A SUPPLEMENT TO

OBG MANAGEMENT The Female Patient

THE WOMEN'S HEALTH ALLIANCE

Hereditary Cancer Risk Assessment in Obstetrics and Gynecology: The Evolving Standard of Care

The 2009 *ACOG Practice Bulletin* reported that "hereditary cancer risk assessment should be a part of routine Ob/Gyn practice."[1] As specialists in women's health, this is our responsibility. Though it may be unfamiliar to many practitioners, the process of cancer risk stratification can be efficient and effective. Using protocol-driven evaluation of cancer susceptibility, personal and family risk factors, and genetic testing, we are now able to create risk profiles and management strategies that demonstrate proven reduction in cancer morbidity and mortality.

The role of the Ob/Gyn involves:

- Recognizing familial disease patterns suggestive of inherited susceptibility to cancer, including the familiar and common syndromes of hereditary breast and ovarian cancer (HBOC) and hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome).
- Integrating risk assessment, genetic testing, and interpretation of results into daily practice.
- Guiding medical management based on risk stratification.

RISK STRATIFICATION

Sporadic Risk, Familial Risk, and Hereditary Risk

More than 10% of patients have a personal or family health history suggesting hereditary or familial cancer susceptibility, and more than 6% of patients meet National Comprehensive Cancer Network (NCCN) criteria for genetic testing.[2-4] Three risk profiles emerge: (1) *sporadic risk*, defined as the average population or low-risk patient; (2) *familial risk*, defined as a family having numerous relatives with a specific type of malignancy; and (3) *hereditary risk,* defined as the presence of a single cancer or a syndrome of malignancies in a family, which are associated with known hereditary deleterious mutations in specific genes (ie, BRCA). Hereditary risk carries the highest percentage of cancer susceptibility, while sporadic risk carries the lowest.

Family history information should be taken as standard practice, using a written questionnaire at each annual visit. This practice should include patients of all ages and is applicable for both obstetric and gynecologic visits; both patient history and the standards of care in medical management are ever changing. With risk stratification, we can identify individuals who may benefit from intensive screening, genetic testing, and interventions such as chemoprevention and surgical risk reduction. Genetic testing of appropriate individuals further enables us to identify patients with hereditary cancer syndromes, for their own benefit as well as that of their entire family.

Once a family history of cancer is identified, common statistical models are used to predict the probability of being diagnosed with a particular cancer and the likelihood of a genetic mutation that predisposes the patient to a hereditary cancer syndrome. Several easily learned and clinically useful models are available online, including the Tyrer-Cuzick Calculator; BRCAPRO; the PREMM1,2,6 model; and the National Cancer Institute Colon Cancer Risk Assessment Tool.

Practitioners should use NCCN guidelines and standards in the risk stratification process.[5] Informed consent, including risks, benefits, options, and expectations, should be adequately dis-

Richard P. Frieder, MD
Medical Director
Cancer Genes Cancer Risk Assessment and Prevention Center of Santa Monica
Santa Monica, California
Assistant Clinical Professor, Department of Obstetrics and Gynecology
David Geffen School of Medicine, UCLA
Los Angeles, California

Steven M. Berlin, MD
St. Joseph Medical Center
Towson, Maryland
Sinai Hospital
Baltimore, Maryland

This supplement is sponsored by Myriad Genetics, Inc.

FIGURE 1. Suggested HBOC syndrome risk scoring tool

Circle each cancer point that applies, then total a+b and a+c
- Any 1 point = Familial risk; possible hereditary risk if small family (LFS)
- Any 2 points = BRCA test candidate

Each primary cancer counts separately
Family = 1st and 2nd degree relatives (sometimes 3rd degree)
Maternal and Paternal scores each add separately to Patient

	Patient (a)	Maternal (b)	Paternal (c)
Breast, <50 years (premenopause)	2	1	1
Breast, <60 years, triple negative	2	1	1
Breast, >50 years, not triple negative	1	1	1
Breast, bilateral, any age	2	2	2
Breast, male, any age	2	2	2
Ovary, epithelial, any age	2	2	2
Pancreas	1	1	1
Known mutation carrier	–	2	2
Ashkenazi Jewish (or other high-risk group)	1	0	0

Total: a+b = ____ points a+c = ____ points

HBOC, hereditary breast and ovarian cancer; LFS, Li-Fraumeni syndrome.
Source: Richard P. Frieder, MD.

cussed (similar to the informed consent for colposcopy in the setting of an abnormal Pap smear or a nonstress test in the presence of decreased fetal movement). Direct advice is necessary in the case of an abnormal Pap smear and is also necessary in the case of an abnormal family or personal cancer history. Nondirect counseling reduces the patient's opportunity for increased surveillance and potential early diagnosis and prevention of cancer, and puts the physician at risk for future liability.

