Prenatal Genetic Screening

Promise and Pitfalls

Anthony R Gregg, MD, MBA, FACOG, FACMG

Tools Test Drive

Two products recommended for the OR

Microarray for prenatal diagnosis

Peer-Reviewed

Techniques for salpingectomy

Mae Zakhour, MD, Malaika W Amneus, MD, and Christine H Holschneider, MD

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Preimplantation genetic diagnosis: its time is now

Indications for PGD have extended far beyond single-gene disorders.

Preimplantation genetic diagnosis (PGD) is 25 years old. Its technology and novel indications have long dazzled, but some continued to feel that the field was just boutique medicine. In 2016 we can now confidently state that PGD is an integral part of not only medical genetics but also, increasingly, reproductive medicine and infertility care. Evolving technology has welded pragmatism with vision. Here I review developments that have made this transition feasible.

Obtaining DNA through trophectoderm biopsy

There have always been 3 sources for obtaining embryonic DNA for PGD: (1) polar body biopsy, prior to or at the time of fertilization, (2) blastomere biopsy from the 3-day 6- to 8-cell cleaving embryo, and (3) trophectoderm biopsy from the 5- to 6-day blastocyst. Initial work in PGD involved removal of a single blastomere, the zona pellucida traversed by mechanical or laser means.

Today, the preferred approach for PGD involves biopsy of the trophectoderm in the 5- to 6-day blastocyst, since more than a single cell can be safely removed, and thus more DNA is available. A further advantage is that the trophectoderm forms the placenta; thus, the 5–10 cells removed were never destined to be part of the embryo itself (inner cell mass).

PGD for single-gene disorders

When first performed, the intention of PGD was to diagnose single-gene disorders. Approximately 20% of PGD cases are now performed on couples at risk for one or more single-gene disorders. Despite the miniscule amount of DNA, PGD can be performed whenever the chromosomal location of the gene causing the disorder is known. The causative mutation need not even be known so long as affected and unaffected family members are available to determine markers linked to the mutation site. This allows one to deduce whether a given embryo has or has not inherited the mutation.

More than 300 different conditions have been tested worldwide. The most frequent are hemoglobinopathies, cystic fibrosis, and fragile X syndrome. In 2015, Rechitsky and colleagues tabulated their experience with single-gene disorders at Reproductive Genetic Innovations (RGI): 2982 cycles involving 1685 patients.1 This yielded 1095 pregnancies and 1118 live births; 47 pregnancies were ongoing at the time of publication.

PGD has certain advantages over traditional PGD. PGD cases can obviously detect abnormalities much earlier than can chorionic villus sampling and amniocentesis, thus avoiding termination of a clinical pregnancy. PGD is also the only practical approach for a couple in which one partner is at risk for an adult-onset disorder, wishes to remain unaware of his or her genotype, and yet does not want to transmit a potentially serious mutation to his or her offspring. Multiple embryos can be screened with only unaffected embryos transferred; the patient can, if desired, remain oblivious to diagnostic results and...
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thus whether he/she is or is not destined to develop the disorder (non-disclosure PGD). The most common indications for nondisclosure PGD are adult-onset cancers, Huntington’s disease, and autosomal-dominant early-onset Alzheimer’s disease.

A third indication pragmatically necessitating single-gene PGD occurs when a couple is at risk for offspring with a genetic disorder involving bone marrow derivatives (e.g., β-thalassemia). The couple may wish not only to avoid another abnormal child with these typically autosomal-recessive disorders, but also to ensure that the transferred embryo has a human leukocyte antigen (HLA) profile compatible with their older, perhaps moribund child. If so, the affected child’s disease could be treated by umbilical cord blood obtained following the birth of its sibling.

Stem-cell transplantation has a high success rate (95%) if the cord blood is HLA-compatible, but less so (65%) if it is not HLA-compatible. Given that only 3 of 16 embryos would be predicted to be both unaffected (3/4) and HLA-compatible (1/4), only PGD is practical.

**PGD aneuploidy to increase ART success**

The “game changer” in PGD is its capacity to determine presence or absence of all 24 chromosomes. It has long been reasoned that transferring only euploid embryos should increase pregnancy rates, even in women who otherwise have no genetic indications for PGD. However, only 5–9 chromosomes could be interrogated on a single cell, and technical expertise was required. Although larger centers performing PGD at that time (late 1990s and early 2000s) never completed a randomized clinical trial (RCT), other centers did and found no significant improvement in pregnancy rates.² Although valid criticisms have been directed at RCTs of that era,³,⁴ enthusiasm predictably diminished. Still PGD aneuploidy continued in many centers, but controversy persisted.⁵

More recently, diagnostic prowess has improved and clinical efficacy has been demonstrated. One reason is that the currently preferred biopsy approach (trophectoderm from the 5- to 6-day blastocyst) has proven more generalizable. The even greater advance has been the ability to interrogate all 24 chromosomes, using either array comparative genome hybridization (array CGH) or 1 of several next-generation sequencing (NGS) methods utilizing either single nucleotide polymorphisms (SNP), quantitative polymerase chain reaction (PCR), or copy number variants (CNV).

Initially the protocol involved blastocyst biopsy and 24-chromosome analysis followed by transfer in the same cycle. The preferred protocol is now to biopsy all blastocysts, then analyze and freeze all normal embryos. Transfer can then occur in subsequent cycles synchronized for embryo implantation, preferably one embryo into a uterus no longer hyperstimulated.

RCTs using 24-chromosome interrogation have shown statistically significant increased pregnancy rates. As an example, Scott et al reported sustained implantation rates (leading to delivery) of 66% after 24-chromosome aneuploidy testing on blastocyst using a quantitative PCR method, compared with 48% without PGD (<0.001).⁶ Impressive RCT results were also shown by Yang et al.⁷ With PGD, aneuploidy miscarriage rates unequivocally fall dramatically,⁸ and pregnancy rates do not show a maternal age effect until age 42.⁹

Another benefit of contemporary PGD aneuploidy testing is its potential to reduce multiple gestations in ART. Multiple embryos have traditionally been transferred in ART be-
cause not all embryos generate viable pregnancies. If all actually did, multiple gestations would result. Forman and colleagues showed the benefit of PGD aneuploidy testing in a RCT involving women of mean age approximately 35 years and requiring ART. In one group 2 morphologically normal blastocysts were transferred without PGD; in the other group, 1 blastocyst known to be euploid by PGD and was transferred. Pregnancy rates were not different (65% vs 61%), but the rate of twins was markedly different (55% vs 0%).

**Unresolved questions**

Two general areas of controversy remain in PGD: 1) What should be the precise indications for PGD-aneuploidy testing when the sole goal is to increase ART pregnancy rates; and 2) Under what circumstances could mosaic aneuploid embryos be offered for transfer should no euploid embryo exist?

**A. Maternal age to improve pregnancy rates**

1) Given that aneuploid embryos are correlated positively with maternal age, PGD-aneuploidy testing and transfer of euploid embryos logically becomes relatively more beneficial with advancing maternal age. In 2014 the proportion of cycles not using FISH for diagnostics but array CGH or next generation sequencing (NGS) was not stated. It would be expected that 24-chromosome array CGH or NGS would increase success in any group. The age below which limited presumptive embryo damage would outweigh predicted benefit of euploid embryo transfer is still unclear. Also unclear are related indications of repeated pregnancy loss or repeated implantation failure. Both these clinical conditions may frequently be the result of aneuploidy. Indeed, in RPL miscarriage rates have long been known to decrease with PGD-aneuploidy, using FISH for only 5–9 chromosomes.

Uncertainties in setting an age threshold do not apply to known benefit of PGD when a balanced translocation is present in either parent. Without PGD the length of time to conception is greatly increased, with a mean of 4-5 years. This reflects the existence of few transferable normal embryos. Thus, with PGD both abnormal offspring and lengthy time to conception can be avoided.

**B. Mosaic embryos**

2) A second area requiring clarification involves status of mosaic embryos: mosaic monosomy (eg, monosomy 46, XX, -3/46, XX) or mosaic trisomy (eg, 46, XX, +16/46, XX). At first in array 24 chromosome CGH relatively few mosaic embryos were reported because sensitivity was designed mostly to detect whole aneuploidies. Next-generation sequencing (NGS) methods now used are more sensitive than array CGH, capable of detecting a single aneuploid cell among the 5–10 in a trophectoderm biopsy.

Of note, trophectoderm cells are destined to develop into the placenta. Thus mosaicism is not a surprise. Recall that confined placental mosaicism (CPM) has been recognized for decades in prenatal diagnosis. Approximately 1%–2% of CVS or amniocentesis samples are mosaic and subjected to diagnostic algorithms. At the May 2016 meeting of the Preimplantation Genetic Diagnosis International Society (PGDIS) it was reported that 20% of mosaic trophectoderm biopsies were mosaic. In turn, earlier this year, a brief letter by Florentino et al pointed out that, if transferred, some mosaic monosomies can lead to a livebirth. At the PGDIS meeting this rate was estimated to be 5%.

Given this small potential for success, when transferring mosaic aneuploidy blastocysts, how should the not-infrequent occurrence of mosaic aneuploid embryos be handled clinically? In most cases, if in a cohort of embryos some are clearly non-mosaic euploid, no controversy exists. It would be illogical to transfer a mosaic aneuploid embryo. If no euploid embryos exist, one should first recommend 1 or more additional cycles, perhaps “batching” embryos for PGD-aneuploidy testing at a single time in hopes of finding a euploid embryo to transfer.

Suppose, however, that there exist only mosaic aneuploid embryos. Suppose further that the patient is relatively older and unlikely to ever
produce few to no non-mosaic euploid embryos. In this circumstance one can consider transfer of mosaic aneuploid embryos. Of course, discussion with the couple is obligatory, and amniocentesis recommended in the event of an ongoing pregnancy. Priority preferential sequence should be devised for transfer of mosaic embryos. For example, embryos trisomic for a chromosome capable of a viable livebirth (Nos. 13, 18, and 21) are clearly less desirable than those mosaic for a chromosome never reported to result in a livebirth.

