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Incorporating hereditary cancer syndrome screening into daily practice

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JOIN THE FIGHT AGAINST HEREDITARY BREAST AND OVARIAN CANCER: ASSESS EVERY PATIENT AT EVERY VISIT

- September is Ovarian Cancer Awareness Month
- October is Breast Cancer Awareness Month
- September 28–October 4 is Hereditary Breast and Ovarian Cancer (HBOC) Awareness Week
- October 1 is National Previvor Day*

*Previvor: An individual who carries a strong predisposition to cancer but has not developed the disease.

As gynecologists, every day we face an increasing number of clinical issues to consider when seeing our patients. While we strive for comprehensiveness, it is important to stratify our patient care to prioritize life-threatening risk factors. Identifying a pathogenic (deleterious) hereditary cancer gene mutation allows the clinician to implement life-saving, preventive management to reduce cancer risk and improve early cancer detection. Knowing a patient's hereditary and familial cancer risk will drive gynecologic management and decision making. Without knowing a patient's personal and/or family history of cancer, the clinician would be unable to determine appropriate treatment options for even the simplest gynecologic issue. Therefore, for every patient at every visit, it is imperative to systematically screen for personal and family risk of cancer and to test appropriate individuals for hereditary cancer syndromes.

The following cases illustrate how knowing a patient's hereditary cancer risk can affect the care we provide.

Disclosure
Dr. Snow reports that she is a consultant and speaker for Myriad Genetics Laboratories.

CASE 1 Managing fibroids—and cancer risk—in a patient with *BRCA1* mutation

YH is a 40-year-old patient, G0P0, who presented for a second opinion regarding large uterine fibroids. Her previous gynecologist treated the fibroids conservatively with medication and a dilation and curettage (D&C) procedure. The patient's menorrhagia became severe, however, leading to anemia. A hysterectomy was recommended, but the patient wanted a second opinion to discuss options for preserving her uterus.

YH's personal history was significant for fibroids, a D&C, and a breast biopsy. Her family history revealed that a paternal aunt was diagnosed with breast cancer at age 50, another paternal aunt was diagnosed with ovarian cancer at age 50, and a paternal cousin was diagnosed with breast cancer at age 30. The patient underwent genetic testing, and mutation of the breast and ovarian cancer susceptibility gene, *BRCA1*, was identified. YH then decided against uterus-preserving options. She underwent robotic-assisted total laparoscopic hysterectomy and bilateral salpingo-oophorectomy (BSO), as well as skin-sparing, nipple-sparing bilateral mastectomy and breast reconstruction, thus markedly decreasing her risk for ovarian and breast cancers. Identifying hereditary cancer syndromes in patients with a family history of cancer is imperative so appropriate surgical options and alternatives can be discussed. Before undergoing genetic testing, YH had been considering endometrial ablation, uterine artery embolization, myomectomy, and hysterectomy without BSO. None of those treatment options reduce the risk for ovarian and fallopian tube cancer—and YH had up to a 44% risk of these cancers.[1-5]

CASE 2 Preconception testing helps direct screening during pregnancy

AP, age 36, G1P0, presented with rectal bleeding at 28 weeks' gestation. Her personal history is noncontributory. Family

TABLE 1 The American College of Obstetricians and Gynecologists recommends hereditary cancer risk assessment

Family history as a risk assessment tool (Committee Opinion No. 478)
• It is recommended that all women receive a family history evaluation as a screening tool for inherited risk.
• Family history information should be reviewed and updated regularly, especially when there are significant changes to family history.
Breast cancer screening (Practice Bulletin No. 122)
• Risk assessment should be used to identify those who may qualify for enhanced screening, such as MRI screening, clinical breast examinations, and risk-reduction strategies.

MRI, magnetic resonance image.
Sources: American College of Obstetricians and Gynecologists. Family history as a risk assessment tool. Committee opinion No. 478. *Obstet Gynecol*. 2011;117(3):747-750; American College of Obstetricians and Gynecologists. Breast cancer screening. Practice bulletin No. 122. *Obstet Gynecol*. 2011;118(2 Pt 1): 372-382.

history revealed that her maternal grandmother had uterine cancer at age 42 and her maternal uncle was diagnosed with colon cancer at age 53.

