded them with rationale'. NRT test results, the authors maintain, may also be useful for women in other situations in life characterized by elevated thrombotic risk, such as pregnancy postpartum, hormone replacement therapy, surgery, long-haul flights and immobilization.

In two subsequent articles, the authors add a consideration that not only concerns the production of information on cost-benefits, but also access to it. While advocating for 'expanded' testing programmes, Hiedemann et al., (2019) contend that the cost-benefit analysis implicitly refers to the collective standpoint of 'a third-party payer', that is health-care services or private insurance company, which is different from the standpoint of a single woman:

[If] from the perspective of third-party payer… screening is 'excessive' because it adds to the already high health-care costs without adding much, if any benefit… [f]rom the patient's perspective the key question concerns whether this knowledge has actionable benefits that could potentially outweigh the costs. Evidence suggests that this may be the case as this knowledge has potential clinical cons.

The exorbitant budget of universal NRT screening should not prevent women from being informed about the predisposition to adverse reactions to combined oral contraceptives. Getting access to individualized risk profiles is economically unsustainable for health-care services or private insurance

companies; yet, this does not exclude that a woman should be informed about this predisposition and decide to eventually pay out of pocket to be tested for it. This advocacy for 'extended NRT testing' is framed within the ideal of personalized (predictive, preventative and participatory) medicine, more specifically of 'the right to know' any potentially relevant information related to health. Being tested should be a choice left to the individual woman. References to 'knowledge', repeated several times throughout the articles, is aligned with taking full responsibility over procreation. Messages of empowerment through self-knowledge emphasize risk visibility by letting the risk outside of the scope of medical competences. This is clearly in tension with the traditional role of medical professionals, as we will see in the next section.

The role of family history: integrating genetics into clinical practice

Most guidelines have validated the practice of selectively testing women with a personal or family history of VTE. Family history works primarily as a surrogate in the search for hereditary predispositions and allows the test to be targeted to a smaller group of women who have a higher probability of being NRT carriers. This technique requires complex clinical work and collaboration from patients in reconstructing past conditions of family members. It allows the medical profession to opportunistically prescribe thrombophilia screening to women for whom results are expected to be clinically relevant. Given the low penetrance of the genetic polymorphism at play, it helps in interpreting the molecular results. According to a recent clinical review, 'screening for hereditary thrombophilia should represent a comprehensive evaluation of the patient's pro-thrombotic state and not a purely laboratory testing'. (Colucci & Tsakiris, 2020: 619). The authors contend that 'carrying out a thrombophilia examination… is often a cause of uncertainty and concern' (618), and that this decision should be left to the discretion of the doctor. Avoiding mass NRT screening does not matter only for its costs, but also for its implications in clinical practice in terms of uncertainty for medical professionals and concerns for women. Learning about being a carrier of such a hereditary susceptibility to form blood clots could provoke needless anxiety, or, inversely for non-carriers, provide a false sense of reassurance. Studies on this topic do not report conclusive results, but they generally indicate medical mediation as a necessary step to decide both which people to test and which pertinent clinical actions to take following the results.

However, several empirical investigations have questioned the relationship between family history and NRT. According to the case-control study of Schambeck et al., (1997: 1480), family history and FVL are 'most prominent, but independent additional risks'—in other words, 'FH is an unreliable criterion to detect FVL carriers'. They conclude that a family history of the disease cannot be a proxy for NRT testing, as testing only women with a family history would miss a relevant number of women at increased risk of thrombotic complications due to hormonal contraception. Other subsequent studies not only confirm these results, but, in some cases, also suggest that family history is a weak predictor of VTE. A systematic review argues that 'a positive family history of venous thromboembolism [is] no better than flipping a coin in predicting thrombophilia' (Grimes et al., 2012). For these authors, NRT is a risk source that cannot be absorbed into clinical symptoms collected individually, but needs to be objectified and made visible.