At present, a blastocyst embryo mosaic for monosomy seems preferable to one with trisomy, because monosomic cells do not survive, leaving only euploid cells.

**Summary**

In 2016 PGD has a well-defined role. Indications have extended far beyond the single-gene disorders that initiated the field 25 years ago to encompass HLA-typing for umbilical and cord-blood stem cell transplantation. Twenty-four-chromosome PGD aneuploidy testing identifies euploid embryos to transfer, thus improving the pregnancy rates in ART while reducing the occurrence of multiple gestations.

Missed rates in ART are greatly reduced using PGD, and transfer of euploid embryos allows pregnancy rates to remain relatively undiminished until age 42. All this enables single-embryo transfer to be practical.

**REFERENCES**


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Testing the water in the credentialing pool

[Regarding “A credentialing test for EFM,” May 2016 Contemporary OB/GYN] The authors attempt to convince us that it’s time we jump in with both feet. I say, “Wait one minute, I want to test the water!” The presumption is (and I’m a believer) that consistent nomenclature improves communication. Roger that. The so-called Category II tracing, without qualification, is insufficient without a lot of detail to make it useful. However, the history of EFM use has taught us to be cautious.

I am from the era when we were taught that EFM was capable of reliably detecting the compromised fetus. Forty years later, after many tarnished careers and billions of dollars, we know the truth. The Grimes article referenced (number 12) tells us that we have been attempting to measure temperature with a barometer. How insane! Haven’t we learned anything? Before we spend time and money on yet another certification, let’s prove it is useful. Please!

Armando P Russo, MD
VINELAND, NEW JERSEY

IN REPLY:
We appreciate the reader’s caution in evaluating the utility of the Perinatal Quality Foundation (PQF) Fetal Monitoring Certification. The limitations of electronic fetal monitoring (EFM) and the NICHD 3-tier classification system are well known. It is also well established that standard nomenclature and an ability to communicate clearly with a resulting common understanding among team members is important.1,2

There is evidence that training in EFM interpretation as a component of a patient safety bundle does lead to better outcomes.3,4 The PQF EFM certification provides a ready-made statistically valid standardized certification that can aid institutions in their quality efforts.

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Mark W Tomlinson, MD
Michael P Nageotte, MD
Marin O’Keeffe, RN

Sexual health education for teens

“How to fill gaps in sexual health education,” May 2016 covered a subject that I am passionate about. As the article said, I have seen less teen pregnancy but more STDs. I take care of many young minority patients who have not been properly educated about their sexual health. I have heard over and over again from my patients who are moms to adolescents that they did not know how to educate them.
I have founded a non-profit called Not On Our Watch (NOOW). This organization is dedicated to educating young women about their bodies and sexual health in a nonthreatening atmosphere. I take local pediatricians and family practice doctors and pair them with local nurses to speak to young ladies in a small group. We partner with the City of Birmingham Division of Youth Services so we can reach the most at-risk students.

An involved parent is important, but I have found that a lot of my teens still do not want to talk to their parents because they think that it means they are sexually active and will be punished. Talking with the girls one-on-one in my office is helpful and they get to ask questions without feeling judged. When they are in a group they feed off of one another’s questions and energy and it is amazing to watch!

I would love to expand this program beyond Birmingham.

Tomeka Roberts, MD, FACOG
BIRMINGHAM, ALABAMA

Malpractice versus ‘malocurrence’

[Regarding “The best of times or the worst of times? A tale of two surveys,” May 2016] I compliment the authors for a well-researched, succinct, and well-written article. The paradox is clear. The problem for the foreseeable future is the inability of our tort system to adjudicate the difference between malpractice and malocurrence. This structural handicap renders actuarial and financial analysis impossible. The American ob/gyns, through their carriers, ultimately pay (mostly through settlements) the price of nature’s faults. There is no question that misjudgments and errors occur during the practice of obstetrics. Yet, in some jurisdictions (including my own) discovery rules prevent us from having meaningful peer review. Thus, we learn little and we share even less.

Couple this with the fact that, as a specialty, we are in the unfortunate position of practicing with a relative lack of Level A evidence. Hence, our clinical judgment is deemed faulty by virtue of poor outcomes. Our tort system thrives on witness inconsistency and diversity of opinion to yield the result most favorable to the party that can mount the best narrative. All this does a disservice to our patients and has created a toxic environment in which to practice. It is no wonder the ACOG survey reports what has been known for years—ob/gyns drop OB as soon as is practicable. What a sad commentary.

Finally, let’s not be fooled by the favorable med-mal rates now. It is all part of the business cycle. Until we solve the unreasonable societal expectation of perfection and have an equitable system to adjudicate patient injury, rates will increase as they did in the 1980s and early 2000s. Worse still, when profitability decreases, carriers will leave the market and scatter like roaches when the lights are turned on. It will be déjà vu all over again!

Armando P Russo, MD
VINELAND, NEW JERSEY

Do you think certification should be required for everyone performing EFM? Has the American tort system created a toxic environment in which to practice ob/gyn? Let us know what you think by tweeting to @ContempOBGYN or sending an email to DrLockwood@advanstar.com.
Expanded carrier screening: Are you prepared?

Expanded screening answers questions that we could not answer in the past, but brings with it new uncertainties.

by ANTHONY R GREGG, MD, MBA, FACOG, FACMG

Next generation sequencing (NGS) technology represents a challenge to traditional prenatal genetic screening for recessive conditions. Specifically, what has been dubbed “expanded carrier screening” (ECS) makes gene-by-gene or a la carte genetic screening menus obsolete. Before the advent of NGS, sequencing was labor-intensive, costly, and slow, and it was difficult to screen large numbers of people for multiple genetic conditions and to evaluate many pathogenic variants (aka mutations) within the same gene. With NGS, genetic information (nucleotides) can be evaluated (sequenced) rapidly and at low cost.1

Two basic principles

The hierarchical approach to carrier screening for single-gene disorders (positive family history followed by racial/ethnic identification) has evolved to include panethnic, multiple-condition screening, using more pathogenic variants. Expanded carrier screening utilizes genetic technology, panels with specific genes and variants as targets or sequencing strategies with results for specific genes whose pathogenic variants are selectively reported.

These technologies can be applied using the hierarchical approach or they can be used in a panethnic fashion to identify carriers in those with unsuspecting ancestry or unknown family history. Importantly, when family history for a single gene disorder is positive, ECS may not be the best choice because family-specific and already-identified pathogenic variants may not be included on commercially available screening panels. Genetic counseling by a trained professional should be

DR GREGG is the BL Stainaker Professor, Chief of Maternal-Fetal Medicine and Director of Obstetrics at UF Health Shands Hospital, University of Florida, Gainesville. He has no conflicts of interest to report in respect to the content of this article.
considered before implementing ECS in cases of a family history of a single-gene disorder. At the heart of ECS is a requirement that patients and providers understand 2 basic principles.

**Principle 1. A population-based approach is used to identify carrier parents who are at risk of having a child with a serious, often intellectually disabling, heritable condition.** Traditionally screening focused on recessive conditions, in which mother and father are carriers but do not manifest a phenotype. Today’s ECS “panels,” however, frequently include semi-dominant (eg, factor V Leiden, prothrombin gene) and sex linked (eg, fragile X mental retardation) conditions. This means that screened parents can learn that they have a previously unrecognized health risk. These conditions might also pose health implications for the unborn child, children already in the home, and relatives. The contrary is also true. Some genes and variants included for screening by ECS laboratories are dubious with respect to pathogenicity. A prime example is MTHFR, and there are others. Furthermore, some conditions on panels demonstrate variable penetrance (age of onset or absence of expression) and variable expressivity (phenotypic variation). When ECS approaches fail to consider these concerns, patient anxiety and cost can escalate.

Adopting ECS either selectively or panethnically clearly can add complexity to posttest counseling compared to gene-by-gene screening for cystic fibrosis (CF) and spinal muscular atrophy (SMA). This aspect of ECS has troubled many and has led to the slow adoption of ECS into clinical practice. One response by industry has been to allow patients and providers to have some autonomy in selecting conditions to be screened. Another response has been to remove potentially important genetic information from screening panels (eg, Factor V Leiden, prothrombin gene). An ethical argument can be made that if health risks of a parent or other family member can be mitigated by results obtained after ECS, patients should be allowed access to this information. If the ethical argument holds, then obstetricians should not be troubled if patients are informed about their own health risks. Recall that when performing fetal imaging patients are not counseled that incidental findings are possible. They are not told that these incidental findings could inform patients of increased health risks. Often ovarian cysts and placenta implantation concerns are identified, but they do not lead to a call to abandon fetal imaging, nor is concealment from the patient an option. Relying on a knowledge base, the response is to convey accurate and useful information. Pretest counseling today requires a brief discussion so that patients understand results of screening may inform them of their own health risks and risk to other family members.

A “serious” condition is easy to recognize by the ravages it imposes. Likewise, the unaffected or unimpaired are easy to spot. Moving from each end of the spectrum creates a problem in defining “serious,” because the term has many shades of gray. The most appropriate conditions for prenatal ECS are difficult to name when they are not the most or least severe. This is due in part to variable expressivity (a spectrum of signs and symptoms that may be expressed differently among persons with the same genetic condition) and/or variable penetrance (proportion of people that will manifest signs or symptoms despite having a pathogenic variant in a disease-causing gene).
Just as patients with placenta previa, preterm labor, and seizure disorder can have a varied clinical course, so too can patients with cystic fibrosis or sickle cell disease.

The problem also lies in the phenotype of the conditions screened. Debate over the conditions to include within the gray zone lacks scientific inquiry and recognition that this may be best determined by a patient or the family undergoing screening. Educated healthcare professionals were asked to rank phenotypes by category⁶ (x-axis in Figure 1). Conditions that impact lifespan (especially in infancy and childhood), affect intellectual function, and those that can be treated were considered most appropriate for screening (Tier 1). Conditions that impair fertility continued on page 16

### Genetic Screening Terms Defined

In 1991 the American College of Obstetricians and Gynecologists (ACOG) provided one of its earliest genetic screening recommendations aimed at those with and without a family history of cystic fibrosis.² *Screening* is the implementation of a public health effort to identify those who do not demonstrate signs or symptoms of the condition being screened. Screening reflects efforts to identify those who would not otherwise be recognized as at risk. In the context of genetics, screening is undertaken to identify carriers of a condition. A *carrier* is one who can transmit a condition, but does not manifest the condition. Every pregnancy carries risk, which can be grouped by categories including those that are maternal (e.g., development of diabetes), obstetrical (e.g., hemorrhage), and genetic (e.g., carrying a fetus with a serious inherited condition). Most obstetricians are familiar with genetic risk in the context of fetal aneuploidy (e.g., Down syndrome) and recessive single-gene disorders (e.g., cystic fibrosis).