Prior to her pregnancy, the patient underwent genetic testing and was found to have a deleterious *TP53* mutation, which placed her at increased risk for colon, uterine, breast, and other cancers. She then had a colonoscopy, endometrial biopsy, and mammography just prior to conception. Knowing that the colonoscopy was normal 8 months prior to the patient's rectal bleeding in pregnancy, her physician performed a proctoscopy and diagnosed internal and external hemorrhoids, which were then treated topically.

An ObGyn clinician does not often evaluate rectal bleeding in an otherwise healthy, young pregnant woman; the most common cause is hemorrhoids. Approximately 25% to 35% of pregnant women experience hemorrhoids.[6,7] In certain populations, up to 85% of pregnancies are affected by hemorrhoids in the third trimester.[8] If a patient has a family history of cancer, however, she may have a deleterious mutation in one of a number of hereditary cancer genes, raising her risk for early onset of colon cancer. Given AP's family history, without knowing her genetic information, colonoscopy would not have been indicated prior to pregnancy. Knowing genetic information helps identify which patients need to be evaluated for rectal bleeding to prevent or detect colon cancer and, ideally, who should undergo screening colonoscopy prior to conception.

CASE 3 Contraceptive choice guided by identified cancer risk

LS, a 44-year-old woman, G1P1, presented to discuss contraceptive options. She was considering a progesterone long-acting reversible contraceptive (LARC), hysteroscopic sterilization via tubal occlusion, and laparoscopic tubal ligation.

While her personal history was nonsignificant, her family history revealed that a maternal aunt was diagnosed with ovarian cancer at age 45, her maternal grandmother was diagnosed with breast cancer at age 65, and her mother was diagnosed with lung cancer at age 32.

The patient underwent genetic testing, and a deleterious *BRCA2* mutation was identified, permitting a thoroughly informed discussion of the risks and benefits of various methods of contraception. LS opted to undergo laparoscopic supracervical hysterectomy and BSO.

Had LS's genetic status been unknown, progesterone LARC and tubal occlusion via Essure or laparoscopic tubal ligation would have been appropriate options; however, none of these methods offer the same benefit as BSO with regard to decreasing this patient's risk of ovarian and fallopian tube cancer. Moreover, BSO would likely not have been considered an option for LS in the absence of hereditary cancer testing.

CASE 4 Pelvic pain and dysmenorrhea: Management influenced by genetic test results

JN is a 46-year-old woman, G3P3, who presented with pelvic pain and dysmenorrhea. Ultrasonography revealed a mildly enlarged uterus with findings suggestive of adenomyosis and normal adnexa.

Her personal history consisted of 3 cesarean sections and a remote history of endometrial ablation. Her family history revealed that a paternal grandmother was diagnosed with colon cancer at age 60 and with ovarian cancer at age 80. Her mother was diagnosed with colon cancer at age 58.

The patient's family history was suggestive of both hereditary breast and ovarian cancer (HBOC) syndrome and Lynch syndrome as well as a number of other hereditary cancer syndromes; she underwent hereditary cancer panel testing. A deleterious *BRCA2* mutation was identified, and results of the remainder of her hereditary cancer panel testing were negative.

JN opted to undergo robot-assisted total laparoscopic hysterectomy and BSO, which relieved her pelvic pain.

Without knowing that JN possessed a deleterious cancer mutation, management may have differed considerably. Treatment options may have included conservative medical management or hysterectomy without BSO. Neither of these options would have significantly decreased JN's risk of ovarian and fallopian tube cancer. Occult ovar-

ian and fallopian tube cancers are noted in 2% to 26% of BSO procedures performed in asymptomatic patients who have a *BRCA* mutation.[9-14] If BSO was performed with hysterectomy without knowledge of JN's genetic information, washings would not have been performed, the specimen may have been morcellated, and the pathologist would not have been alerted to thoroughly examine the specimen for occult cancer. Knowing JN's genetic information changed not only her management decisions but also her intraoperative care.

CASE 5 Fertility options informed by genetic test results

KB is 31 years old, G0, and has attempted to conceive without success for 12 months. She presented to discuss fertility options.

Her personal history is noncontributory. In her family history, however, there is a known *MLH1* mutation on her maternal side.

KB was tested and found to carry a deleterious *MLH1* mutation.

She opted to undergo in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD) for *MLH1*.

