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OBG MANAGEMENT

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APRIL 2011

Cost-Effectiveness of Genetic Screening for Lynch Syndrome

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Is risk-assessment-based population screening for Lynch syndrome a clinically beneficial and cost-effective strategy for improving health outcomes? A recent study by Dinh and colleagues showed that such screening could be economically feasible.[1] Because there is a strong link between Lynch syndrome and a woman's risk of developing cancer, and because clinically relevant genetic testing for Lynch syndrome is widely available, this recent study may show that screening the general population followed by testing for gene mutations associated with Lynch syndrome may be an important and cost-effective measure to reduce the morbidity and mortality associated with the development of certain malignancies in women.[1] If such screening is associated with our patients' long-term health, ObGyns should better understand this syndrome and consider the details of this study.

KEY POINTS

- Lynch syndrome is a hereditary predisposition to colorectal and endometrial cancers (and other specific malignancies), resulting from a gene mutation
- Lynch syndrome is the most common heritable cause of colorectal cancer and endometrial cancer
- Practice guidelines limit risk assessment of Lynch syndrome to 1) genetic testing in people in whom malignancies have already developed and 2) mitigation of the impact of disease by colonoscopic and endometrial surveillance, and surgical prophylaxis
- No primary screening strategies currently exist for Lynch syndrome
- Over 50% of women with Lynch syndrome who develop two primary cancers develop a gynecologic cancer before colon cancer
- Guidelines issued by ACOG recommend that ObGyns incorporate identification and management of women who have hereditary breast and ovarian cancer syndrome into practice; similar guidelines do not exist for Lynch syndrome
- A new and powerful study has established evidence for a protocol of primary screening of Lynch syndrome at a particular threshold of individual risk
- Specifically, primary screening for unaffected patients, with risk assessment conducted beginning between 25 and 35 years of age, followed by genetic testing of people whose risk exceeds 5%, has the potential to improve health outcomes in a cost-effective way

Significant mortality but underrecognized

Lynch syndrome is caused by a germline mutation in one of several genes in the mismatch repair (MMR) system and is characterized by an increased risk for several malignancies, including colorectal, endometrial, and ovarian cancers.[2,3] As with other genetic conditions, inheriting the gene does not guarantee the development of any particular malignancies, although the lifetime risk of developing at least one of the several associated malignancies for a woman is well over 80%.[4]

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CLINICAL RESOURCES

For an in-depth discussion of clinical guidelines for Lynch syndrome testing, see the 2010 NCCN guidelines.[11] For a more detailed discussion of all clinical aspects of Lynch Syndrome, see some of the many available review articles.[5,12-14] In addition, several publications discuss details of current screening approaches for Lynch syndrome.[3,15]

Lynch syndrome is the most common heritable cause of colorectal cancer, and colorectal cancer is the second leading cause of cancer-related mortality in the United States, leading to about 52,000 deaths in 2007.[3] Of those individuals with colorectal cancer, about 1 in 30 (2%–4%) have Lynch syndrome.[3] Furthermore, Lynch syndrome is also the most common heritable cause of endometrial cancer, with about 2% to 5% of all diagnosed endometrial cancers being associated with Lynch syndrome mutations.[5] Overall, Lynch syndrome confers a potential lifetime colorectal cancer risk as high as 80%, and a lifetime endometrial cancer risk as high as 71%.[2,6]

Although these statistics present a clear cause for concern, Lynch syndrome remains considerably underrecognized in clinical practice.[7] Since there are strategies for mitigating the carcinogenic impact of the syndrome, including colonoscopic and endometrial surveillance and surgical prophylaxis, the potential for population-based screening deserves serious consideration, especially given the recent study by Dinh and colleagues. See the sidebar, "Clinical Resources," for Lynch syndrome resources.

Moving from reactive to proactive

Current clinical practice guidelines for Lynch syndrome recommend that a molecular diagnostic workup be initiated when clinically suspicious malignancies are detected.[3] Patients who have been identified as "at risk" for Lynch syndrome but in whom malignancies have not yet developed (unaffected patients) are typically referred for genetics consultation; only family members of known Lynch syndrome mutation carriers are offered genetic testing. These current strategies do not include any type of population-based screening for Lynch syndrome. If all individuals were assessed for Lynch syndrome mutations using available risk algorithms, with those found to be at "high risk" referred for genetic testing, early detection could then identify those people who would benefit most from surveillance and prophylactic interventions.

Some experts compare the potential benefits of population-based screening for Lynch syndrome to current screening recommendations for Hereditary Breast and Ovarian Cancer syndrome (HBOC).[1] In fact, ACOG guidelines now support the incorporation of population-based screening for HBOC into women's health care.[8] The results of the Dinh study are an initial step to provide evidence for a population-based screening approach to Lynch syndrome.

