

# CLEVELAND CLINIC JOURNAL OF MEDICINE

**Viruses change; we can, too**

**Smallpox and monkeypox:  
Looking back, looking ahead**

**Mass under the lip**

**Pheochromocytomas  
and paragangliomas:  
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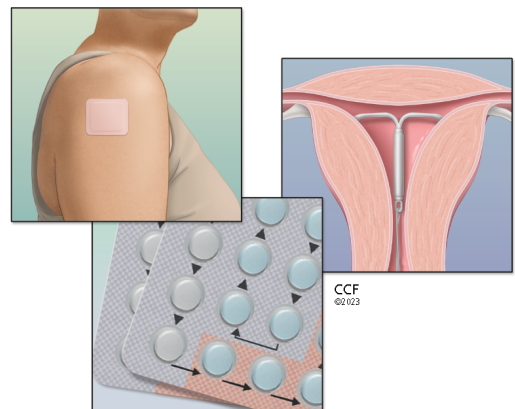
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Should my patient stop taking PPIs?**

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**Measuring bone mineral density  
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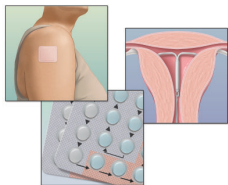
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## Viruses change; we can, too

Maybe we are coming out of the COVID-19 tunnel. Not that it is gone, it certainly is not. And we are currently dealing with the coincident impact of circulating influenza and respiratory syncytial viruses. But there was a sense of relative quiet on the infectious disease front. Then came monkeypox (mpox), a fairly unknown relative of the smallpox virus, with sinister implications. The questions of public health preparedness and social coping strategies came flooding back. Have we learned anything? Are we in a better position to deal with this than with COVID-19 or, for that matter, than we did initially with HIV? Fortunately, it seems that the answers are yes and yes, assisted by the limited lethality and public transmissibility of this infection—although as of February 1 this year, the US Centers for Disease Control and Prevention (CDC) website had reported 30,123 cases in the United States, with 28 deaths.

Mpox, a double-stranded DNA virus, was first identified in 1958 in a primate research colony in Denmark. It is an endemic animal infection in Central and Western Africa, affecting rodents, other small mammals, and nonhuman primates. The first human infection was reported in an African toddler in 1970. Sporadic human infections, primarily in Africa, were mainly attributed to direct contact with infected animals via bites, scratches, and the handling and preparation of infected meat. Cases outside that continent were associated with exportation of infected animals. Although there is shared immunity between smallpox and mpox viruses, the role that international smallpox vaccination has played in limiting mpox infection is unclear. Two major mpox variants (“clades”) have been described, each predominantly localized to a specific region in Africa, and each with overlapping but distinct clinical characteristics. Clade 1 exhibits a slightly higher morbidity and mortality than clade 2, possibly due to its ability to interfere with human complement activation. Double-stranded DNA viruses tend to have stable genomes and so do not mutate frequently.

In 2003, the CDC reported on 47 US cases of mpox. Patients were presumed to have contracted the virus from pet prairie dogs that had become infected from co-housed exotic mammals transported from Africa.<sup>1</sup> There was no confirmed person-to-person transmission. Human illness was assumed to have occurred through direct contact with infected animals, and perhaps via the upper respiratory tract. In one descriptive series of 34 patients (notably 50% female), 15% were severely ill, although none died, and 56% of the patients had the triad of rash, fever, and chills.<sup>2</sup> The rash was described as monomorphic in 68% and centrifugal in 48%, similar to that described previously in patients having contracted the infection from animals. By 2020, more than 80,000 human cases had been reported spanning 110 countries.

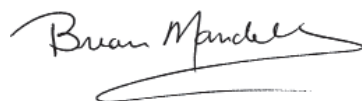
Forward to 2022, when significant local human clusters of mpox were reported in Europe and the United States,<sup>3-6</sup> these outbreaks were characterized by direct human-to-human transmission. The initial source of these infections is not clear, but unique demographic and clinical characteristics of the infected persons are apparent. Reports stemmed from infectious disease and sexually transmitted disease clinics, and infected patients were overwhelmingly men who practice sex with men (MSM). There was a high proportion of skin lesions in genital and perianal areas as well as oral lesions and penile swelling. Adenopathy was common, as in earlier described patients, although seemingly more striking in the inguinal area. Pharyngitis and rectal pain were common. Of concern from the public health perspective is that some infected patients recalled no contact with persons having confirmed infections, and some infections were contracted from individuals who were asymptomatic at the time of sexual contact. Whether this is explained by the demon-

strated presence of viral DNA in semen and other body fluids remains to be proven. Additionally, occupational spread to healthcare workers through sharp-instrument punctures has been described.