Calculating the risk that a parent is a carrier of a heritable change in a gene (aka *mutation* or *pathogenic variant*) capable of causing an abnormal phenotype depends on a hierarchy that begins with family history. When a first-degree relative is the proband, risk can be determined using straightforward Mendelian genetic calculations. When a second-degree or more distant relative is identified, risk calculations often rely on more complex Bayesian analysis. When family history is negative or unknown, risk can be refined by using population carrier frequency information, which is often specified for race and ethnicity (e.g., Tay-Sachs disease in Ashkenazi Jewish patients).

*Carrier frequency* is the percent of a defined population that carries a pathogenic variant, but is unaffected. Carrier frequency can be determined using the Hardy-Weinberg equilibrium equation: $p^2 + 2pq + q^2$ where $q^2$ is the frequency of those affected, $2pq$ the carriers, and $p^2$ those who are neither affected nor carriers. Knowledge of the observed frequency of a condition in the population ($q^2$) allows one to work backwards solving for the number of carriers ($2pq$), since $q + p = 1$. Population carrier frequency ($2pq$) is necessary to determine parental risk of being a carrier for any heritable condition absent a family history. It is used to refine the risk estimate when carrier screening results are negative. *Residual risk* is the risk left over after a negative screening test result. Traditionally, posttest counseling is provided after gene-by-gene screening produces negative carrier results. During that session, a patient receives information about her residual risk of being a carrier.

Genetic screening implemented without regard to a person’s race or ethnicity is termed *panethnic*. In 2005 ACOG called for panethnic screening for cystic fibrosis.³ The rationale for this paradigm shift was the difficulty patients had in self-assigning to a single race or ethnicity. The carrier frequency of cystic fibrosis varies among racial ethnic groups (from 1/29 in Northern European Caucasians to 1/94 in people of Asian ancestry). This is a feature of many single-gene disorders. In these cases, the inability to self-assign leads to imprecise counseling and risk information.⁴ In 2008 ACMG recommended panethnic screening for spinal muscular atrophy. This recommendation followed data that demonstrated a relatively high (~1/40–1/60) carrier frequency.⁵
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Prenatal genetic testing

Principle 2. A negative screening test does not eliminate the possibility that a patient is a carrier.

Recall that residual risk is risk that remains after a negative test result. Ob/gyns are familiar with this concept. After a negative mammogram it is still possible that the test missed a lesion. The same can be said of colposcopy, colonoscopy, and other forms of screening. Before ECS, calculating residual risk was easy (carrier frequency x (1- detection rate)). The factors required to calculate residual risk, populations specific carrier frequency, and detection rate were known when gene-by-gene screening was performed on targeted racial ethnic groups. This calculation was possible because screening occurred for relatively few conditions that had high visibility compared to conditions on ECS platforms. Today, some conditions screened for are so rare that detection rate and populations carrier frequency are unknown. Adding more pathogenic variants to the screen will improve the detection rate, but the zeal to do this at low cost has been complicated by the observation that not all variants screened are pathogenic. False positives occur when clinical validity of variants is not considered. False-negative and false-positive results are inherent in any screening program. The solution is not to abandon the technology, but to rely on resources that can facilitate interpretation of test results.

Negative results are straightforward. Patients can be told they were screened for a large number of conditions and that the results for those specific conditions suggest a very low likelihood that they are carriers. Emphasize that it is still possible to be a carrier, because there is always a residual risk. Therefore, the chance of having an affected child for the conditions screened will depend on the carrier frequency in the population and the variants tested. It may be difficult to calculate the residual risk for each condition screened, because population carrier frequency (2pq) may be unknown, or ethnic-specific and the percent contribution of specific variants may be unknown.

When results are positive, check that the variant reported is pathogenic before providing information to patients. Laboratory-employed genetic counselors can provide information and are an important resource. Web-based resources may also be helpful (eg, genetics home reference, gene reviews). Consider the utility of the Clinical and Functional Translation of CFTR site (www.CFTR2.org) to clarify pathogenic variants in cases in which a rare CFTR variant is identified. In obstetrics and gynecology there is often a need to consult radiologists and pathologists after receiving non-genetic test results. Providers readily search Internet resources, textbooks, and journals in order to convey accurate information to patients. The principle with ECS and genetic testing in general is no different; enlist help when needed.

It is virtually impossible to accurately calculate residual risk for each condition on an ECS panel (although some laboratories report values). Genetic counselors and others have expressed concern over lack of precise residual risk data. When discussing ECS it may be helpful to consider residual risk as diagrammed (Figure 2). On the x axis are the conditions being
screened. Risk is on the y axis. Each condition is depicted as a filled circle before screening (eg, pretest risk = population carrier frequency) and an open circle after screening (eg, post-test risk = residual risk). The downward arrow depicts the detection rate. This arrow is elongated by employing more pathogenic variants in the screen and/or when the pathogenic variants screened make up a substantial portion of disease burden. CF, a condition with relatively high carrier frequency in certain populations (A in the figure), is screened using mutations that move the arrow towards the x axis (eg, zero risk), but the residual risk never reaches this position. This is because laboratories do not screen/report all of the nearly 400 variants that might be present. Condition B is frequent, but less common than CF, similar to that of SMA with a low residual risk after screening (~98% detection rate). Hurler syndrome is depicted by C, low carrier frequency and modest detection rates leaving a residual risk greater than that for SMA. Notice that some conditions have a low residual risk by virtue of their low carrier frequency even when the number of variants screened is minimal (C in the figure). Likewise, some conditions may have a high residual risk because of a high carrier frequency and few pathogenic variants are screened.

**Conditions on panels**

In the era of NGS, gene-by-gene screening is replaced by efforts to screen the aggregate of known recessive disorders. Therefore, we must consider how residual risk across a spectrum of conditions (common to rare) changes the residual risk for the entire pregnancy. The addition of conditions, from common to rare, to an ECS platform causes the residual risk of the entire pregnancy to fall, but not at a constant rate. Screening first for common conditions with known common pathogenic variants has the greatest impact. As conditions are added, the number of rare conditions screened increases. Eventually, conditions with modest carrier frequency and low detection rates do little to further lower the residual risk of the pregnancy (Figure 3).

Why then do laboratories that offer ECS continually add to their platforms conditions with which even trained geneticists are unfamiliar and that can befuddle a clinician when a carrier patient is encountered? First, the additional cost is trivial. Second, the motive may be altruistic. Patients may benefit from the addition of very rare conditions. Third, as the ECS space becomes more competitive, companies will need to do more marketing to survive.

**Pitfalls**

Two serious and hidden pitfalls, which are recognized by most geneticists, lurk in the condition menu of ECS platforms.

Hemoglobinopathies are best screened using red cell indices on the complete blood count (CBC) and hemoglobin electrophoresis. The ACOG guideline on this topic remains relevant today. Every clinically significant point mutation in the β chain is not on a molecular based “panel” and α-thalassemia deletions are not usually on carrier screening platforms.

Carrier testing for Tay–Sachs disease is complicated by a wide range of carrier frequencies across racial ethnic groups. Furthermore, there is a lower detection rate when the carrier frequency is low (short arrow, Figure 2) as is the case in certain populations. The pathogenic variants used on ECS platforms for low carrier frequency groups are not robust. Therefore carrier testing using NGS as it is applied is inefficient. The filled circle (Figure 2) is constrained and doesn’t move to a lower position when starting in a low carrier frequency range. Screening for Tay–Sachs disease is performed most
Techniques for salpingectomy at time of hysterectomy

Once considered an innocent bystander, the fallopian tube is now thought to play an important role in development of one of the most deadly gynecologic cancers. Several studies evaluating risk-reducing salpingo-ooophorectomy specimens in women who are BRCA gene mutation carriers implicate the fallopian tube as the most common site of occult carcinomas. Serous tubal intraepithelial carcinomas (STIC), which representative pre-invasive fallopian tube pathology, are also identified in these patients, and believed to be a part of the pathway of malignant transformation that results in high-grade serous carcinomas (HG-SCs).1-3 Gene expression and molecular profiling studies demonstrate that ovarian HGSCs more closely resemble fallopian tube epithelium than ovarian surface epithelium.4-6 TP53 mutations are extremely common in both STIC lesions and ovarian HGSCs, and more importantly, the particular mutations in these 2 lesions have been shown to be identical.7

While much of the evidence supporting the fallopian tube as the ori-

In light of data and recommendations, many providers and institutions are now offering patients opportunistic salpingectomies at the time of hysterectomy.

An abdominal, laparoscopic, or vaginal approach may be used, and techniques for each are described here.

QUICK TAKE

by MAE ZAKHOUR, MD; MALAIKA W AMNEUS, MD; AND CHRISTINE H HOLSCneider, MD
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gin of HGSC is derived from high-risk patients, several studies demonstrate that this is also the case for the remainder of the population at baseline risk, including some research that shows a decreased risk of ovarian cancer in women who have undergone tubal ligation.8-11

Patients with germline BRCA mutations are particularly predisposed to ovarian cancer. However, 85%-90% of ovarian HGSCs arise in patients without a currently identified genetic susceptibility.12 Nearly 70% of those cancers are thought to arise from the fallopian tube, implying a potential role for salpingectomy as a means for ovarian cancer risk reduction in the general population.4,12 While it remains to be determined whether the risks outweigh the benefits of performing a bilateral salpingectomy as a stand-alone procedure in an average-risk patient, bilateral salpingectomy certainly should be considered in patients who are already undergoing hysterectomy for other indications. The operative safety of salpingectomy in this setting has been demonstrated in a large retrospective cohort study of more than 40,000 women.13

Hysterectomy remains one of the most common surgical procedures, with approximately 600,000 of these surgeries performed annually in the United States. Approximately 90% of hysterectomies are performed for benign indications, the most common of which are related to symptoms of uterine leiomyomas.14,15 In the general population, the lifetime risk of ovarian cancer is approximately 1 in 70 women and approximately 22,000 women are diagnosed annually in the United States.16

Bilateral oophorectomy, when performed concurrently with hysterectomy for benign disease, has been demonstrated to increase risk of all-cause mortality and coronary artery disease. Parker and colleagues’ report that estrogen replacement therapy in the

FIGURE 1. The fallopian tube is isolated distally from the ovary during initial steps of laparoscopic salpingectomy, carefully incorporating tubal fimbriae into the specimen.

