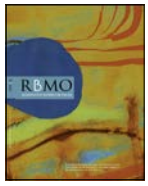
RBMO



COMMENTARY

# The neglected role of preimplantation genetic testing for Lynch syndrome

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## ABSTRACT

Preimplantation genetic testing for monogenic/single-gene disorders (PGT-M) is a procedure employed in the field of assisted reproductive technology to avoid the transmission of genetic diseases to the offspring. Hereditary cancer syndromes represent a diffuse and accepted indication for PGT-M, but take-up differs among the different disorders. Its use is markedly lower for the genes causing Lynch syndrome compared with the breast cancer type 1 or 2 susceptibility genes (*BRCA1/2*), despite the similar prevalence and severity of the two conditions. Reasons to explain this difference have not been explored. First, Lynch syndrome may be more frequently undiagnosed compared with hereditary breast and ovarian cancer syndrome. In addition, the different take-up may be due to different patient perceptions of the conditions and of the management options. Finally, this distinct attitude may depend on the awareness and sensibility of the professionals caring for affected patients. The authors' considerations are, however, speculative, and specific studies aimed at disentangling the causes of the different receptions of PGT-M are warranted to understand how to tackle this gap. In the meantime, we believe that empowerment regarding PGT-M of all individuals with hereditary cancer syndromes, including Lynch syndrome, is ethically due, and plead for a more active involvement of caregivers.

Preimplantation genetic testing for monogenic/single-gene disorders (PGT-M) is a procedure employed in the field of assisted reproductive technology to identify embryos carrying genetic diseases. Embryos are biopsied and genetically tested to allow the transfer only of those which are not affected, or at least to favour the transfer of those not affected in the first place. In rare circumstances, and with full patient consent, an affected embryo may also be transferred if that is the couple's wish.

From a technical point of view, this procedure is feasible for any single-gene disorder. PGT-M was initially advocated for clinically severe diseases with a high penetrance, early age of onset, and poor or ineffective treatment options. However, indications have subsequently expanded to genetic mutations exposing a person to an enhanced risk of developing pathological conditions during their lifespan, including hereditary cancer syndromes (HCS) (*Ethics Committee of ASRM, 2018*).

Approximately 5–10% of cancers occur in the context of HCS. In individuals with these syndromes, the cancers are typically characterized by a young age of onset, and there is a high lifetime risk of multiple neoplasms and familial clustering. Among HCS, hereditary breast and ovarian cancer syndrome (HBOC) and Lynch syndrome are the two most common, affecting about 1 in 300–500 and 1 in 400–500 individuals, respectively, in the Wester world (*Somigliana et al., 2022*).

HBOC is an autosomal dominant condition characterized by germline pathogenic variants in either of the breast cancer type 1 or 2 susceptibility genes (*BRCA1* or *BRCA2*), which lead to a susceptibility to breast and ovarian

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## KEY WORDS

*BRCA*
Hereditary cancer syndromes
Lynch syndrome
Monogenic disorders
Preimplantation genetic testing
Preimplantation genetic testing for monogenic/single-gene defects (PGT-M)

cancer, and less frequently to tumours of other organs, such as the fallopian tubes, endometrium, prostate and pancreas (*Somigliana et al., 2022*). *BRCA1/2* carriers undergo strict surveillance and disease prevention with oral contraceptives until the time of risk-reducing surgery (bilateral salpingo-oophorectomy and bilateral mastectomy). Surgical castration (bilateral salpingo-oophorectomy) is advocated once childbearing is complete, and no later than 35–40 years of age for *BRCA1*, and 40–45 years for *BRCA2*. Risk-reducing surgery lessens the risk of ovarian cancer and breast cancer by approximately 80–90% and 60%, respectively. Recent evidence suggests also performing hysterectomy to temper the enhanced risk of endometrial cancer (*Berger and Golshan, 2021*).

Lynch syndrome (also named hereditary non-polyposis colorectal cancer) is an autosomal dominant condition linked to germline mutations or epimutations in one of the genes involved in the DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6* or *PMS2*). It is the most common hereditary colorectal cancer syndrome, characterized by a 25–70% lifetime risk of colorectal cancer. Moreover, carriers are exposed to a higher risk of endometrial cancer (12–46%) and, less frequently, to many other extracolonic tumours, including carcinoma of the ovary, stomach, small bowel, pancreas, hepatobiliary tree, brain and urinary tract (*Somigliana et al., 2022*). To reduce the risk of gynaecological cancers, female carriers may consider transvaginal ultrasonography and endometrial biopsy on an annual basis, starting from the age of 30–35 years, until the time of risk-reducing surgery, which consists of total hysterectomy and bilateral salpingo-oophorectomy (*Cunningham et al., 2022*).

Despite these conditions having a similar prevalence and overlapping risks of cancer diseases, the current authors have observed a markedly different demand for PGT-M by carriers of *BRCA1/2* and Lynch syndrome mutations. The latest published report of the European Society for Human Reproduction and Embryology (ESHRE) consortium on PGT-M, referring to the period 2016–2017 and including 3098 analyses for monogenic disorders, listed HBOC (*BRCA1/2*) as the second most common indication (6.9%) after Huntington disease (9.2%) (*van Montfoort et al., 2021*). Lynch syndrome was not listed among the top 10 indications, suggesting that the frequency is at least below 2%. The most recent results of the consortium for the years 2019–2020, presented at the last ESHRE annual meeting in Milan, Italy, showed comparable findings (*van Montfoort et al., 2022*). Of note, the latest available report of the consortium that listed in detail all genetic diagnoses reported 28 cases of HBOC (*BRCA1/2*) and only three cases of Lynch syndrome (*Moutou et al., 2014*). Finally, it is worth highlighting that there are several contributions in the literature advocating the use of PGT-M for *BRCA1/2*, including economic analyses (*Vuković et al., 2021*). In contrast, similar contributions for Lynch syndrome could not be identified.