Has the mpox virus changed, or are we seeing the behavior of essentially the same virus manifesting in a specific host demographic by way of mucosal surface inoculation? The skin lesions may or may not spread from the genital, perianal, and oral areas, and may appear on the palms and soles and mimic other sexually transmitted infections including disseminated herpes and syphilis, particularly in immunosuppressed patients. Those with underlying HIV seem to fare less well. There continues to be an enormous male predominance, particularly including MSM, as noted in ongoing updates on [www.cdc.gov](http://www.cdc.gov).

So how has our reaction to this infection differed from prior international (and national) infection challenges? An early difference is that the World Health Organization in 2022—in an “aim to minimize unnecessary negative impact of names on trade, travel, tourism, or animal welfare, and avoid causing offence to any cultural, social, national, regional, professional, or ethnic groups”—proposed a name change to the virus (from monkeypox to mpox) and, for its previously geographically named major clades, a change to numbers and letters.<sup>7</sup> Lesson learned from the apparent adverse social ramifications stemming from referring to coronavirus as “China flu.” There has also been a rapid recognition that although the current clusters are concentrated in the community of MSM, we have in the past clearly experienced specific demographic localized infections spreading to the wider population, and there needs to be wider vigilance for spread of the infection. This has been done without excessive stigmatization within the medical community.

Fortunately, there is already baseline knowledge about the mpox virus. As discussed by Sossai et al in this issue of the *Journal*,<sup>8</sup> understanding its relationship to variola (smallpox) has been quickly exploited to provide some therapeutic and prophylactic vaccination options.



Brian F. Mandell, MD, PhD  
Editor in Chief

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## REVIEW

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# Smallpox and monkeypox: Looking back and looking ahead

## ABSTRACT

The monkeypox (mpox) epidemic was declared a global health emergency in July 2022. The mpox virus belongs to the same virus family as the smallpox, or variola virus, but the infection is a less lethal threat than smallpox. Nevertheless, its relationship to smallpox is a worldwide concern, as is the discontinuation of universal smallpox vaccinations since the 1980s. Newer therapies and vaccines are available for both infections, including 2 antiviral drugs that can be used under certain conditions. Two vaccines have been developed for mpox prevention, but clarity is needed on when and how to use them. Preventive public health measures and prioritization of resources for managing infectious disease are concerns.

## KEY POINTS

Smallpox, with a case-fatality rate that at one time ranged from 30% to 50%, was declared eradicated in 1980, and worldwide vaccination ceased shortly thereafter.

In North and South America in 2022, there were 57,338 reported cases of mpox and 58 deaths.

Newer therapies and vaccines are available under certain conditions, but when and how to use them is not always clear.

**F**EW CLINICIANS TODAY have seen and treated a patient with smallpox, a disease the World Health Organization (WHO) declared eradicated in 1980.<sup>1</sup> Yet as recently as July 23, 2022, WHO declared monkeypox (mpox), whose causative virus is in the same family as the smallpox virus, a global health emergency.<sup>2</sup>

The smallpox or variola virus is a member of the genus *Orthopoxvirus*, belonging to the *Poxviridae* family.<sup>3</sup> The *Poxviridae* family includes the vaccinia virus (cowpox), mpox, and molluscum contagiosum, although the molluscum contagiosum genus differs from that of the other viruses in the family. All of these diseases are characterized by papulopustular skin lesions. The symptoms of smallpox and mpox are similar, but illness with mpox is milder and rarely fatal.

## ■ SMALLPOX: ERADICATED BUT STILL RELEVANT

The world's population has been subjected repeatedly since 100 AD to waves of smallpox. Naples, a city of 400,000 in 1768, lost 60,000 people to smallpox over a period of a few weeks.<sup>4</sup> Some 30 years later, in 1796, Edward Jenner inoculated a child with pustular material from a woman infected with the vaccinia virus, and the child did not contract smallpox.<sup>4</sup> Before Jenner's discovery, which was the first modern vaccine of any kind, the variolization method was used to prevent infectious disease. Pustular material was aspirated with consequences that included the onset of smallpox.