FIGURE 2. Correct placement of the cautery instrument immediately adjacent to the fallopian tube incorporating as little of the mesosalpingeal vessels as possible.

85% TO 90% OF OVARIAN HGSCs ARISE IN PATIENTS WITHOUT A CURRENTLY IDENTIFIED GENETIC SUSCEPTIBILITY. NEARLY 70% OF THOSE CANCERS ARE THOUGHT TO ARISE FROM THE FALLOPIAN TUBE.
setting of oophorectomy may mitigate these negative long-term effects was an observational study which limits our understanding of the reasons behind estrogen use or non-use in some patients. Moreover, concerns remain about patient compliance with hormone therapy.\textsuperscript{17,18}

The potential long-term risks of oophorectomy, in conjunction with data supporting the fallopian tube as a precursor lesion of HGSC, may make bilateral salpingectomy at the time of a hysterectomy with ovarian preservation a procedure with a more optimized risk-benefit ratio.

While the safety of risk-reducing salpingectomy at the time of hysterectomy has been demonstrated in retrospective studies,\textsuperscript{19,20} one frequently raised concern is the potential decline in ovarian function after salpingectomy. A retrospective study and a randomized controlled trial (RCT) both have demonstrated preservation of normal ovarian function after salpingectomy at the time of hysterectomy, as measured by surrogate markers of ovarian function, such as serum anti-mullerian hormone (AMH), follicle-stimulating hormone (FSH), and estradiol levels.\textsuperscript{5,21,22} However, the long-term effects on ovarian function are less well described in the literature.

In January 2015, the American College of Obstetricians and Gynecologists (ACOG) published a Committee Opinion that underscores the potential benefits of salpingectomy at the time of hysterectomy, including the potential risks and benefits.\textsuperscript{23} Like ACOG, AGO reports a lack of sufficient evidence to justify a universal recommendation for opportunistic salpingectomy. The Society of Gynecologic Oncology (SGO) put forth a Clinical Practice Statement in November 2013 stating that, for women at average risk of ovarian cancer, salpingectomy should be considered at the time of hysterectomy or at the time of other pelvic surgery.\textsuperscript{25} SGO reaffirmed this recommendation in a 2015 publication.\textsuperscript{26}

In light of these data, many providers and institutions are now offering patients opportunistic salpingectomies at the time of hysterectomy. Here we suggest techniques for bilateral salpingectomy at the time of hysterecto-
my, including abdominal, laparoscopic, and vaginal approaches.

Surgical techniques

Laparotomy

In general, we recommend that salpingectomy at the time of abdominal hysterectomy be performed prior to hysterectomy because it allows for complete removal of the entire fallopian tube without the need to reisolate any surgical pedicle. The ampullary portion of the fallopian tube is grasped with a Babcock clamp and elevated.

Fenestrations should be made within the mesosalpinx, isolating the small vessels that lie between the ovary and fallopian tube. These vessels are branches of the ovarian and uterine arteries and may provide additional blood supply to the ovaries. Small clamps, such as Kelly or tonsil clamps, are placed across these vessels, favoring the tubal side of the mesosalpinx, in order to preserve as much ovarian blood supply as possible. Each pedicle is then transected and ligated.

Alternatively, a monopolar electrosurgery device with coagulation current or an electrosurgical vessel sealing device can be used. These devices should be placed immediately adjacent to the tube in order to cauterize and transect the mesosalpinx.

Be sure to incorporate the entire fimbriated distal portion of the tube, which sometimes requires careful dissection of tubal adhesions or distal tubal cysts off the ovary and its blood supply. At the cornual segment of the fallopian tube, take care to avoid entry into the uterine myometrium, as this region can be particularly vascular. Once detached from the mesosalpinx, the fallopian tubes can be left attached to the uterus as the hysterectomy is then performed and can be removed en bloc with the uterus.
Laparoscopy

Both traditional and robotic approaches to laparoscopy allow for bilateral salpingectomy at the time of hysterectomy. A grasper should be used to hold onto the infundibular portion of the fallopian tube and to provide gentle traction toward the anterior abdominal wall. This allows for better exposure and visualization of the plane between the ovary and fallopian tube. Any laparoscopic instrument that allows for electrosurgical vessel sealing and transection of tissue can be used to dissect across the mesosalpinx.

Alternatively, a monopolar electrosurgery device can be used to cauterize the mesosalpinx before transection with endoscopic scissors. Again, transect the mesosalpinx as close to the fallopian tube as possible while ensuring that the tube is entirely removed. As in the open approach, the fallopian tubes can be left attached to the uterus while the hysterectomy is performed and removed as a single unit once the hysterectomy is complete.

Vaginal

Salpingectomy at the time of vaginal hysterectomy is often the most challenging of these procedures. In this situation, the hysterectomy is performed as usual up to the level of the “triple pedicles.” At that point, the first triple pedicle—incorporating the utero-ovarian ligaments, the fallopian tubes, and the round ligaments—is clamped and transected from the uterus. A large clamp, such as a Zeppelin, Heaney, or long Pean, should be used.

Then place gentle upward traction on the uterus to keep the operative field clear of intraperitoneal contents.

Next evaluate the feasibility of transvaginal salpingectomy by gently turning the clamp on the triple pedicle in order to make an anatomic assessment. In a technique described by Kho and colleagues, the round ligament can first be divided to allow better mobilization of the adnexa and access to the proximal fallopian tube. The challenge from this point is to incorporate the entire fallopian tube into the salpingectomy specimen. Leasing the triple pedicle clamped rather than suture-ligating it allows for the clamp to become a handle with which gentle traction and manipulation of the tube can be performed.

Once identified, the fimbriated end of the fallopian tube should be brought into the operative field with a Babcock clamp. Transection of the mesosalpinx begins with freeing the fimbriated end from the ovary. Again, this can be done by clamping, transecting, and ligating isolated vascular pedicles of the mesosalpinx, or with monopolar cautery or an electrosurgical vessel sealing device. In our experience, an electrosurgical vessel sealing device allows for more dexterity and easier sealing and transection of the mesosalpinx during vaginal surgery than individually clamping, cutting, and ligating each pedicle.

Once the isthmic portion of the tube is reached, place a second large clamp just cephalad to the large clamp that contains the triple pedicle. This second clamp should incorporate only the utero-ovarian ligament and the round ligament, leaving the fallopian tube free. The first large clamp can then be removed, allowing for completion of the salpingectomy while the utero-ovarian ligament and the round ligament remain clamped at all times. Then remove the fallopian tube in its entirety. Clamp and transect the contralateral triple pedicle, and remove the uterus before performing contralateral salpingectomy. A surgical sponge on a Forester clamp can be used to gently push the intraperitoneal contents out of the operative field. Complete the contralateral salpingectomy in a similar fashion after removing the uterus.

Summary

Salpingectomy at the time of hysterectomy with ovarian preservation will likely become more common as growing evidence implicates the fallopian tube as the site of origin of high-grade serous ovarian cancer. Operative considerations include removal of the fallopian tube in its entirety and preservation of ovarian blood supply. The techniques described here allow for removal of the fallopian tubes while respecting these considerations.

Salpingectomy can be performed safely at the time of hysterectomy via an open abdominal, minimally invasive, or transvaginal approach.

For references visit contemporaryobgyn.net/salpingectomy-techniques
Chromosomal microarray analysis (CMA) is a high-resolution whole-genome screening technique that can identify most chromosomal imbalances detected by conventional cytogenetic analysis, as well as smaller submicroscopic deletions and duplications known as copy-number variants (CNVs). CNVs may cause a range of disorders, including neurodevelopmental disorders and congenital anomalies. CMA is recommended as the first-tier test in postnatal evaluation of congenital abnormalities and neurodevelopmental disorders.

With accumulating experience over the last decade and data demonstrating improved detection of chromosomal abnormalities compared to conventional karyotyping, CMA is proving to be a valuable diagnostic tool in the prenatal setting. CMA can be performed on uncultured DNA samples, including those obtained from chorionic villus sampling (CVS) and amniocentesis, which may lead to quicker turnaround than karyotyping.

Q | What are the different types of microarray?
Two major microarray platforms are used in prenatal diagnosis: single nucleotide polymorphism (SNP) arrays and comparative genomic hybridization (CGH) arrays. With SNP and CGH arrays, DNA from a fetal sample, such as CVS or amniocentesis, is hybridized to an array platform consisting of DNA probes on a solid surface, such as a microscope slide or a silicon chip.

CGH compares the fetal DNA sample with a normal reference DNA sample. An SNP is a variation at a single position in a DNA sequence among individuals. With SNP arrays, only the DNA test sample is hybridized to the array platform. While CGH arrays are able to detect only copy number variants, SNP arrays can also detect triploidy and regions on the 2 homologous chromosomes that are identical to each other, as occurs with uniparental disomy (UPD) and consanguinity. In the case of UPD, both copies of a chromosome are inherited from the same parent, instead of one from each parent. UPD has been associated with genetic disorders such as Prader-Willi syndrome. SNP arrays can also detect some cases of maternal cell contamination and mosaicism.

Arrays may include probes that cover the whole genome, or may be targeted, with concentrated coverage in known disease-causing regions of the genome and more limited coverage of the rest of the genome.