The simulation-model virtual study design

This study by Dinh and colleagues was conducted using the Archimedes Model, a large-scale simulation model that uses statistics and mathematical equations to assess data on patients, conditions, and health-care systems.[1] The model has been validated and is considered a valuable tool for evaluating the cost-effectiveness of clinical interventions.[9] It has been used extensively in diabetes, cardiology, and other significant conditions, and is now being applied to oncology. The alternative to this model is a decade-long cohort study.

For Lynch syndrome, the model used data on screening, diagnosis, surveillance, and treatment that were captured from health-care system databases of patients with Lynch syndrome and their first-degree relatives. For colorectal cancer, the model employed aggregate data from clinical trials, colonoscopy studies, retrospective analyses, and population surveys. Added to the mix were data from genetic testing panels and assays; biopsies; transvaginal ultrasound results; prophylactic procedures; and cancer treatments including surgery, pharmacologic treatment, and radiation therapy.

All of these clinical data were collected with the ultimate goal of determining cost effectiveness of population-based screening, so the cost of the medical tests and treatments were included using Medicare reimbursement rates. Parameters for calculating quality-adjusted life-years (QALY) were established; the generally accepted benchmark of $50,000 per QALY was used.[10] A QALY less than $50,000 is generally considered a good intervention.

Once the foundational information was collected, the authors performed a "virtual" clinical trial in which 100,000 simulated individuals within a 5-generation family history model were tracked from the age of 20 and were exposed to each of 20 primary screening strategies. The strategies involved risk assessment at various ages (20–40) followed by a 4-gene (MLH1, MSH2, MSH6, and PMS2) mutation panel testing of people whose risks for carrying a mutation exceeded various thresholds (0%–10%). While the trial used the PREMM1,2,6 risk assessment model (available at www.dfci.org/premm), the study authors

suggest that practicing clinicians consider using the MMRpro model (available at www4.utsouthwestern.edu/breasthealth/cagene/).

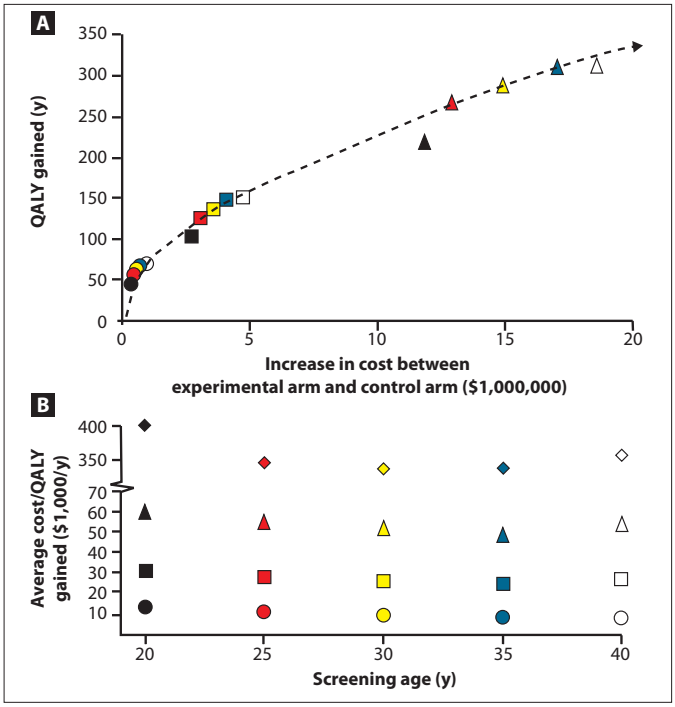
Results: evidence for primary (population-based) screening

The trial results provided information that can contribute to identifying strategies to reduce both the cost and clinical burden of Lynch syndrome by using a primary screening approach. Universal genetic testing (0% risk threshold) starting at age 20 reduced the incidence of colorectal and endometrial cancers in mutation carriers 43.9% and 39.6% respectively, compared with current practice. It also increased the average life-years by 4.07. As might be expected, as the risk threshold was increased with the various strategies, the reductions in cancers were decreased. Indeed, at the highest risk threshold, colorectal and endometrial cancer incidence was only reduced 5.3% and 3.6%, respectively.

As middle ground, the authors determined that risk assessment starting at ages 25, 30, or 35, followed by genetic testing of patients with mutation risks higher than 5%, reduced colorectal and endometrial cancer incidence in mutation carriers by about 12.4% and 8.8% respectively.[1] This strategy increased QALY by about 135 for a population of 100,000 individuals with 392 mutation carriers, with an average cost-effectiveness of $26,000 (**FIGURE 1,** part B).[1] The authors assert that this cost-effectiveness rate is comparable to the already incorporated primary cancer screening protocols for breast cancer and cervical cancer. Therefore, a population-based risk screening conducted beginning between the ages of 25 and 35 and followed by genetic testing of unaffected patients whose risk exceeds 5%, can potentially improve health outcomes in a cost-effective manner. If the outcomes found by Dinh and colleagues are corroborated in other rigorously performed studies, a change in our current clinical approach to Lynch syndrome screening to a population-based approach may be justified and would be especially important to the ObGyn practice.