Since 1984, WHO has authorized only 2 sites for smallpox retention: the US Centers for



Disease Control and Prevention (CDC) in Atlanta, GA, and the Research Institute of Viral Preparations in Moscow. In 1994, viral preparations were transferred from the Moscow Research Institute to the State Research Center of Virology and Biotechnology in Novosibirsk, Russia.<sup>5</sup> There is concern that the fall of the Soviet Union on December 26, 1991, led to the illegal transfer of certain smallpox containers to organizations and countries other than those initially authorized by WHO.<sup>3</sup>

### ■ TRANSMISSION AND CLINICAL PICTURE

Smallpox is transmitted from human to human. After an incubation period of 10 to 14 days, the patient develops fever, headache, and vomiting. Transmission is predominantly by airborne droplets and lesions of the mucous membranes and skin. Unlike chickenpox skin lesions, which coexist in all stages of the disease, smallpox skin lesions are all in the same evolutionary stage. They have a centrifugal progression, starting on the face.

If smallpox is suspected, polymerase chain reaction testing of variola DNA is needed to confirm the diagnosis. However, the presence of antibodies is not specific to smallpox, but rather to orthopoxvirus.

Before the eradication of smallpox, the death rate in unvaccinated individuals with smallpox ranged from 30% to 50%. Causes of death were coagulopathy and multiple organ failure with sepsis from bacterial superinfection.

### ■ ANTIVIRAL TREATMENT

The US Food and Drug Administration (FDA) has approved 2 oral antiviral therapies for use in patients with orthopoxvirus infections under the FDA's Animal Rule, which allows findings from well-controlled animal efficacy studies to support approved use when efficacy trials in humans are unfeasible or unethical. Under these limitations, tecovirimat was approved in 2018 and brincidofovir in 2021. Tecovirimat is a potent inhibitor of an orthopoxvirus protein required for the formation of an infectious virus protein. Brincidofovir is a prodrug of cidofovir that inhibits viral DNA synthesis. Although not commercially available, both drugs can be used in patients with orthopoxvirus infections, including smallpox and mpox.<sup>6</sup>

### Vaccine cessation

Since smallpox eradication in 1980, vaccination rates worldwide have decreased from 80% to less than 30%.<sup>6</sup> Population-based surveys suggested that in

West and Central Africa before 1986, orthopoxvirus antibodies were present in 12% to 15% of children (mean age 4.4 years).<sup>7</sup>

### ■ MONKEYPOX

Mpx, a zoonotic disease whose reservoirs include rodents, rats, and dogs from the grasslands of Central and Western Africa, is spreading worldwide. The mpx virus was first isolated in 1958 in monkeys and in 1970 in a 9-month-old boy in the Democratic Republic of Congo (formerly Zaire).<sup>8</sup> Monkeys are the principal infected animals with a risk of transmission.

Until the 1970s and 1980s, the case-fatality rate associated with mpx was 15% to 20% in Africa.<sup>9</sup> Currently in Africa, where the disease is endemic, the case-fatality rate is 5% to 10%.<sup>9</sup> This lower rate is probably a consequence of improved health conditions in Africa.<sup>9</sup>

Two mpx clades, ie, viruses with a common ancestry, have been identified in Africa. Clade 1 from the Congo basin has a case-fatality rate of at least 10% and clade 2 from Western Africa has a case-fatality rate of about 3.6%.<sup>10</sup> In 2022, when WHO declared a health emergency during a new European and North American outbreak, a new clade (variant) was identified and designated as 2b.<sup>11</sup>

The main risk factors for transmission of mpx in endemic areas include slaughtering or handling infected animals such as monkeys and rodents. Household contact is also a risk factor. Human-to-human transmission occurs through close contact with lesions, bodily fluids, respiratory droplets, and contaminated materials.