In discussing these results, Cosmi et al., (2003) raise the question of access to information. They oppose an *epidemiological* perspective versus a *clinical* perspective. Even if, epidemiologically, mass screening is not cost-effective, single practitioners, they argue, should provide complete information about pill-related risks and the possibility of NRT testing to their patients. Not doing so would be unethical and could also lead to litigation. Without calling for universal screening, they suggest

providing information about the test to all women wishing to take the pill, independently of the individual evaluation of their profile.

Practical initiatives also relaunched the 'extended' NRT testing strategy, in particular several score systems developed to assess the risk of VTE associated with hormonal contraceptives. These systems aim to strengthen the predictive capacity of genetics by triangulating it with environmental risk factors, notably obesity and smoking, in order to produce more efficient ways to predict VTE in young, healthy women. By providing individualized risk profiles based on standardized indicators, the scores propose a version of risk assessment that appears to be more transparent and able to bypass medical expertise. Hence, the temptation of commercializing these scores as direct-to-consumer screening tests. For example, a private Swiss laboratory, Gene Predictis, has turned the score system devised by a team at the University Hospital of Marseille (Suchon et al., 2017) into a commercial product. Pill Protect® is advertised directly to the general public as 'a fantastic breakthrough in women's care', and 'the most optimal and safest contraceptive pill/method for every woman'[4]. These new systems are part of a panoply for personalization of health care, motivated to inform and involve patients in preventive processes. Risk visibility is part of the rhetoric of self-knowledge and, as such, it participates to a movement of health marketization that blurs the boundaries between the clinic and the outside, transforming tendentially medical professionals from prescribers of tests to informers of risk.

CONCLUSIONS

Risk visibility provides a descriptive and interpretative framework to explore political and epistemological implications of screening as a medical and social intervention typical of a mode of governmentality based on surveillance. By turning the focus on the actors and the socio-technical contexts that contribute to the recognition of a risk and that control its publicization, visibility helps in analysing the processes that govern the flows and restrictions of NRT. This reveals interesting intertwined dynamics among medical prerogatives, women's responsibility and drug safety. Accordingly, the medical debate over NRT testing before the first prescription of hormonal contraception is an interesting moment to characterize issues on risk visibility for adverse reactions from oral contraception.

The medical profession has traditionally guaranteed and monitored the safety of these pharmacological treatments. Analysing its role in the visibility of the thrombotic risk attached to these drugs implies considering the conditions of its control over NRT prescription and interpretation. In selective screening strategies, prescriptions are placed under the supervision of physicians. Integrated into and filtered through medical decisions, the prescriptions are de facto restricted and localized in a subgroup of 'at-risk' women, with additional clinical, familial or behavioural risk factors. The traditional medical prerogative to select the relevant information to give to patients is extended to risk factors, especially genetic ones. With the goal of curbing the circulation of what is viewed as 'useless information' and optimizing the use of health-care resources to answer 'good' clinical questions, this allocation of NRT solely to the medical sphere contributes to the limitation of thrombotic risk visibility.

In contrast, the proponents of universal screening frame the possibility of receiving a genetically informed measure of susceptibility to thrombosis as a woman's right, rather than as a doctors' prerogative. Doctors are not considered as intermediators of relevant information and guardians of collective health and economically viable care, but as humble providers of information to women, who become responsible, at least partly, for their decision to arbitrate between different contraceptive risks.

Similarly, in 'extended testing' strategy, physicians are strongly encouraged to advise their patients of the risk factors, regardless of their low clinical utility. Informing women is a moral/legal obligation and not doing it could, indeed, lead to medical litigation. Universal or extended screening thus implies a loss of medical control and a correlated increase in risk visibility.