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Approximately 10% of breast and ovarian cancers occur in women with an inherited susceptibility.[6-8] This autosomal dominant genetic disorder is predominantly caused by deleterious mutations in tumor suppressor genes BRCA1 and BRCA2, though other less common genes contribute to 15% of HBOC syndrome.[9]

"Red Flags" for HBOC syndrome

Personal and 3-generation family history including[10]:

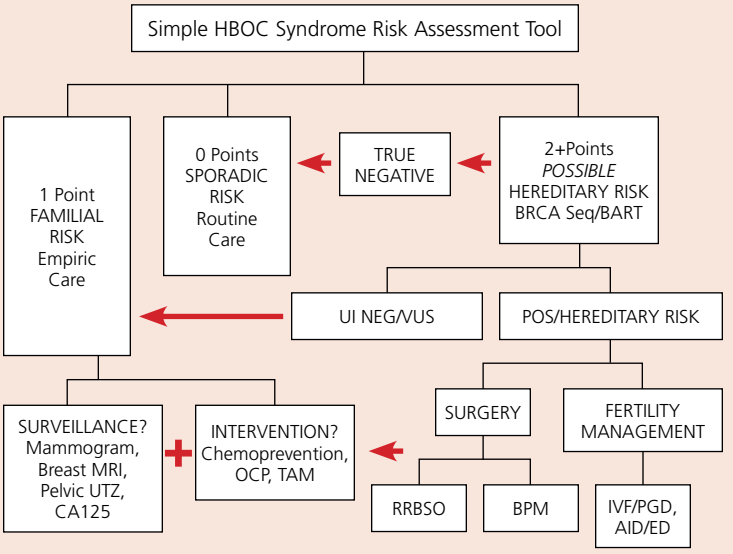
- Breast cancer: premenopause or under age 50 years, bilateral, triple negative, or male
- Ovarian cancer: any age, usually epithelial, high grade serous
- Pancreatic cancer, melanoma, or prostate cancer: under age 50 years
- Ethnic predisposition: Ashkenazi Jewish and others (eg, Mexican, Icelander, Dutch, Hungarian)
- A known BRCA mutation in the family

HBOC syndrome risk stratification: To test or not to test?

The gold standard NCCN guidelines are revised at least annually and set testing criteria that approximate a 5% to 10% pretest probability of finding a mutation in a given patient.[5] This includes both affected patients with possible hereditary cancers (index patients), as well as unaffected patients who only have various cancers in their family history. Both affected and unaffected patients may be appropriate for genetic testing.

We have developed a simple numerical teaching tool that can be used to estimate a patient's candidacy for BRCA testing (**Figure 1, Figure 2**). This tool approximates NCCN guidelines by assigning 1 or 2 points to each person with each "red flag" relevant cancer in the 3-generation family tree. The patient's points are added together with the maternal points and then again with the paternal points. A sum of 0 points would indicate a sporadic (low) classification. A sum of 1 point would usually indicate a familial (medium) risk classification; however, a 1-point patient may

Figure 2. Suggested HBOC syndrome simple risk assessment tool



AID, artificial insemination by donor; BART, BRACAnalysis rearrangement test; BPM, bilateral prophylactic mastectomy; CA125, cancer antigen 125; ED, egg donation; HBOC, hereditary breast and ovarian cancer; IVF, in vitro fertilization; MRI, magnetic resonance imaging; OCP, oral contraceptive pills; PGD, preimplantation genetic diagnosis; POS, positive; RRBSO, risk-reducing bilateral salpingo-oophorectomy; TAM, tamoxifen; UI NEG, uninformative negative; UTZ, ultrasound; VUS, variant of uncertain significance.