Q | What can CMA detect? How does it differ from a karyotype?
A standard karyotype can detect aneuploidies (abnormalities in chromosome number), relatively large structural abnormalities such as deletions or duplications that are microscopically visible to a resolution as low as approximately 5–10 Mb, and balanced or unbalanced translocations and inversions. CMA has a higher resolution than conventional karyotyping, allowing for detection of much smaller
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submicroscopic deletions and duplications, typically down to a 50–100 kb level. CMA can also detect some copy number changes near the chromosomal breakpoint sites in rearrangements that appear to be balanced on a conventional karyotype.

Another advantage of CMA is that this technique does not require dividing cells, unlike conventional karyotyping, which requires cell culture. This difference can allow for quicker turnaround. Also, CMA can be performed on macerated tissue obtained from stillbirth specimens that may not grow in tissue culture, and thus, may be more likely to provide a result as long as sufficient good-quality DNA can be obtained.

**Q** What are the limitations of CMA?
Because CMA looks for genomic imbalance, it cannot detect totally balanced chromosomal rearrangements, such as translocations or inversions. Most balanced rearrangements, however, result in normal outcomes. In addition, CMA does not provide information about the chromosomal mechanism of a genetic imbalance. Therefore, a karyotype should be performed in such cases to rule out a translocation that may have been inherited. Low-level mosaicism may not be detected by CMA and some arrays do not detect triploidy. SNP arrays, however, are generally able to detect lower levels of mosaicism, as well as triploidy. CMA will not detect all CNVs, such as those that are in regions not represented on the array platform and very small CNVs that are below the level of detection. In some cases, a postnatal CMA may identify a CNV that was not identified prenatally due to the higher resolution of postnatal arrays. In addition, CMA will not detect point mutations within single genes, including those that cause disorders such as sickle cell anemia, cystic fibrosis, and many skeletal dysplasias.

CNVs are more likely to be pathogenic, an abnormal fetal outcome cannot always be excluded even if a parent with the same CNV as a fetus is normal, as some have a variable outcome. When interpreting VUS, it may be helpful to evaluate the specific genes that are contained in the deleted or duplicated regions. In general, small duplications are less likely to be clinically significant than are small deletions.

**Q** What are the risks and disadvantages of CMA?
A disadvantage of CMA is the inability to precisely interpret the clinical significance of a previously unreported CNV or to accurately predict the phenotype of some CNVs that are associated with variable outcomes. CNVs are characterized as benign, clinically significant (ie, pathogenic), and VUS. The overall prevalence of VUS is approximately 1% to 2%. Additional information on the classification of CNVs is rapidly accumulating, which should lead to a decrease in incidence of VUS.

Patients in whom a fetal VUS is detected should be counseled by experts who have access to databases with updated information on genotype-phenotype correlations. Patients should be educated about the significance of the finding including the potential range of outcomes, and should be provided with resources and support. Further testing should be offered if indicated. One of the initial steps in the evaluation is to determine if either parent has the same CNV as was detected in the fetus. Although de novo CNVs are more likely to be pathogenic, an abnormal fetal outcome cannot always be excluded even if a parent with the same CNV as a fetus is normal, as some have a variable outcome. When interpreting VUS, it may be helpful to evaluate the specific genes that are contained in the deleted or duplicated regions. In general, small duplications are less likely to be clinically significant than are small deletions.

**Q** When should array be offered, and what are the indications?
The American College of Obstetricians and Gynecologists (ACOG) and SMFM recommend that “[A]ll pregnant women should be offered prenatal assessment for aneuploidy by screening or diagnostic testing regardless of maternal age or other risk factors ...” CMA in particular is recommended when genetic analysis is performed in cases of fetal structural anomalies and/or fetal demise. CMA replaces the need for fetal karyotype in these cases. ACOG and SMFM recommend that fetal karyotype or CMA be performed when invasive prenatal diagnosis is performed in cases with structurally normal fetuses.

Some providers now recommend CMA as a first-line test whenever fetal chromosomal analysis is planned, while others reserve CMA for cases of
fetal structural abnormalities to avoid the possibility of discovering a VUS. The prevalence of significant abnormalities identified by CMA in cases with a normal karyotype and normal ultrasound was 1/60 (1.7%) in the study by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. This prevalence is high enough that providers should discuss the benefits and limitations associated with CMA and conventional karyotype with their patients who are considering amniocentesis and CVS.

Chromosomal microarray analysis should be considered as further evaluation when an apparently balanced de novo rearrangement is detected by karyotyping in order to exclude an imbalance at one or both of the translocation breakpoints. CMAs may also prove helpful in identifying the chromosomal origin and gene content of marker or ring chromosomes identified with conventional karyotype.

Q When is it appropriate to perform just a karyotype? Conventional karyotype and/or rapid FISH testing may be more appropriate when a common aneuploidy such as trisomy 21, 18, 13 or monosomy X is strongly suspected based on prenatal ultrasound findings. In these circumstances, conventional karyotype and FISH analysis may provide a more rapid turnaround, allow for more sensitive detection of low-level mosaicism, and rule out a translocation-associated trisomy. A CMA can be performed in the event that the FISH or karyotype is normal. Conventional karyotype to identify potential balanced translocations is the most appropriate first-line test for couples with a history of recurrent miscarriage. Due to limited data, CMA is not currently recommended as a first-line test to evaluate first-trimester pregnancy losses.

In some situations a karyotype should be performed following an abnormal microarray result. When trisomy of an acrocentric chromosome (13, 14, 15, 21, or 22) is identified by CMA, a karyotype should be performed to rule out an unbalanced Robertsonian translocation that might have been inherited. Depending on the size, either FISH or a karyotype is sometimes recommended to rule out inherited rearrangements in some cases involving smaller copy number gains. This information may provide accurate information regarding future recurrence risks.

Q How should patients be counseled prior to CMA? Trained genetic counselors, geneticists, or other providers with expertise in the complexities of interpreting CMA results should perform pre- and post-test counseling. Providers should be familiar with the microarray platform used by their laboratory, including the rate of VUS. Patients should be informed that compared with conventional karyotype, CMA will detect a potentially pathogenic CNV in an additional 6%–7% of cases with fetal structural abnormalities on ultrasound and in 1%–1.7% of cases with a structurally normal fetus. Patients should also be informed of the 1.4%–2.1% chance that a VUS will be detected.

Pretest counseling should include a discussion of the spectrum of disorders that can be detected with CMA, including disorders with severe neurologic phenotypes as well as those with more mild or adult-onset phenotypes. Patients should also be informed that CMA does not detect every genetic disease or syndrome, including autosomal recessive disorders associated with single-gene point mutations. Patients should also be informed that CMA can detect consanguinity and non-paternity in some cases.

Q What samples can be used? CMA may be performed on DNA obtained from amniocentesis, CVS, fetal cord blood, and stillbirth specimens. DNA obtained from the mesenchymal core cells of the chorionic villi and uncultured amniocytes is preferable to DNA from cultured cells to allow for quicker turnaround and to avoid the possibility of culture artifacts. Some labs require that a maternal blood specimen be sent with the original CMA specimen, while other labs request parental samples only when a CNV is detected, in order to distinguish between an inherited and a de novo CNV.

Q Are there differences between prenatal and postnatal microarray?
In many prenatal cases, patients opt to have CMA for reassurance. CMAs are recommended as the first-tier diagnostic test for postnatal evaluation of children with multiple congenital anomalies, developmental delay/intellectual disability, and/or autism spectrum disorders, with clinically significant findings reported in approximately 15% of cases with normal conventional karyotypes.

In postnatal cases, identifying a diagnosis is important to parents for many reasons, including obtaining resources, planning future care for the child, and planning future pregnancies. The benefit of finding a clinically significant abnormality with CMA may offset the downside of finding a VUS. In the prenatal setting, particularly in cases with a structurally normal fetus on ultrasound, a VUS may cause considerable stress and anxiety as parents may consider the option of a termination. It may be difficult to interpret the significance of a CNV prenatally due to the limitations of fetal imaging and limited data correlating prenatal CNV findings with postnatal phenotypes.

To decrease the likelihood of identifying a VUS, many specialists advocate using a targeted rather than a whole-genome approach in prenatal cases. Targeted arrays use platforms that primarily identify CNVs in which clinical interpretation is non-equivalent, including trisomies, or well-documented microdeletion/duplication syndromes. However, targeted arrays also may result in a lower diagnostic yield. The probe density of targeted arrays has increased recently, and as knowledge regarding classification of CNVs continues to expand, the difference between whole genome arrays and targeted arrays is narrowing.

### SUMMARY OF RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
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<tbody>
<tr>
<td>1 We recommend that CMA be offered when genetic analysis is performed in cases with fetal structural anomalies and/or stillbirth, and that it replaces the need for fetal karyotype in these cases.</td>
<td>1A Strong recommendation, high-quality evidence</td>
</tr>
<tr>
<td>2 We recommend that providers discuss the benefits and limitations of CMA and conventional karyotype with patients who are considering amniocentesis and CVS, and that both options be available to women who choose to undergo diagnostic testing.</td>
<td>1B Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>3 We recommend that trained genetic counselors, geneticists, or other providers with expertise in the complexities of interpreting CMA results perform pre- and post-test counseling.</td>
<td>Best practice</td>
</tr>
<tr>
<td>4 We recommend that patients be informed that CMA does not detect every genetic disease or syndrome, and specifically does not detect single-gene point mutations, and that CMA can detect consanguinity and non-paternity in some cases.</td>
<td>Best practice</td>
</tr>
<tr>
<td>5 We recommend that patients in whom a fetal variant of uncertain significance (VUS) is detected receive counseling from experts who have access to databases that provide updated information concerning genotype-phenotype correlations.</td>
<td>Best practice</td>
</tr>
<tr>
<td>6 We recommend against the use of CMA as a first-line test to evaluate first-trimester pregnancy losses due to limited data.</td>
<td>1C Strong recommendation, low-quality evidence</td>
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</tbody>
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Postnatal CMA does generally have a higher resolution than in a prenatal setting, and therefore may identify a CNV that was not identified prenatally in some cases.

What about the cost of CMA and insurance coverage for it?