FIGURE 1

Cost effectiveness of primary screening strategies for gene mutations in a simulated population of 100,000 individuals, representative of the general US population.



Note: Risk thresholds representing the probability of carrying a gene mutation above which to initiate genetic testing: ◆ 0.0%, ▲ 2.5%, ■ 5.0%, ○ 10%. Symbol color denoting screening initiation age: black = age 20, red = age 25, yellow = age 30, blue = age 35, white = age 40. Graph A represents increase in QALY versus increase in cost for 15 screening strategies for Lynch syndrome compared with current practice. Dashed line is the efficient frontier, representing sequential strategies, starting from the origin, with the greatest gain of QALYs per incremental cost. Strategies to the southeast of the efficient frontier are referred to as dominated. The inverse of the slope of the efficient frontier is the incremental cost-effectiveness ratio, representing the incremental cost per QALY compared with the next best strategy on the efficient frontier. Graph B represents average cost per QALY of 20 screening strategies for Lynch syndrome as functions of age, compared with current practice.

QALY = quality-adjusted life-years.

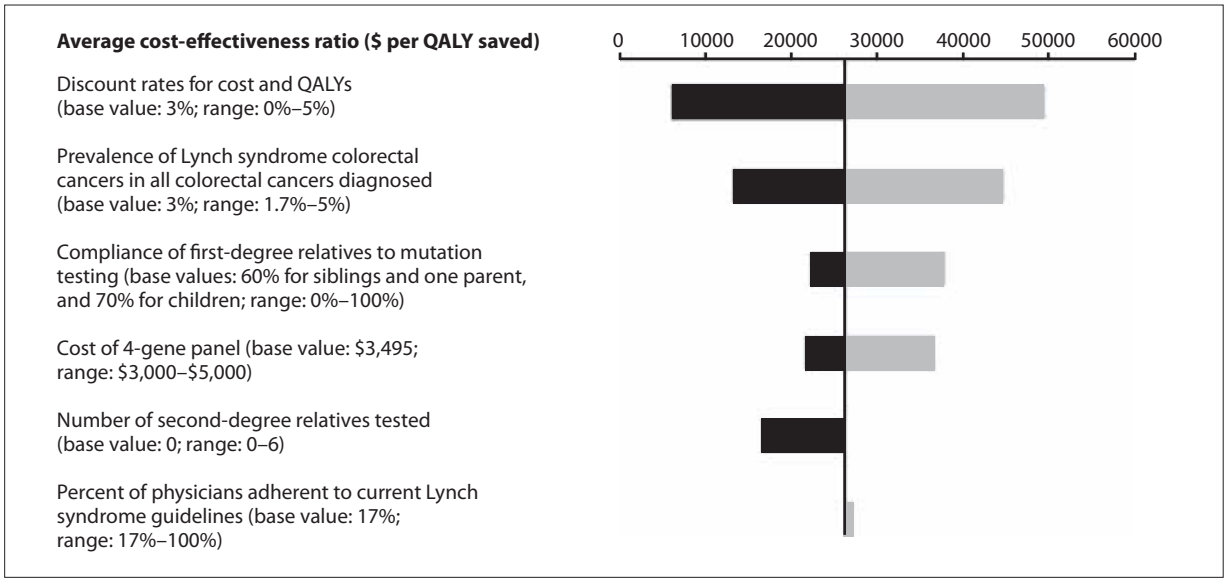
Adapted with permission from: Dinh TA, Rosner BI, Atwood JC, et al. Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. Cancer Prev Res. 2011;4(1):9–22.

Conclusion

Current clinical practice guidelines limit assessment for Lynch syndrome to genetic testing in people for whom malignancies have already developed or are first-degree relatives (children, siblings, parents) to those with known Lynch syndrome gene mutations. Robust analysis was conducted and showed that as more family members were tested in a family with a positive result for Lynch syndrome, overall cost-effectiveness increased significantly (**FIGURE 2,** page S4).[1] Results from this recent simulation study show that appropriate implementation of primary screening for Lynch syndrome gene mutations could be clinically beneficial and cost effective and would involve

FIGURE 2

One-way sensitivity analysis of Strategy 13 (derived from Tables 2–4 in Dinh).[1] Sensitivity of the average cost-effectiveness ratio as each parameter varies within the specified range.



QALY = quality-adjusted life-years.

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assessing risk based on personal and family history using one of the available online risk protocols mentioned, followed by genetic testing in people whose risks indicate a higher possibility of Lynch syndrome. Genetic tests are commercially available and would potentially allow for the detection of deleterious Lynch syndrome gene mutations before the development of cancer so as to allow for the use of novel surveillance algorithms and the consideration of prophylactic interventions to reduce the frequency and severity of Lynch syndrome-associated malignancies. ■

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