Source: Richard P. Frieder, MD

FIGURE 3. Suggested Lynch syndrome risk scoring tool

Circle each cancer point that applies, then add the total
- Any 1 point = Familial risk; possible hereditary risk if small family
- Any 2 points = Lynch test candidate

Each primary cancer counts separately
Family = 1st and 2nd degree relatives
Maternal and Paternal sides count separately

	Patient (a)	Maternal (b)	Paternal (c)
Endometrial, <50 years	2	1	1
Colon, <60 years	2	1	1
MSI or IHC abnormal path (colon, endometrial)	2	2	2
Endometrial, >50 years	1	1	1
Colon, >60 years	1	1	1
Ovary, epithelial, any age	1	1	1
Pancreas, brain, renal pelvis, gastric	1	1	1
Small bowel, biliary, sebaceous adenoma	1	1	1
Known mutation carrier	–	2	2

Total: a+b = ____ points a+c = ____ points

IHC, immunohistochemistry.
Source: Richard P. Frieder, MD

still qualify for genetic testing if there is a limited family structure or an ethnic predisposition to BRCA mutations. A sum of ≥2 points will generally qualify for BRCA testing, although combinations that involve third-degree relatives may be evaluated to determine if testing is warranted. This tool should only be used as an estimate, and not a conclusive testing guide.

LYNCH SYNDROME

Approximately 20% of colon and endometrial cancer diagnoses are associated with a strong family history of cancer.[11,12] Five percent of these cancers occur in the context of autosomal dominant, genetically-defined, high-risk syndromes, of which Lynch syndrome is by far the most common.

"Red Flags" for Lynch syndrome:
Personal and 2-generation family history including[13]:
- Colorectal or endometrial cancer diagnosed before age 50 years, or at any age with abnormal MSI or immunohistochemistry
- Colorectal cancer in ≥2 generations on the same side of the family
- Ovarian or gastric cancer at any age
- Two or more individuals with any 2 Lynch spectrum cancers (colon, endometrial, ovarian, gastric, brain, biliary, pancreatic, small bowel, uroepithelial or skin sebaceous adenocarcinoma)
- Affected relative with a known genetic mutation (MLH1, MSH2, MSH6, PMS2, EPCAM)

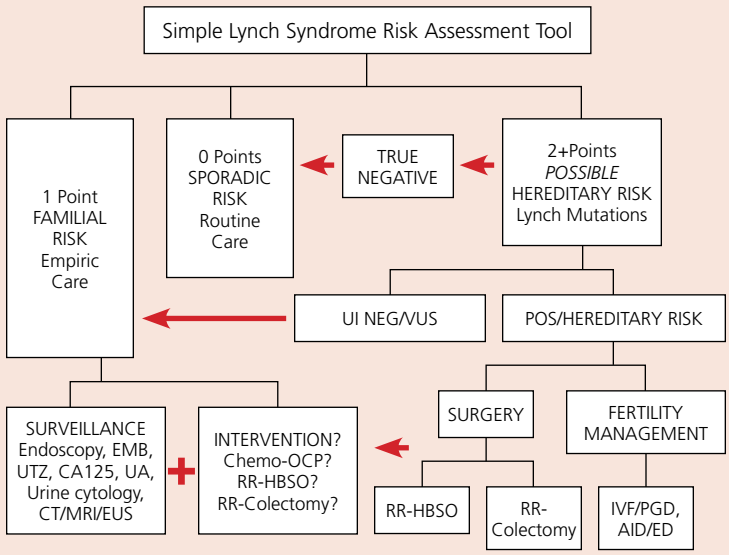
There is no specific ethnic susceptibility for Lynch syndrome.

Lynch syndrome risk stratification: To test or not to test?
We have also developed a risk assessment tool similar to that of HBOC syndrome that can be utilized for determination of Lynch syndrome testing. This tool uses the same 0, 1, or ≥2 point summation; however only a 2-generation pedigree is used for Lynch syndrome (**Figure 3, Figure 4**). Again, this tool should only be used as an estimate, and not a conclusive testing guide.