Chromosomal microarray currently is more expensive than conventional karyotyping but the cost is expected to decrease with increasing volumes and technical advances. Insurance coverage in the United States largely conforms to the recommendations of the joint ACOG and SMFM Committee Opinion.
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A demanding condition requires a demanding test. Vaginitis accounts for approximately 10 million office visits each year. Most women will experience vaginitis symptoms. Recurrence is common. This condition commands a great deal of your daily patient care time. You need a test with diagnostic accuracy to help treat patients properly on the first visit and help reduce recurrence.

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You take women’s health care personally, and so does LabCorp.

A demanding condition requires a demanding test. Vaginitis accounts for approximately 10 million office visits each year. Most women will experience vaginitis symptoms. Recurrence is common. This condition commands a great deal of your daily patient care time. You need a test with diagnostic accuracy to help treat patients properly on the first visit and help reduce recurrence.

Bacterial
The NuSwab Bacterial Vaginosis (BV) test:
- uses 3 quantitative organisms: Atopobium vaginae, BVAB-2, Megaspheara
- distinguishes normal flora from BV.
- is 97% sensitive and 92% specific according to a published clinical study.

Fungal
The NuSwab C albicans and C glabrata test:
- targets the 2 most common Candida species.
- helps guide treatment – C glabrata is often resistant to fluconazole.
- allows for add-on testing of 4 additional Candida species in refractory or recurrent cases.

Parasitic
The NuSwab Trichomonas vaginalis (Tv) test:
- is 100% sensitive and 99% specific for Tv diagnosis.
- shown to be more sensitive than culture, microscopy, and Affirm™ VPIII.
- can be used as a follow-up test to confirm negative wet mounts.

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Fighting Zika with prevention

Top mosquito repellent recommendations from dermatologists

by LISETTE HILTON AND CHRISTINE BLANK

Contemporary OB/GYN asked ob/gyns and dermatology experts to share recommendations for insect repellents to prevent mosquito bites that might spread the Zika virus.

With summer here and concern growing about the spread of the Zika virus to the United States, physicians might notice more patients inquiring about how to safely repel mosquitoes and their disease-inducing bites.

The Centers for Disease Control and Prevention (CDC) is urging everyone to take steps to prevent mosquito bites with such things as appropriate clothing and Environmental Protection Agency (EPA)-registered insect repellents. The repellents, according to the CDC, should have 1 of the following active ingredients: DEET (N,N-diethyl-meta-toluamide); picaridin (2-[2-hydroxyethyl]-1-piperidinecarboxylic acid 1-methylpropylester); IR3535 (3-[N-acetyl-N-butyl]-aminoproprionic acid ethyl ester); or oil of lemon eucalyptus (para-methane-3.8-diol). The CDC states that the EPA does not recommend any additional precautions for repellent use among pregnant and nursing women.

Contemporary OB/GYN asked ob/gyns and dermatology experts to share their best patient recommendations for insect repellents.

Since it was developed in 1957, DEET has been demonstrated to be the best insect repellent humans have ever invented.

Quick Take

- The Environmental Protection Agency does not recommend any additional precautions for repellent use among pregnant women.
- Barrier clothing and mosquito nets are also useful in the fight against insect bites.

“In a 20% to 50% concentration, it is effective and safe, according to the US Agency for Toxic Substances and Disease Registry. In addition, use of long sleeves and pants will help reduce the incidence of mosquito bites,” Wheeland says.

Dermatologist Joel Schlessinger, MD, president of LovelySkin.com, says that although DEET is very important for protection, the use of barrier clothing and nets in the home (particularly around the bed area) are essential.

“Mosquito repellent will never be
completely effective and, for that reason, it is imperative to put other roadblocks between the mosquito and you,” Schlessinger says. “If any of your patients are considering going to an infested area, they can purchase hats with netting on them and clothing that is long sleeved in advance. During the night, they should sleep in beds that have netting around them. One particularly effective tool is to spray clothing with DEET-containing repellent. This allows for better control of bugs and potential Zika vectors.”

Sandy Tsao, MD, assistant professor, Harvard Medical School, Boston, Massachusetts, and a dermatologist at the Dermatology Laser and Cosmetic Center at Massachusetts General Hospital, Boston, says DEET is her go-to recommendation for repelling mosquitoes. Tsao says she uses OFF! Deep Woods, but there are other OFF! products, such as OFF! FamilyCare Smooth and Dry and Off! Skintastic FamilyCare Insect Repellent, that are less concentrated.

“DEET is seen as one of the most effective products for repelling insects, but the concern is that it can be neurotoxic,” Tsao says. She also recommends permethrin clothing treatment that lasts for 6 washes. Using these products, which impregnate clothing with insect repellent, could lead to less need for DEET and other insecticides, she says.

“Biting insects, including mosquitoes, are most attracted to where carbon dioxide is being emitted, so your face and ears are prime targets for a bite,” Tsao says. “As well, insects tend to gravitate to areas of heavy sweat.” She recommends that patients apply the insecticide to any areas of exposed skin—making sure to not forget the ankles, feet, hands, and scalp.

Medina, Ohio, dermatologist Helen M Torok, MD, says she has trepidation about recommending DEET, but will talk to patients about DEET if asked about mosquito repellents. “[If] those [patients] are also uncomfortable with DEET, then I recommend the lemon-eucalyptus products,” she says. Dr Torok adds that although patients may be reluctant to use it, the FDA has approved DEET for pregnant and lactating women. Other prevention strategies she recommends are to avoid wearing bright clothing and shiny jewelry and being near standing water.

Is there a Zika vaccine on the horizon?
The U.S. Department of Health and Human Services’ Office of the Assistant Secretary for Preparedness and Response (ASPR) plans to help bring a vaccine for the Zika virus to market immediately via Emergent BioSolutions Inc., which also developed the anthrax vaccine.

Emergent BioSolutions said that it obtained a contract with ASPR’s Biomedical Advanced Research and De-
development Authority (BARDA) to develop and manufacture three cGMP lots of a Zika vaccine for use in a phase 1 clinical trial is valued at up to $21.9 million.

“The threat posed by Zika presents an urgent need for vaccines and diagnostics,” said Richard Hatchett, MD, acting BARDA director. “To meet that need as quickly as possible, we need to leverage the infrastructure, experience and expertise available within BARDA, other federal agencies, industry and academia.”

The first US test for the Zika virus became available in early May after Quest Diagnostics received an Emergency Use Authorization (EUA) for its Zika Virus RNA Qualitative Real-Time RT-PCR test (Zika RT-PCR test).

Until then, the only Zika tests authorized by FDA were available from the Centers for Disease Control and Prevention (CDC), and were only used in qualified laboratories designated by the CDC.

Emergent Biosolutions will conduct a variety of studies via BARDA’s Center for Innovation in Advanced Development and Manufacturing (CIADM) in Baltimore, to move quickly through early stages of vaccine development and submit an investigational new drug request to FDA to begin clinical studies. To further speed development time, Emergent will use vaccine technology similar to that used in vaccines being developed to protect against similar viruses, such as Dengue.

Over the next 30 months, BARDA will provide more than $17.9 million to Emergent with the potential for additional work, totaling approximately $21.9 million.

However, at any stage in development, BARDA could transfer the technology to other vaccine manufacturers to utilize the technology to produce and market the Zika vaccine, HHS said.

In addition to this vaccine development, BARDA is sponsoring development of pathogen reduction technologies to reduce the risk from Zika in the blood supply. BARDA also is using its clinical studies network to collect blood samples needed to speed development of diagnostic tests.

BARDA is seeking additional proposals for products that could be used to prevent or detect Zika or other illnesses and injuries associated with public health emergencies. The U.S. Department of Health and Human Services’ Office of the Assistant Secretary for Preparedness and Response (ASPR) plans to help bring a vaccine for the Zika virus to market immediately via Emergent BioSolutions Inc., which also developed the anthrax vaccine.

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**FOR YOUR PATIENTS**

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**From Editor-in-Chief Charles J Lockwood, MD, MHCM:** This advice could not be more timely given the imminent threat of Zika-bearing mosquitoes appearing in the continental US and their rapid spread across the US Commonwealth of Puerto Rico. For the latest Zika news, including information on where the newest cases have been identified, visit the Contemporary OB/GYN homepage at [www.contemporaryobgyn.net](http://www.contemporaryobgyn.net).
CONTINUOUS FROM PAGE 17

efficiently using hexosaminidase A enzyme analysis for low carrier frequency groups (non-Ashkenazi). Because of racial/ethnic mixing, it may be best to include this as part of any screening approach.

Implementation of carrier screening

Carrier screening can be performed before conception or antenatally, and sequentially (maternal then paternal) or simultaneously. Most patients are not screened in the preconception period. In many cases, this is because of issues with insurance and public healthcare coverage for genetic testing rather than lack of awareness on the part of patients or their physicians. Patients need education around these problems, and as a result, the window of time for consent and pretest counseling often is so short that maternal and paternal carrier screening have to be done simultaneously.

Documenting the information provided during pretest counseling is important. Key concepts include:

- All genetic screening and testing is voluntary and confidential.
- Accurate fetal risk assessment requires screening of the biologic father.
- Testing positive for at least one condition is common.
- Patients may learn about health risks important to them and to family members.
- Conditions screened for range in spectrum of severity—some are mild and others are quite severe.
- A negative test result does not eliminate the possibility of being a carrier (residual risk)
- Repeat screening in subsequent pregnancies is not necessary.

- A plan to provide accurate information is needed in cases of a positive test result.

Follow-up

The follow-up required after implementing carrier screening depends on several factors: The nature of the condition screened (recessive, semi-dominant or X-linked), test result (positive or negative), spectrum of the condition, and literacy level of the patient. Follow-up respects the patients’ need to react, respond, and adjust to their results. Having a plan consistent with the provider’s office infrastructure is important (eg, is a geneticist on site, who calls results to patients). These tips may be helpful.

Staff:

Designate 2 people in the office to assist in tracking genetic screening reports. This allows uninterrupted review of results when employees are on vacation.
- Be sure to train staff on the voluntary nature and confidentiality of genetic testing.
- To ensure privacy, request that ECS reports for each partner are distinctly separate.
- Establish a tracking system for reports with different names.