We speculated what the reasons might be for the different awareness of and attitudes to the acceptability of PGT-M in these two groups of individuals. Determinants behind this remarkable difference have been poorly explored (*Rich et al., 2014*). Some hypotheses can, however, be drawn. First, Lynch syndrome is underdiagnosed (*Monahan et al., 2017*). There are ongoing efforts to improve this issue, but there is still a consistent proportion of undiagnosed cases, potentially also explaining the lower rate of referral for PGT-M. Discussing in depth this issue is, however, beyond the scope of this manuscript.

Second, HBOC is perceived as pathological mainly in women, because these cancers typically affect organs associated with female reproduction. Even if men are also exposed to an increased risk of cancer (breast, prostate, pancreas, and colon) and can transmit the mutations, the clinical relevance is deemed inferior and the need for preventive measures felt to be less stringent. One may speculate that the involvement of the female reproductive organs may enhance women's sensitivity towards reproductive issues, including PGT-M. The 'Angelina Jolie Effect' may have further strengthened this aspect. In *BRCA1/2* mutation carriers, a mutilating and castrating surgery for prevention is recommended. Conversely, Lynch syndrome is better known as a syndrome linked to colorectal cancer (as also reflected by its previous name of hereditary non-polyposis colorectal cancer), that frequently does not even require surgery for prevention, but only requires early diagnosis (*Cunningham et al., 2022*). In other words, women at risk of transmitting *BRCA1/2* pathogenetic variants to their offspring could be more sensitized to reproductive issues and could feel a more stringent need for PGT-M. This may also be valid for unaffected women conceiving with a male carrier. Of note, even if male carriers are also exposed to an increased risk of cancer, the condition is perceived differently, to the point that couples may decide to transfer an affected male embryo.

The acceptance of PGT-M may not strictly depend on the personal history or on the severity of the disease, but rather on the individual perception of the disease itself and of its burden; this is passed on through the experience of affected family members, the witness of death and suffering among close relatives, the personal ability to deal with the risk of developing cancer, the perceived quality of life and the confidence in current and future management options (*Rich et al., 2014*). Usually, the disease is perceived as more burdensome when it has a childhood onset and lacks a surgical risk-reduction option. However, this aspect cannot explain the different attitude toward PGT-M in individuals carrying *BRCA1/2* pathogenic variants and in those with Lynch syndrome, since both are characterized by a young onset of cancer that can be partly prevented by surgery performed at an appropriate time.

It can be hypothesized that it is not only the availability of risk-reducing surgery, but also the type of surgery needed that makes the difference: bilateral mastectomy and oophorectomy performed in HBOC impacts negatively on body image and sexuality, potentially explaining the higher interest in PGT-M among individuals with HBOC. In patients with Lynch syndrome colorectal cancer risk is reduced through colonoscopy follow-up, frequently without the need for surgery. This may explain the lower take-up of PGT among these patients. Although it is plausible, this potential reason for explaining the different uptake of PGT-M is not, however, rational. Lynch syndrome not only means colorectal cancer, but, to the same extent as for HBOC, also involves a higher risk of gynaecological cancers. Hysterectomy and bilateral salpingo-oophorectomy

are also typically advocated for Lynch syndrome, even if they are not systematically performed (*Cunningham et al., 2022*).

So far, this paper has focused on patients' attitude toward PGT-M. What about healthcare providers? Previous studies have highlighted a scarce and limited knowledge of PGT-M for hereditary cancers among physicians. This aspect is noteworthy and, somehow, worrisome: women with HCS are scared and confused, especially at the time of diagnosis, when they obviously have different priorities from reproduction. However, during their subsequent long clinical journey, they need to be carefully guided toward all the reproductive options available by specialists in that field, to be able to finally make a completely informed decision (*Somigliana et al., 2022*). For that reason, the availability in oncological centres of experts in genetics and reproductive medicine is highly recommended. Of relevance here is that this insufficient sensitivity may be even more patent for Lynch syndrome since, in general, these cases are not managed by gynaecological oncologists. However, even if not directly engaged in reproductive medicine, some of the latter physicians may be more familiar with reproductive issues and PGT-M because of their cultural background.

It can be concluded that the different attitude toward PGT-M between Lynch syndrome and HBOC may have several causes. Our considerations are, however, speculative. Specific studies aimed at disentangling the determinants of this different sensitivity are warranted. Of relevance is discerning whether this lower uptake is due to a well-informed decision of affected individuals, to underdiagnosis of the condition or to the scant awareness of the carriers or the caregivers. In the latter two situations, one would have to foresee strategies of intervention to tackle this gap.

In the meantime, it must be underlined that the empowerment of affected individuals is ethically due. Caregivers managing women and men with Lynch syndrome should be aware of PGT-M. People of reproductive age and in particular those planning for parenthood should receive a multidisciplinary consultation that also includes experts in genetics and in reproductive medicine. Full awareness of the couple with respect to the mutation they are carrying and the potential consequence for their offspring is crucial. In fact, even in this area, medicine is becoming increasingly personified, shared and tailored to the needs of the patients, their experience and their family history.

## AUTHOR CONTRIBUTIONS

Author contributions were as follows: E.S. and F.F. – conceptualization; C.D. and A.R. – writing, original draft; F.M., M.T.R. and M.V. – writing, revision and editing; P.V. – supervision.

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