SCREENING AND DIAGNOSTIC TOOLS

Cancer risk assessment is one of the key components of the annual well woman examination. As one of the most important screening tests in clinical use today, standard use of the Pap test decreased the incidence of cervical cancer in the United States over several decades.[14,15] As recommended by ACOG, family history and genetic testing should also be routinely used as screening and diagnostic tools in the risk stratification

Figure 4. Suggested Lynch syndrome simple risk assessment tool



AID, artificial insemination by donor; CA125, cancer antigen 125; CT, computed tomography; ED, egg donation; EMB, endometrial biopsy; EUS, endoscopic ultrasound; HBSO, hysterectomy/bilateral salpingo-oophorectomy; IVF, in vitro fertilization; MRI, magnetic resonance imaging; OCP, oral contraceptive pills; PGD, preimplantation genetic diagnosis; POS, positive; RR, risk-reducing; UA, urinalysis; UI NEG, uninformative negative; UTZ, ultrasound; VUS, variant of uncertain significance.

Source: Richard P. Frieder, MD

of patients. The Pap test is a screening tool, much like a family history questionnaire. Colposcopy is a diagnostic tool used to follow up on an abnormal screening test, and is in many ways analogous to a genetic test. The identification of high-risk cervical dysplasia or human papillomavirus demands a high-risk management plan to prevent invasive cervical cancer; just as the identification of a BRCA or Lynch syndrome mutation demands a high-risk management plan to prevent breast, ovarian, endometrial, or colon cancer. All of these cancers are preventable, or at least may be diagnosed earlier, by effective risk stratification, genetic testing, and high-risk management that were not possible just a few years ago.

OFFICE PROTOCOL

Effective implementation of an office protocol requires planning and consistency. Like an operating room team, everyone has a job and it is done exactly the same way on every patient, every day. The communication skills that lead to success must be predetermined at each level of interaction with the patient. To avoid mixed messages, each member of the team should be instructed on what to say to the patient. Everyone on the staff must understand the importance of this process to benefit the patient and protect the physician.

In our office, every patient completes an annual family history questionnaire at the time of her routine or problem visit. The physician reviews the questionnaire during the course of her examination. Patients with familial risk are advised to return in 1 week for further discussion of a "cancer prevention plan." Patients who qualify for genetic testing are given a brief informed consent, advised to submit a specimen, and instructed to return in 3 to 4 weeks for further discussion of a "cancer prevention plan," using her test results. The patient produces a saliva specimen in the examination room, which is collected along with her Pap smear and cultures. The patient then carries her specimen to the sign-out station, where the receptionist receives the specimen and books an appointment in 3 to 4 weeks to discuss the cancer prevention plan and her results. The specimens are collected by a courier service each day. We have found that with experience, there is minimal time impact of this process.

The familial risk patient then returns in 1 week, at which time we run a risk model and institute appropriate surveillance and management strategies.

The genetic test patient returns in 3 to 4 weeks, at which time we create a cancer surveillance and prevention plan using her genetic test results. The "test negative patient" is treated as a familial risk category. The "test positive patient" is reclassified as a hereditary risk, and NCCN management guidelines are reviewed. Appropriate referrals are made to other specialists, which may include breast surgery, plastic surgery, gastroenterology, dermatology, psychotherapy, and peer support groups. A primary care physician or advocate for this patient is identified and he/she will coordinate ongoing care and counseling.

As a hypothetical example, in a practice that treats 5000 patients per year, with 10% expected positive family histories, and 6% of patients appropriate for genetic testing, we would expect that approximately 300 patients per year would qualify for genetic testing (about 1 patient per day). At a 5% to 10% pretest probability of finding a mutation, we would find about 25 patients with genetic mutations in the hereditary risk category, and 475 patients in the familial risk category, all of whom require an increased level of care due to their increased risks of cancer.

CODING AND BILLING

Standard *International Classification of Diseases, Ninth Revision* (ICD-9) and Current Procedural Terminology (CPT®) billing codes apply to patients with family history, personal history, or known genetic mutations. **Tables 1** and **2** illustrate examples of current billing codes used in our office for categories of activities.

V-codes are typically used for personal or family history of specific cancers. Evaluation and Management (E&M) codes are typically used for patient encounters, including problem oriented visits, as well as risk reduction counseling. 25-modifier is typically used when procedures are performed at the time of a visit, such as ultrasound or endometrial biopsy. Most patients with familial risk and all patients with hereditary risk are seen at least twice yearly for ongoing surveillance, counseling, referrals, chemopreventive management, discussion of surgical options, review of recent imaging results, and up-to-date advice.