Without knowing the patient's *MLH1* status, multiple treatment options would be considered, such as ovulation induction with intrauterine insemination and IVF without PGD. The option of PGD, with the opportunity to select against *MLH1* mutation, would not have been considered without genetic testing.

Understanding a patient's genetic information not only allows for appropriate preventive and early detection care but also permits patients to explore their reproductive options and to consider the option of preventing hereditary cancer genes being passed to offspring.

HOW TO ASSESS A PATIENT'S RISK FOR HEREDITARY CANCER

Collecting and evaluating a cancer family history already should be standard of care for your practice (**TABLE 1**).[15] However, many clinicians don't implement this data collection for every patient at every visit. Putting a protocol in place is essential for successful patient safety and management. It is not a difficult process.

The first step is to obtain a thorough cancer family history, preferably using a family history questionnaire, from every patient on arrival at the office. Next, evaluate the family history to determine whether the patient meets criteria for testing.[16,17] For appropriate candidates, after obtaining informed consent for genetic testing, perform a simple blood draw or obtain a mouth-wash sample. Last, disclose the results to the patient and formulate a relevent management plan depending on whether the results are negative or positive (**TABLE 2**).

In the past, clinicians felt it was necessary to refer all patients for genetic testing to a master's level genetic counselor. Unfortunately, the United States has fewer than 1000 cancer genetic counselors, and most of them are located in urban areas.[18,19] Further, in many instances, more than 50% of the patients referred for genetic counseling either fail to keep appointments or have issues that preclude them from being evaluated by a genetic counselor.[20-22] Current assessment protocols utilizing a "point of service" model take these public health concerns into consideration. Many physicians' organizations recognize this public health issue as well as the responsibility of all clinicians to make this assessment.[23]

TABLE 2 A simple office protocol for assessing hereditary cancer risk

1) Screen
Capture a cancer family history with all patients at every visit

2) Evaluate
Review cancer family history using red flags

3) Diagnose
Test appropriate patients with a hereditary cancer genetic panel test

4) Manage
Manage patients based on individualized risk

HEREDITARY CANCER PANEL TESTS

In light of data suggesting that multiple genes may be responsible for similar family presentations of hereditary cancer and recent advances in molecular biology,[24] ordering a hereditary cancer genetic panel test is a comprehensive approach. Panel testing recognizes that multiple genes are associated with a single cancer site and that multiple cancer sites are affected by a single gene. They offer a simple process by which to identify hereditary cancer risk, and using them enables a simplified conversation around testing for multiple cancers and identifying more mutations. Overall, panel tests provide a greater sense of security regarding your patients' cancer risks and your medical management of those patients' care.

As we observe Ovarian Cancer Awareness Month in September and National Breast Cancer Awareness Month in October, it is important to recognize the beneficial role played by hereditary cancer risk assessment and hereditary cancer panel tests in breast and ovarian cancer prevention and early detection. It all starts with a standardized protocol to collect and utilize cancer family history for every patient at every visit.

NOT ALL LABS ARE EQUAL

Genetic information is irrelevent if you don't send tests to a laboratory that will provide accurate results. With multiple new genetic tests being offered over the past year, it is important to research which lab provides the most accurate results and offers the support resources you need to manage test results. Know your lab. Consider its accuracy, if it has programs to correctly identify genetic variants, and whether its medical genetic experts are available to assist you with test results.

THE MOST IMPORTANT PART OF OUR JOB

In our Hippocratic oath we vow to "first do no harm." Extrapolated, this includes knowing all the salient factors regarding a patient's condition before recommending treatment options. Even during a simple appointment, such as a discussion of contraception, it is imperative to understand a patient's risk of hereditary cancer. Not obtaining this information prohibits us from appropriately counselling the patient on treatment options. Management mistakes can increase a patient's risk of life-threatening cancers. Identifying patients at risk will allow for risk reduction and early detection of cancer. For every patient at every visit, a we must assess which factors may be life-threatening. Preventing life-threatening illness, such as hereditary cancer, is the most important part of our job.

