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Exploring Gene-Specific Guidelines for Risk Management of Gynecological Cancer in Lynch Syndrome

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Lynch syndrome is a unifying term for a hereditary cancer syndrome associated with abrogation of the DNA mismatch repair (MMR) pathway. Heterozygous pathogenic variants (PVs) in the MMR genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* are associated with an increased risk of a spectrum of cancers, with colorectal cancer (CRC), endometrial cancer (EC), and ovarian cancer (OC) being the most common. Providing precise gene-specific cancer risks while minimizing ascertainment and selection bias is challenging but vital for guiding appropriate decision-making for patient care.[1] Improving the ratio of clinical benefit to potential harms is important given that many individuals identified with PVs do not have cancer or are at increased risk of a second metachronous cancer owing to improved survival stemming from advancements in early detection and cancer treatment.[2] Although colonoscopy screening guidelines are increasingly targeted to individuals' gene-specific CRC risk, current clinical guidelines for management of MMR-associated gynecological cancers are more conservative and based generally on the more highly penetrant gene risks associated with *MSH2* and *MLH1* (EC risk, 35%-47% to age 70 years; OC risk, 11%-17% to age 70 years). While screening for EC and OC is offered in some settings, there is insufficient evidence of clinical effectiveness, and therefore most guidelines recommend risk-reducing surgical treatment in the form of total hysterectomy and bilateral salpingo-oophorectomy (hyst-BSO) from ages 35 to 40 years or after completion of childbearing.[1] Unlike colonoscopy, BSO may be associated with increased mortality and morbidity and reduced quality of life. Our understanding of the outcomes associated with premature surgical menopause and the potential mitigation associated with menopausal hormone therapy is still evolving, but BSO is associated with an increased risk of sexual dysfunction, osteoporosis, cognitive dysfunction, and cardiovascular disease.[3]

Wright and colleagues[4] report the outcomes of a simulation model–based cost-effectiveness analysis evaluating the gene-specific timing and uptake of gynecologic risk-reducing surgical treatment and screening among individuals with Lynch syndrome. The risk management strategies evaluated comprised EC and OC screening at varying ages, synchronous hyst-BSO, and a 2-stage approach of hyst-salpingectomy with delayed oophorectomy (hyst-BS + BO). The authors found that the 2-stage surgical approach (hyst-BS at age 40 years and BO at age 50 years) was cost-effective for individuals with *MLH1* and *MSH6* PVs and single-stage hyst-BSO at age 40 years was preferred for individuals with *MSH2* PVs. In contrast, delaying hyst-BSO until age 50 years was optimal for individuals with *PMS2* PVs. Similar to the findings of a previous study,[5] none of the optimal strategies included EC or OC screening. These results strengthen the proposal that management of Lynch syndrome as 4 distinct inherited cancer syndromes may be associated with benefits among individuals with MMR PVs.[2]

This is the first study, to our knowledge, to explore the cost-effectiveness of hyst-salpingectomy with delayed oophorectomy among individuals with Lynch syndrome. This 2-stage surgical approach is a recent development in OC risk-reduction strategies that may be associated with decreases in potential adverse outcomes associated with premature surgical menopause[6] without decreases in clinical effectiveness. This approach is gaining research traction and relies on evidence that some epithelial OCs originate in the distal fallopian tube. Applying this approach to women with Lynch syndrome requires caution, however, given that the tubal hypothesis is associated with the high-grade serous OC subtype, whereas 80% of individuals with MMR-associated OC have nonserous

histology. OC itself is a unifying term for molecularly and clinically heterogeneous disease. The oncological safety of the 2-stage approach is currently under investigation for several hereditary OC predisposition syndromes (including the presence of *MLH1*, *MSH2*, *MSH6*, and *PMS2* PVs) in the Women Choosing Surgical Prevention Study (MD Anderson Cancer Center, NCT02760849).

Simulation modeling can be an invaluable tool in this context. Modeling allows assessment of the short-term and long-term outcomes associated with proposed changes to clinical practice and is an important component in decision-making regarding the adoption of new health technologies and services. Models can also demonstrate how sensitive clinical outcomes are to specific parameters (such as risk reduction after surgical prevention), thereby highlighting key research questions that need to be addressed. Simplifying assumptions are necessary in even the most complex models, from assumptions associated with unobservable aspects of a disease's natural history to assumptions concerning limiting the number of clinical pathways patients may follow. Wright et al[4] should be commended for making the model source code publicly available for review, given that lack of transparency is a common issue in complex cost-effectiveness models.

In this study,[4] EC and OC screening were associated with improvements in quality-adjusted life years (QALYs) for several scenarios. This benefit, however, appeared to be associated with the modeled assumption that all women who had a false positive screening result (for EC or OC) were assumed to immediately undergo hyst-BSO irrespective of age, an outcome that occurred among up to 6% of women screened each year within the modeled population. The assumption of surgical treatment for false positives was likely reasonable in this context; however, the observed benefit associated with screening needs to be viewed with caution considering the limited direct clinical evidence of early detection (downstaging) or improved survival associated with screening.[1,7]

Wright et al[4] highlighted the limitations on modeling gynecological cancer among individuals with Lynch syndrome due to the high degree of uncertainty for certain model inputs. The evidence that individuals with *PMS2* PVs are at an increased OC risk compared with the general population is limited; in a sample of 233 women from the international Prospective Lynch Syndrome Database, there was 1 incident diagnosis of OC over 957 person-years.[2] In addition, unlike OC diagnosed among individuals with *BRCA1/BRCA2* PVs and the general population, 67% to 80% of MMR-associated OC is diagnosed as early-stage disease, with a reported favorable 10-year survival rate of 84%.[2,7] Given this uncertainty, it may be reasonable for individuals with *PMS2* PVs to opt for hysterectomy alone for EC prevention; therefore, it is interesting that this option was not explored in the current study. A possible reason for this omission is that the authors assumed that women or their health care practitioners may be too risk averse to accept this recommendation. How to effectively implement risk mitigation recommendations that are less intensive than previous guidelines in a manner acceptable to patients and clinicians will be an important area to explore. The previously mentioned issues, as well as other risk factors, should be considered in discussions of uptake and timing of gynecological cancer risk management for women with MMR PVs. This should be done to enable informed decision-making and to empower women to make the most personally appropriate decision given their personal circumstances and cancer risk.

A 2019 report[1] arising from a meeting of the Manchester International Consensus Group highlighted the absence of comprehensive clinical guidance regarding management of gynecological cancer among individuals with Lynch syndrome. As universal screening of colorectal and endometrial cancers for individuals with Lynch syndrome becomes more widespread, it will likely lead to increased identification of individuals with lower-penetrance *MSH6* and *PMS2* PVs. Ensuring appropriate gene-specific guidelines for clinical management will be increasingly important. By using clinical evidence generated through trials and observational studies, models such as that developed by Wright et al[4] may assist in delivering value-based health care to maximize clinical outcomes in a cost-effective way.

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