Insurance denials are usually resolved by written appeals, using standard form letters of medical necessity, with the individual cancer history written into the blank areas. Today, almost all insurance carriers cover genetic testing and management, though the criteria are variable and lag somewhat behind the most current NCCN guidelines. We cannot treat patients differently based on the carrier's criteria; we must offer the same care to all patients, based on scientific and professional guidelines. Withholding testing recommendations based on insurance obstacles may be considered "willful negligence," which may not be covered by malpractice insurance.

LIABILITY, RISK MANAGEMENT, AND PATIENT SAFETY

As screening for hereditary cancers has become more readily available, many questions surrounding liability, risk management, and patient safety have emerged. As in all medicolegal issues, these areas of concern generally pertain to standard of care, documentation, consent, patient expectations, and follow up.

Standard of care

Many providers feel that hereditary cancer screening is not standard of care in the primary care office. However,

TABLE 1. ICD-9 diagnosis codes

Family Cancer History	
Breast	V16.3
Ovary	V16.41
Endometrium	V16.49
Colon	V16.0
Personal Cancer History	
Breast	V10.3
Ovary	V10.43
Endometrium	V10.42
Colon	V84.09
Suspected carriers status	V82.71
Confirmed mutation carrier (BRCA or Lynch)	
Breast	V84.01
Ovary	V84.02
Endometrium	V84.04
Colon	V84.09
Health risk reduction counseling	V65.40

TABLE 2. CPT® encounter/procedure codes

Encounters	
New patient, problem	99201-99205
Established patient, problem	99211-99215
Consultation	99241-99245
Risk reduction, preventive care	
New patient	99385-99387
Established patient	99401-99404
Telephone management	99441-99443
Procedures	
TV ultrasound	76857
Hysteroscopy/biopsy	58558
IUD insertion	58300
Breast ultrasound	76645
Breast cyst aspiration	19000
Anoscopy	46600
FIT (occult blood)	82274
Surgery	
Risk-reducing BSO	58661
Risk-reducing LSH/BSO	58544
Risk-reducing total hysterectomy/BSO	58541, 58542, 58552

BSO, bilateral salpingo-oophorectomy; FIT, fecal immunochemical test; IUD, intrauterine device; LSH, laparoscopic supracervical hysterectomy.

there are 3 points that are very important to remember. It is standard of care to obtain a comprehensive and complete family history and update it on a routine basis. It is standard of care to give patients appropriate information based on that family history so that they can make educated decisions about their medical care. Finally, it is standard of care to thoroughly and completely record whatever was discussed with the patient. If you adhere to these 3 points, then it would seem that screening for hereditary cancers is, in fact, standard of care.

Documentation

Once you have identified someone that fits criteria for genetic testing, how much documentation is needed? Is it adequate to have your note state: "information on genetic testing given" or "brochure given?" Although it is nice to see your plan documented, it is much more important to see the reasoning behind the plan. In this instance, an expanded note such as: "Based on family history, genetic testing recommended. Patient understands that if the test is positive there is a substantial increase in the risk of ovarian and/or breast cancer or [the particular Lynch syndrome cancer you are screening for]." Although we know that we discussed cancer risks, the patient can easily contradict what is not documented in their chart. Patients may argue that if they understood their risks, they would, of course, have consented to the test.

Incorporating some sort of tracking system into your office is prudent. This can allow for you to follow-up with a patient after she has been referred for genetic counseling. Without this type of tracking and follow-up, a troubling question can be raised: "if you felt it was important enough for the patient to have this testing, why wasn't it important enough for you to see if the test was done?"

Informed refusal

Informed consent and informed refusal need to be addressed when discussing hereditary risk assessments. Typically, informed consent has dealt only with informing patients of risks associated with invasive procedures. However, there has been an expansion of what adequate informed consent includes. As part of adequate informed consent we are now asked to give all treatment options, along with the risks and benefits of each option. Therefore, if we do not give appropriate patients the option of genetic testing (along with its risks and benefits), we may be found to be negligent on a consent basis should there be an adverse event.

This is where informed refusal may come into play.