### The 2022 outbreak

The first mpx outbreak in the Western Hemisphere occurred in the United States in 2003 with 81 cases and no deaths. Those who were infected had close contact with pet mammals. The 2022 mpx outbreak was a worldwide epidemic attributable not to direct contact with reservoir animals but to transmission between humans in the same manner as smallpox—ie, close contact and transmission of respiratory secretions. As of January 2023, the recorded and confirmed cases and deaths were as follows<sup>12</sup>:

- North and South America: 57,338 cases, 58 deaths
- Europe: 25,743 cases, 5 deaths
- Africa: 1,214 cases, 15 deaths.<sup>12</sup>

Individuals affected are predominantly young, sometimes with homosexual contacts or immunodeficiency, or both.

### Disease manifestations

Mpox presents similarly to smallpox, with systemic symptoms and cutaneous and oral mucosal manifestations. The incubation period varies from 5 to 20 days. The clinical signs appear in 2 stages—a prodrome stage and an eruptive stage. The prodrome stage lasts about 5 days and is characterized by fever, swelling of lymph nodes, myalgia, back pain, and severe fatigue. The eruptive stage appears about 3 days after the prodrome stage, with skin rashes that consist of papules, vesicles, and pustules, which last 2 to 3 weeks and evolve into scabs. The rash develops initially on the face and then on the palms of the hands and the soles of the feet. The skin lesions share the same evolutionary stages as those caused by smallpox. Papules, vesicles, and pustules can be found in the oral mucosa, on external genitalia, and in the conjunctiva, as well as on the skin.

Systemic complications can include bronchopneumonia, septicemia, and encephalitis. The duration of the disease is approximately 3 to 4 weeks, during which transmissibility is high. Treatment is supportive, although in severe cases antivirals are used, including tecovirimat and brincidofovir.

### Prevention

Previous vaccination against smallpox can reduce the severity of mpox symptoms. The 2 vaccines for mpox prevention, both of which are live vaccines, are as follows:

**Modified Vaccinia-Ankara–Bavarian Nordic vaccine** (MVA-BN, JYNNEOS) is approved for the prevention of smallpox, and it received emergency use authorization from the FDA for individuals at high risk of mpox infection.<sup>13</sup> Administration requires 2 subcutaneous doses.<sup>13</sup>

**ACAM2000** was approved for smallpox prevention in 2007. In the United States, it is only available under the FDA Expanded Access program for investigational new drugs and is administered in 1 percutaneous dose.<sup>12</sup> However, ACAM2000 is associated with serious adverse effects including myocarditis, pericarditis, and cerebral edema—effects that have not been observed with MVA-BN.<sup>13</sup> ACAM2000 is not available commercially.

Because of safety considerations, only MVA-BN is approved for emergency use in patients at high risk of mpox infection. Definitive data are lacking on the clinical efficacy of these vaccines.<sup>14</sup> In addition to preventive use, they may be administered to a sick patient after exposure, but preferably within 4 days of exposure. The CDC considers vaccination to be practical until the 14th day after exposure.<sup>15</sup>

### ADDITIONAL CONSIDERATIONS

Vaccination strategies, preventive measures, and resource utilization are relevant considerations in addressing the mpox epidemic.

#### Vaccination

It may be time to consider a smallpox vaccination campaign targeting several vulnerable populations. These include adolescents and young adults who have not been vaccinated against smallpox; individuals who are immunodeficient because of neoplasia, transplants, or autoimmune disease; and healthcare personnel at risk of infection who are not already vaccinated against smallpox. The objective of a vaccine strategy in these groups would be to reduce the disease burden on healthcare facilities.

The negative effects from a reduction in the overall workforce caused by an mpox outbreak must also be considered. WHO advised against mass vaccinations in its report of June 14, 2022, but it continues to advise vaccination coverage for those who have been in close contact with infected individuals (post-prophylaxis exposure) and for healthcare personnel or others at risk because of their work (pre-exposure prophylaxis).<sup>15</sup> The vaccines recommended by WHO are second-generation (ACAM2000) or third-generation (MVA-BN, LC16) vaccines, which have fewer reported adverse events than vaccines used before 1980.

### CURRENT TRENDS, FUTURE NEEDS

The mpox epidemic is taking place during the COVID-19 pandemic with all of its variants, as well as during the Ukrainian-Russian war. Wars are excellent amplifiers of infectious disease.<sup>16</sup> It is significant that the preventive measures for mpox are the same as those for COVID-19, ie, distancing and masking. The relaxation of COVID-19 preventive measures now occurring will likely result in a higher disease burden of COVID-19 and mpox than if we remained more vigilant to transmission.