Genetic Counseling:

When one member of a couple tests positive, sequencing the partner’s gene is not recommended. Instead the partner should also be screened. Establish a relationship with a professional trained in genetics and genetic counseling. Other family members who might benefit from test results should be considered. Be prepared to discuss specific conditions, spectrum of conditions, treatment options, and available support groups. Rely on legitimate resources (not blogs).

Fetal Testing:

- Fetal testing can be performed using amniocentesis or chorionic villus sampling.
- Laboratories that perform ECS generally do not handle fetal specimens.
- Identify a resource lab for testing fetal specimens.
- Recognize that families will individualize their use of genetic screening and testing information.

Summary

Professional organizations have not stated whether all patients should be made aware of ECS. However, this method of screening is increasingly being covered by private insurance as well as state and federal healthcare programs. ECS can be offered to patients without fear as long as basic principles used in everyday ob/gyn practice are adopted to allay anxiety. As the entirety of medicine adopts molecular-based diagnostics and therapeutics, clinicians have a duty to stay current on the implementation of these into clinical practice.

Genetics is not an arcane discipline practiced only by certified geneticists. Genetics should be viewed in the same way as ultrasound, which is now a part of most medical disciplines. Proactive learning can fend off efforts to mandate certification as these technologies become a routine part of state-of-the-art obstetric care.

FOR REFERENCES VISIT contemporaryobgyn.net/expanded-carrier-screening
Electro Lube
This anti-stick solution for electrosurgery is designed to keep instruments clean.

**Company** Eagle Surgical Products (Austin, TX)

**Website** www.electrolubesurgical.com  |  **List Price** $500 (per box of 20)

**Design/Functionality** ★★★★  |  **Innovation** ★★★★  |  **Overall Score** ★★★★★

**Background**
Core surgical rule: hemorrhage bad; hemostasis good. With that insightful gem out of the way, let’s turn our focus to electrosurgery, in which electrical current is employed to coagulate bleeding blood vessels by denaturing blood and blood vessel proteins. While that technique is generally effective, the process often results in unwanted sticking and char build-up on the coagulating device. Because both of those effects are detrimental to achieving hemostasis, preventing them is important. Electro Lube is that prevention in a bottle.

**Design/Functionality**
Approved by the US Food and Drug Administration in 2004, Electro Lube is typically recognized by surgeons as “that yellow goop” that is applied to Da Vinci monopolar scissors to minimize the risk of current arcing. While it is helpful for minimizing arcing, its real modus operandi is preventing sticking and char buildup during electrosurgery. Derived from soybean oil, it is a lecithin-based phospholipid mixture that is non-synthetic, non-flammable, and non-allergenic. It comes in a sterile single-use 8-cc plastic vial and is applied to the tip of any electrosurgical instrument prior to the instrument’s use.

In clinical use, Electro Lube worked exactly as expected. In my parlance, it was just like good sports referees: If you don’t notice them, they are doing their job. In our operating room (OR), the Storz RoBi bipolar Maryland forceps is our go-to coagulation workhorse. With Electro Lube applied, I have yet to need to clean an instrument during a case or to experience sticking to tissues.

**Innovation**
Instrument sticking and char build-up is definitely a real problem in certain coagulation-heavy procedures.
WiCAM Wireless Digital Endoscope Camera & LED Light Source

**Company** The Prometheus Group (Dover, NH)

**Website** www.theprogrp.com  |  **List Price** $3,200 (including tablet PC)

**Design/Functionality** ★★★ |  **Innovation** ★★★★★ |  **Overall Score** ★★★★★

**Background**

Through the generosity of the Greek deity Prometheus, man was introduced to fire. Let there be no doubt, fire was a major enabling technology in humankind’s evolution and ranks only below the iPhone as the most significant advance since we arose from primordial muck. Given this legacy, it should be of little surprise that once again, Prometheus is trying to change mankind; only this time, instead of fire, we are getting an unethered endoscopic camera and light source.

**Design/Functionality**

The WiCAM Wireless Digital Endoscope Camera and LED Light Source has multiple components that integrate to make any standard endoscope (cystoscope, hysteroscope, laparoscope, etc.) cordless. The camera is a standard-sized, lightweight (.35 lb, 158 g) device with a standard c-coupler that fits onto any standard eyepiece. Real-time images are wirelessly transmitted from the camera head to a USB receiver plugged into a monitor, laptop, or tablet and a rechargeable battery screws a lightweight LED light source directly onto any standard light port.

In use for an office hysteroscopy, the Prometheus wireless digital endoscope camera and LED light source was pretty “wow.” When stationary, the picture was excellent with full 640 x 480 resolution and the light was comparable to what I am used to. There were only 2 buts. But #1: During rapid movement of the camera there were occasions when the image deteriorated as the transmission speed lagged behind the image. This problem is minimized by keeping the camera and tablet at high power and selecting another channel on the

**CONTINUED ON PAGE 38**
Typing the word “wearable” into Amazon returns information on more than 600,000 products, ranging from activity trackers, to fitness trackers, to smart clips, to arm- and wristbands, to smart watches. FitBit, Jawbone, Misfit, Garmin, and Apple Watch are just a few of the names associated with these devices. Regardless of the manufacturer or the form, all of these devices have the same general idea; they passively monitor daily activity and the data aggregated are streamed via a hardwire connection or Bluetooth and accessed through a mobile application or web-based portal. Since the advent of wearable devices, the products have gotten significantly smaller and lighter and are jam-packed with (sometimes) highly accurate sensors.

The missing capability
As these devices have increased in popularity, discussions about prescribing exercise have become much easier. But one capability is still missing: collection, compilation, and streaming of data in a meaningful way directly into a patient’s electronic health record (EHR). While I love seeing a device on my patient’s wrist, I am often at a loss when she is unable to tell me about her data. I have found that patients like knowing that they have walked 10,000 steps in a day, but they rarely can tell me (or mine as her doctor?) their daily step count or their daily weight. Did their weight go down when they increased their steps the preceding month? Some patients use dietary tracking apps such as MyFitnessPal, and I often ask patients about the effects of dietary modifications on their wellness (weight, sleep, energy level, etc). Few can answer. While patients can often show me that they are consuming only 1750 kcals a day, they often can’t show me how that affects their wellbeing. But is it the patient’s job to do that, or is it the patient’s job to do that, or

I think there is something awkward about asking a patient to send me a screenshot of her data.

What’s the holdup?
Third-party vendors have made great strides in helping data “flow” from a patient’s device to her permanent record, but big-box EHR manufacturers have not made that a priority because the data are hard to map. Until all health data are standardized on phones and sent the same way from each device, it is almost impossible for an EHR to use that information because the system has no idea where to put the data.

Furthermore, as more EHRs offer portals that allow patients the ability to view their records, it seems almost archaic that the data cannot just flow
The National Health Service (NHS), the publicly funded healthcare system in England, has launched an initiative to link devices and apps with improvements in certain public health disorders (ie, diabetes, heart disease, asthma, sleep disorders, chronic health conditions, obesity, etc). One software manufacturer, Medelinked, is providing their service free to NHS patients, doctors, and healthcare professionals in the hope of closing the aforementioned gap.

And, as more providers and patients look to consolidate this information, and attempt to “log” this data, either in the EHR or on a phone, we are going to have more data entry errors because we are all manually entering disconnected information. For example, if a patient types in a cholesterol level of 33 instead of 330, she may falsely believe that she has a low average serum cholesterol and not watch her food intake.

The NHS initiative
The National Health Service (NHS), back to the patient’s phone so that it can all be consolidated into one place. Patients are going online to look at their most recent cholesterol levels but logging their daily exercise and nutrition in an app that cannot integrate that data.

For example, patients and providers can share data on blood glucose and cholesterol levels, calorie intake, weight, waist size, exercise level, blood pressure, as well as comments on symptoms and wellness. The bidirectional tool allows patients to send data to their health providers and caretakers to send data to their patients. It is one of the first such tools to allow patients access to and ownership of their health data.

Moving beyond a fashion statement
As someone who embraces technology, and at times, even tries to force its use in healthcare, the inability to stream and flow patient-derived data is my big healthcare disappointment of 2016.

Everyone is collecting data. In fact, most people don’t know that the iPhone has a built-in pedometer; so even when you are just walking with your phone, it is tracking you. However, at the halfway point of 2016, I am still unable to access these data, and as such, I feel that wearables are as much fashion statements for the nondominant hand as they are quasi-healthcare tools.

Dr Levine is Practice Director, CCRM New York, and Attending Physician, Lenox Hill Hospital, New York. He has no conflicts of interest to report in respect to the content of this article.

ABOUT OUR EDITORIAL PROCESS
All of Contemporary OB/GYN’s review articles are written at the invitation of the magazine’s editorial board. These papers are then subject to peer review by experts to ensure that the content is relevant to clinical practice, scientifically accurate, objective, and balanced.

Only submissions that meet our editorial board’s quality criteria are published in the magazine. This quality control process is the foundation for our delivery of evidence-based information to busy ob/gyns. Additionally, our content is not influenced by industry in any way. Authors and board members are required to disclose any industry ties that may present a conflict of interest.
When there is active bleeding, you really want a fully functional coagulation instrument and Electro Lube is the “grease that helps the wheel turn.” In addition, less char build-up means less scraping and less scraping means less damage to expensive, delicate surgical instruments. Given all these pluses, I think this soybean oil by-product is pretty clever.

INNOVATION SCALE: ★★★★★

Summary
I don’t think that a bottle of Electro Lube needs to be opened for every OR case but I do think every OR needs to stock it. In this day and age, surgery—particularly minimally invasive surgery—is too refined to allow something as common as char build-up to reduce an instrument’s functionality when something as simple as Electro Lube is readily available.

OVERALL SCORE: ★★★★★

WiCAM Wireless Digital Endoscope Camera & LED Light Source

When there is an interference but it is still a little annoying. But #2: The company is a little vague about the cleaning and sterilization protocols for the devices. The company says they intend to remedy this issue with proprietary sterile drapes or bags but, as of this writing, they are not available.