Lesser tests prescribed in selective screening rather than in a universal setting lead to reduced visibility. Still, the impact on risk visibility is not only a quantitative one. Qualitatively, visibility is also related to the ambivalent nature of risk factors, on the border between the normal and the pathological and the uncertainty attached to this status. In universal screening, the duality, which highlights the risk factor dimension of NRT, is fully present. In fact, many clinicians deplore the uncertainty, especially in women presenting unique and isolated risk factors, for whom the tests tend to provide information about thrombotic risk with no utility from a purely clinical perspective. In contrast, when embedded in clinical settings, the duality of NRT is less apparent. The test results tend to be assimilated with pathological signs or discarded as unimportant and benign.

Visibility also offers an interesting perspective to analyse the influence of additional actors. Medical discourse on NRT is, for instance, in a confrontation with DTC firms that make genetic risk factors a growing market. Still, their influence is not exerted directly on medical procedures but rather by their aggressive marketing practices promoting a larger visibility for the thrombotic risk.

The introduction of NRT affects the distribution system for hormonal contraception and questions its safety by pointing to situations in which the risk of adverse reactions is enhanced. Limiting NRT visibility only to the medical profession can thus be interpreted as an attempt to preserve the image of pharmacological control on fertility. Still, thinking in terms of risk visibility allows us to point out two different ways in which competitive sources of danger are perceived and managed, within the medical community. On the one hand, those who consider that the general image of oral contraception as safe should be actively protected call for strong limitations on NRT testing. This follows a risk 'illiteracy approach', under which, in the eye of the public and of many non-expert clinicians, a risk is either present or absent, whatever its value, and priority is placed on minimizing the risk visibility, by limiting the testing, including inside the medical sphere. On the other hand, those who consider that NRT testing can help in the personalization of contraceptive choice, advocate that a proper handling of the risk is possible provided that it is controlled by clinicians. In doing so, the risk remains visible, but its filtering and offer to women with a hereditary risk of adverse reaction contribute to obscuring its visibility.

Finally, visibility points to what is missing in the medical debate, particularly as to which risk becomes visible. Individualized molecular risk factors magnify the medical decision-making process inherent in contraception, while overshadowing all other questions that could be implied in a choice on medical treatment or intervention, such as the meanings and relationships implied in fertility control. Contraception is, thus, biomedicalized, not necessarily in the sense that it becomes a pure prerogative of medical doctors, but in the sense that its choice is framed as dictated by molecular or clinical indicators. Both critics and advocates of universal or extended thrombophilia screening share a common commitment, which is deploying NRT testing as a means to lessen the uncertainties surrounding contraceptive practices. In so doing, they all avoid considering a broader criticism, such as the one raised by AVEP and Marion Larat, of hormonal contraception as a socio-cultural practice embedded in sexuality and procreation.

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Mauro Turrini: Conceptualization (lead); Funding acquisition (equal); Investigation (lead); Methodology (lead); Project administration (equal); Writing-original draft (lead); Writing-review & editing (lead). **Catherine Bourgain:** Funding acquisition (supporting); Project administration (supporting); Writing-original draft (supporting); Writing-review & editing (supporting).

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ENDNOTES

[1] Although other contraceptive techniques, such as the patch, the implant, or the injection are also associated with a risk increase, less study are available. Further, for progesterone-only contraception, generally considered safer regarding VTE, the thrombotic risk is still a matter of debate.

[2] Here are the details: ((("Contraceptives, Oral"[Mesh]) AND ("Thromboembolism/chemically induced"[Mesh] OR "Thromboembolism/genetics"[Mesh] OR "Thromboembolism/prevention and control"[Mesh] OR "Thrombophlebitis/genetics"[Mesh])) AND (Factor V); (Screening thrombophilia[Title/Abstract]) AND (contraceptives[MeSH Terms]).

[3] Analogously, additional thrombotic risk from 3rd generation pills were taken into consideration for the first time by a national healthcare agency in 2007 (HAS—Haute Autorité de Santé 2007).

[4] Gene Predictis. Pill Protect ®https://genepredictis.com/cms/wp-content/uploads/2015/09/Press-release_Pill-Protect_september-2015_ang1.pdf.

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