If a patient does not want to do what the provider feels is appropriate, or has not followed up with a genetic counseling referral when you referred her to one, documenting their refusal, or lack of follow-up, may ultimately be more important than documenting their consent. Informed refusal documents that the physician has done what is prudent and that it is the patient's choice to not follow through. Many states have some element of contributory negligence, and this can go a long way in defending a potential lawsuit. One may even go a step further and document the reason for the patient's refusal; fear of the test result, unwillingness to do anything about the result, or financial reasons may be part of a patient's decision to refuse testing.

Presently, one of the major causes of malpractice cases involves issues with breast cancer. Typically, allegations include both delayed diagnosis and failure to diagnose. We are now seeing a new allegation that is being referred to as a failure of our "duty to inform" or "duty to warn." This pertains to the failure to identify a patient at risk for a hereditary cancer so that increased surveillance could have been implemented to diagnose the cancer earlier or that risk-reducing or prophylactic surgery could have been performed. These types of cases will be very difficult, if not impossible, to defend without proper documentation, including documentation of a patient's refusal of testing, and documentation of the explanation of very specific cancer risks.

SUMMARY

Primary care and OB/GYN physicians are uniquely positioned to identify individuals at increased hereditary or familial risk of cancer. The early identification of a suspected hereditary cancer syndrome can lead to additional evaluation and cost-effective interventions that can substantially decrease cancer risk, with proven reduction in both morbidity and mortality. Web-based tools for collecting and summarizing family history information for certain cancers and familial syndromes are easily accessible. Individuals with a high likelihood of an inherited syndrome should be counseled to undergo genetic testing, which will further allow appropriate risk stratification and appropriate management of those individuals who are found to carry genetic mutations.

REFERENCES

1. American College of Obstetrics 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 cancer syndrome. *Obstet Gynecol.* 2009;113(4):957-966.
2. Hughes KS, Roche C, Campbell CT, et al. Prevalence of family history of breast and ovarian cancer in a single primary care practice using a self-administered questionnaire. *Breast J.* 2003;9(1):19-25.
3. Pal T, Permuth-Wey J, Betts JA, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. *Cancer.* 2005;104(12):2807-2816.
4. Dominguez FJ, Jones JL, Zabicki K, et al. Prevalence of hereditary breast/ovarian carcinoma risk in patients with a personal history of breast or ovarian carcinoma in a mammography population. *Cancer.* 2005;104: 1849-1853.
5. National Comprehensive Cancer Network. NCCN Guidelines. http://www.nccn.org/professionals /physician_gls/f_guidelines.asp. NCCN Web site. Accessed August 29, 2012.
6. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med.* 2002;346(21):1609-1615.
7. 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.
8. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet.* 2001;358(9291):1389-1399.
9. Lindor NM, McMaster, ML, Lindor CJ, Greene MH; National Cancer Institute, Division of Cancer Prevention, Community Oncology and Prevention Trials Research Group. Concise handbook of familial cancer susceptibility syndromes—second edition. *J Natl Cancer Inst Monogr.* 2008;(38):1-93.
10. National Comprehensive Cancer Network. NCCN Guidelines: Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer. http://www.nccn.org /professionals/physician_gls/pdf/genetics _screening.pdf. NCCN Web site. Published April 27, 2012. Accessed September 4, 2012.
11. Grady WM. Genetic testing for high-risk colon cancer patients. *Gastroenterology.* 2003;124(6):1574-1594.
12. Burt RW. Colon cancer screening. *Gastroenterology.* 2000;119(3):837-853.
13. National Comprehensive Cancer Network. NCCN Guidelines: Colorectal cancer screening. http://www .nccn.org/professionals/physician_gls/pdf/colorectal_ screening.pdf. NCCN Web site. Published May 2, 2012. Accessed September 4, 2012.
14. Saslow D, Solomon D, Lawson HW, et al; American Cancer Society; American Society for Colposcopy and Cervical Pathology; American Society for Clinical Pathology. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol.* 2012;137(4):516-542.
15. FUTURE II Study Group. Quadrivalent vaccine against papillomavirus to prevent high-grade cervical lesions. *N Engl J Med.* 2007;356(19):1915-1927.

Disclosures

Dr Frieder reports that he is a consultant and on the speakers' bureau for Myriad Genetics, Inc, and that he is a consultant for Phenogen Sciences, Inc; Perlegen Sciences, Inc; and Genetic Technologies Group. Dr Berlin reports that he is on the speakers' bureaus for Myriad Genetics, Inc and Qiagen.