DESIGN/FUNCTIONALITY SCORE: ★★★

Innovation
Game changer alert! This wireless product may be the first of its kind that you use but it will not be the last. Rather, I suspect within short order most of our wired cameras and light cords will go the way of wooden teeth, iron lungs, and written medical records.

INNOVATION SCALE: ★★★★★

Summary
The Prometheus wireless digital endoscope camera and LED light source is super cool. After years of using scopes with camera heads connected to cameras via wires and illuminated by light transmitted through fiber-optic cords, the fully wireless Prometheus almost defies belief.

For those of us old enough to remember our first mobile phone experience, this camera has that same otherworldly feel. The device does present some challenges. It has some digital lagging issues when it is moved too quickly and the company definitely needs to clarify its cleaning and sterilization procedures. But overall, I am convinced this is the future of office endoscopy and perhaps OR endoscopy as well.

OVERALL SCORE: ★★★★★

The views of the author are personal opinions and do not necessarily represent the views of Contemporary Ob/Gyn.

Dr Greenberg personally tests all the products he reviews. He has no conflicts of interest with these products or the companies that produce them.
**Bowel perforation during fibroid surgery**

A 44-year-old Illinois woman visited a gynecologist in 2010 with a complaint of uterine fibroids. During a hysteroscopic procedure, the woman’s uterine wall and colon were inadvertently perforated. The gynecologist then converted to a laparoscopy and upon finding the perforation in the uterine wall, performed a laparotomy to repair the tear. When the patient became severely ill with peritonitis 3 days later, a surgeon performed a bowel resection with colostomy. A second operation to reverse the colostomy was performed a year later.

The woman sued the gynecologist, alleging negligence in perforating the uterus and bowel and failing to recognize and repair the bowel perforation in a timely manner, which caused her to have abdominal scarring.

The physician argued that he did look at the adjacent organs while repairing the uterus and either there was no hole at that time or it was too small for him to detect any perforation.

**THE VERDICT** The patient was awarded $200,000 in damages.

**Preterm delivery results in CP**

A Michigan woman with a history of cesarean delivery at 24 weeks’ gestation was offered synthetic progesterone injections at the beginning of her prenatal care in a subsequent pregnancy. She claimed she could not afford the injections. Three weeks after her initial visit, she returned to the high-risk clinic and was again offered the progesterone injections, which she rejected.

During her return visit, 4 weeks later, her cervical length on ultrasound was 3 cm. She again declined the progesterone. At a follow-up visit 2 weeks later, the woman’s cervical measurement was 2.5 cm and she once again did not consent to progesterone injections.

Another ultrasound performed 2 weeks later showed a cervical length of 1 cm. The woman was admitted to the hospital but before any orders could be written for tests to rule out early labor and/or delivery, she left the hospital to care for her other children. She was to return after arranging care for them, but did not come back.

Five days later the woman’s cervical length was 1 cm and she received a progesterone injection. Over the next 4 weeks, she had 4 more injections but she did not return for the fifth or for cervical measurement.

The day after the woman’s missed appointment, she presented to the hospital with cramping. She was admitted and given steroids and medication to stop the contractions. An ultrasound showed that the fetus was breech. The patient consented to a cesarean, but before the procedure was started, the baby was born vaginally. The child suffers from mild brain damage, cerebral palsy, developmental delays, and learning disabilities.

The woman sued those involved with her care during the pregnancy and alleged that the healthcare providers should have offered her vaginal progesterone, which was less expensive than the injections, that steroids should have been given to her earlier to improve neonatal development, and that vaginal delivery should have been prevented.

The defense argued that the infant delivered precipitously on the way to the operating room.

**THE VERDICT** The case was settled for $3.5 million.

**Depression from uterine wall perforation**

A 48-year-old Arizona woman was seen by her primary care physician, who performed a Pap test that came back with abnormal results. She was referred to a gynecologist, who recommended a colposcopy, which revealed abnormal cells in the cervix and severe dysplasia.

The gynecologist recommended surgery, which was scheduled for a month later. During the procedure the woman’s cervix was removed and her uterus was punctured and repaired. She claimed she suffers depression as a result.

The woman sued the gynecologist and alleged that despite the doc-
tor’s assertion that the operation was needed immediately, no one from her office contacted the patient, and the patient herself contacted the office to schedule the surgery and it was not performed for over a month after the recommendation.

The gynecologist argued that there was no departure from the standard of care, uterine perforation is a known complication and was managed appropriately, and that 9 weeks after the operation the patient returned to work and had no complaints for more than a year afterward.

The verdict
A defense verdict was returned.

Circumcision requires revision procedure
A Michigan woman alleged that her son suffered pain as a result of a circumcision that was performed the day after his birth. She sued the obstetrician and claimed that the circumcision was improperly performed, necessitating a revision operation 2 1/2 years later that resulted in the development of meatal stenosis at age 7 years. She alleged that once her son was able to talk, he indicated that his penis hurt.

She first complained to the physician about the pain when the child was 18 months old. She reported that the baby suffered constant penile pain from the time of circumcision at age 1 day until the revision surgery 2 1/2 years later.

The obstetrician denied any deviations from the standard of care and contended that redundant foreskin is often left following a circumcision.

The verdict
The jury found in favor of the defense.

Brachial plexus injury
In 2005, an Illinois woman with elevated blood pressure was admitted to a hospital for induction of labor at 38 weeks’ gestation. She was started on oxytocin and around midnight, the fetal heart rate monitor showed some possible fetal complications. The obstetrician was not in the hospital but was called and ordered preparations for a cesarean delivery. Once he arrived at the hospital and evaluated the patient, he found no fetal concern and decided to proceed with the plan for vaginal delivery.

By 3:30 am the patient was fully dilated and pushing when the obstetrician decided to utilize a vacuum extractor to assist with the delivery due to the patient’s elevated blood pressure, headache, shortness of breath, and fatigue. Upon delivery of the head, a shoulder dystocia was encountered and the physician immediately called for assistance. He attempted various maneuvers to deliver the shoulder and successfully delivered the infant.

The child was subsequently diagnosed with near-total brachial plexus injury, consisting of tears and avulsions of all 5 brachial plexus nerves with trauma to some of the cervical nerve roots, requiring multiple operations for nerve grafts and other orthopedic procedures.

The verdict
The jury rendered a defense verdict.

Pregnancy after tubal ligation
A Maryland couple expressed their decision to not have another child to a gynecologist, who recommended a laparoscopic tubal ligation. Several months later the woman became pregnant and gave birth to a son. The parents are now raising 4 children, the youngest of whom has language delays and learning disabilities.

The parents sued the physician and claimed that this additional child put an increased economic hardship on the family.

The gynecologist contended that a common known complication of
the procedure can be the regrowth and reattachment of the Fallopian tubes, resulting in an unintended pregnancy.

**Amputation after bowel perforation**

A 46-year-old woman went to a Florida hospital for removal of an ovarian cyst. The procedure was performed by her gynecologist. Afterward, the patient experienced pain and low blood pressure, which was treated with medication. The next day the incision opened and serosanguinous fluid began to drain. The patient was transferred to the intensive care unit with acute respiratory failure with possible sepsis and organ failure.

The next day a trauma surgeon ordered emergency abdominal surgery and discovered a bowel transection. The lower half of the patient’s stomach and abdominal muscles were removed due to necrotizing fasciitis.

She suffered severe organ, tissue, and muscle damage, and severe hypotension with severely low blood flow to her extremities, resulting in amputation of all 4 extremities. She had 11 additional operations, including placement of an ostomy bag, and was in an induced coma for 1 month.

The woman sued the physician and claimed he was negligent in deciding to perform the original surgery laparoscopically despite the risks, transecting her bowel during the procedure, and failing to order emergency surgery in a more timely manner based on her symptoms.

The physician denied any negligence in performing the operation and claimed that the bowel perforation was a known complication of the procedure.

**THE VERDICT** A defense verdict was returned.

**SUBMIT YOUR PUZZLER!**

Have a puzzling ob or gyn case that you’d like to share with fellow readers? We’re looking for stories about intriguing diagnoses that have stumped the experts!

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Claim of failure to test for cystic fibrosis
Case illustrates the importance of documenting each patient visit.

A 44-year-old Montana woman gave birth to a child who was subsequently diagnosed with cystic fibrosis (CF). The woman sued those involved with her prenatal care, including the certified nurse practitioner (CNP) and the physician who performed chorionic villus sampling (CVS), claiming that had she known the child had CF, she would have terminated the pregnancy.

The woman alleged that she asked for genetic testing, including testing for CF, when she had her prenatal visit with the CNP.

The nurse argued that the patient requested testing for concerns related to advanced maternal age and not CF, but that the patient was provided with brochures that included information about testing for CF. The brochure was clear that the initial screening for CF was a blood test of the parents to determine if they were carriers of the CF gene, and that if the results from both were positive, the material gathered from amniocentesis or CVS would be tested.

The nurse alleged that the patient did not request the necessary blood tests for CF carrier screening or any CF testing. The patient admitted that she did not read the brochure on CF testing that was provided to her.

The patient contended that the physician did not tell her what the material obtained from the CVS procedure would be tested for and that she did not have genetic counseling.

The physician argued that he informed the patient that the test was for conditions related to advanced maternal age, such as chromosomal abnormalities including Down syndrome. He further contended that he specifically informed the patient of the availability of blood testing for CF carrier screening of both parents, which is necessary prior to testing for CF in the fetus because of the more than 1000 mutations of CF.

He claimed that the patient declined the CF blood tests at that time.

During this case, it was revealed that while the patient admitted that she was referred to the medical genetics department for genetic counseling, she claimed she was confused as to whether she was to contact them or they were to contact her and as a result, she did not call for an appointment until shortly before the scheduled procedure. She then claimed she was told there were no counselors available on such short notice right before a holiday. During trial, witnesses for the genetics department testified that counselors were available when the patient called. They provided documentation in the medical record that the patient declined genetic counseling due to the cost of the service. This illustrates the importance of documenting in the record a patient’s decision to not undergo a recommended service and her reasons for declining.

A defense verdict was returned.

Ms Collins is an attorney specializing in medical malpractice in Long Beach, California. She can be reached at dawncfree@gmail.com.
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