REFERENCES

1. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet. 1998;62(3):676-689.
2. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72(5):1117-1130.
3. Easton DF, Ford D, Bishop DT; Breast Cancer Linkage Consortium. Breast and ovarian cancer incidence in BRCA1 mutation carriers. Am J Hum Genet. 1995;56(1): 265-271.
4. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE; Breast Cancer Linkage Consortium. Risks of cancer in BRCA-1 mutation carriers. Lancet. 1994;343(8899): 692-695.
5. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med. 1997;336(20):1401-1408.
6. Abramowitz L, Sobhani I, Benifla JL, et al. Anal fissure and thrombosed external hemorrhoids before and after delivery. Dis Colon Rectum. 2002;45(5):650-655.
7. Abramowitz L, Batallan A. Epidemiology of anal lesions (fissure and thrombosed external hemorrhoid) during pregnancy and post-partum. Gynecol Obstet Fertil. 2003;31(6):546-549.
8. Gojnic M, Dugalic V, Papic M, Vidakovic S, Milicevic S, Pervulov M. The significance of detailed examination of hemorrhoids during pregnancy. Clin Exp Obstet Gynecol. 2005;32(3):183-184.
9. Rebbeck TR, Lynch HT, Neuhausen SL, et al; Prevention and Observation of Surgical End Points Study Group. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. 2002;346(21):1616-1622.
10. Colgan TJ, Murphy J, Cole DE, Narod S, Rosen B, et al. Occult carcinoma in prophylactic oophorectomy specimens: prevalence and association with BRCA germline mutation status. Am J Surg Pathol. 2001:25(10):1283-1289.
11. Olivier RI, van Beurden M, Lubsen MA, et al. Clinical outcome of prophylactic oophorectomy in BRCA1/BRCA2 mutation carriers and events during follow-up. Br J Cancer. 2004;90(8):1492-1497.
12. Leeper K, Garcia R, Swisher E, Goff B, Greer B, Paley F. Pathologic findings in prophylactic oophorectomy specimens in high-risk women. Gynecol Oncol. 2002;87(1):52-56.
13. Callahan MJ, Crum CP, Medeiros F, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. J Clin Oncol. 2007;25(25):3985-3990.
14. Hirst JE, Gard GB, McIllroy K, Nevell D, Field M. High rates of occult fallopian tube cancer diagnosed at prophylactic bilateral salpingo-oophorectomy. Int J Gynecol Cancer. 2009;19(5):826-829.
15. American College of Obstetricians and Gynecologists, ACOG Committee on Practice Bulletins—Gynecology, ACOG Committee on Genetics, Society of Gynecologic Oncologists. ACOG Practice bulletin No. 103: Hereditary breast and ovarian syndrome. Obstet Gynecol. 2009;113(4):957-966.
16. Daly MB, Axilbund JE, Buys S, et al; National Comprehensive Cancer Network. Genetic/familial high-risk assessment: breast and ovarian. J Natl Compr Canc Netw. 2010;8(5):562-594.
17. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: genetic/familial high-risk assessment: colorectal. 2014, version 2. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#detection. Accessed August 5, 2014.
18. Cohen SA, McIlvried DE. Improving access with a collaborative approach to cancer genetic counseling services: a pilot study. Commun Oncol. 2013;10(8): 227-234.
19. National Society of Genetic Counselors. 2012 Professional status survey reports. March 11, 2013. National Society of Genetic Counselors Web site. http://nsgc.org/p/cm/ld/fid=68. Accessed August 5, 2014.
20. Wham D, Vu T, Chan-Smutko G, Kobelka C, Urbauer D, Heald B. Assessment of clinical practices among cancer genetic counselors. Fam Cancer. 2010;9(3): 459-468.
21. Mouchawar J, Hensley-Alford S, Laurion S, et al. Impact of direct-to-consumer advertising for hereditary breast cancer testing on genetic services at a managed care organization: a naturally-occurring experiment. Genet Med. 2005;7(3): 191-197.
22. Lauritzen A. Why do individuals choose not to attend cancer genetic counseling appointments? Paper presented at: National Society of Genetic Counselors Annual Education Conference; September 17-20, 2014; New Orleans, LA.
23. American Medical Association. AMA House of Delegates Report of Reference Committee A. Resolution 115: Opposition to genetic testing restrictions based on specialty. June 2014. http://www.mag.org/sites/default/files/downloads/ama14-refcommA-report.pdf. Accessed August 5, 2014.
24. Tung N, Battelli C, Allen B, et al. Prevalence of gene mutations among hereditary breast and ovarian cancer patients using a 25-gene panel. Paper presented at: 36th Annual San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, TX.