In recent decades, great importance has been placed on the diagnosis and treatment of chronic diseases such as cardiovascular and respiratory illnesses. This shift in priorities is contributing to the dismantling of facilities dedicated to infectious diseases, and the misperception that many infectious diseases have been eradicated is contributing to the shift. Tuberculosis dispensaries, infectious disease clinics, and laboratories with dedicated sections of microbiology and virology are no longer standard.

We believe it is time for an organizational review and implementation of training for specialists in the infectious disease sector. ■

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### DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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## THE CLINICAL PICTURE

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# Mass under the lip

A 60-YEAR-OLD MAN WAS REFERRED by his primary care physician to the oral and maxillofacial surgery clinic with a mass under the upper lip. The mass had grown slowly over the past 2 to 3 weeks while the patient was in rehabilitation after a stroke that had occurred 3 months earlier. He reported no symptoms other than minor bleeding of the gums after brushing his teeth. He was not a smoker. His oral hygiene during his hospitalization and rehabilitation had been poor.

On physical examination, a large, firm, non-tender, sessile mass was visible on the gingiva of the upper incisors (Figure 1). The surface was erythematous and smooth with no ulceration. Excisional biopsy of the entire mass was performed under local anesthesia. Histopathology revealed a fibroma with fibrous strand proliferation and no dysplastic changes, suggesting a diagnosis of benign fibroma. No additional treatment was necessary.

The patient was instructed on the importance of maintaining oral hygiene. At a 2-week follow-up visit, the gingiva had healed with restoration of its contour. The patient had no bleeding gums or other symptoms.

### DIFFERENTIAL DIAGNOSIS OF GINGIVAL MASS

The differential diagnosis of a gingival mass includes peripheral ossifying fibroma, peripheral giant cell granuloma, and pyogenic granuloma.<sup>1</sup> Fibromas are benign growths that occur most commonly along the buccal mucosa secondary to accidental biting of the cheek.<sup>2</sup> Due to their slow growth, they typically have a subacute onset.

The gingival fibroma in our patient stemmed from poor oral hygiene resulting in plaque with a calculus deposit acting as an irritant. This is histologically different from a cutaneous fibrous neoplasm, which is rarely seen in the mucosal tissue in the head and neck.<sup>3</sup> Excisional biopsy is diagnostic and curative. Laser removal has been described in the literature.<sup>4</sup>



**Figure 1.** A large, firm, non-tender, sessile mass was seen on the gingiva of the upper incisors.

Recurrence is prevented with attention to good oral hygiene.<sup>5</sup>

The development of the oral mass in this patient illustrates the importance of oral health, which is often overlooked in the hospital and outpatient settings. Patients at risk include those with prolonged stays in the hospital and in rehabilitation facilities. Patient education and attention to oral hygiene can prevent oral infections and will improve the overall health of patients. ■

### DISCLOSURES

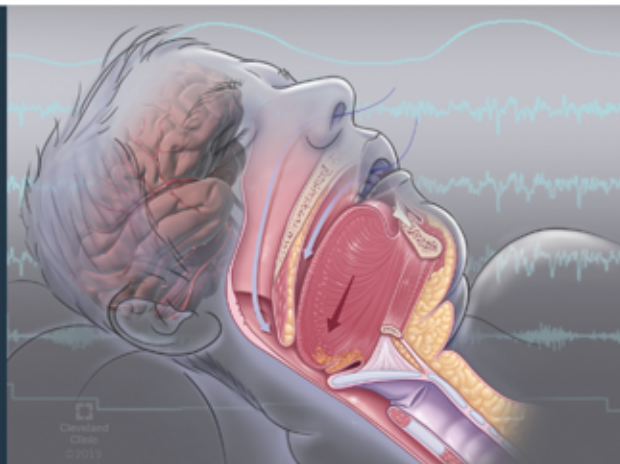
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BRIEF  
ANSWERS  
TO SPECIFIC  
CLINICAL  
QUESTIONS

# Q: What is the rationale for the laboratory workup for suspected pheochromocytomas and paragangliomas?

**A:** Selection of screening tests for pheochromocytomas and paragangliomas (PPGLs) is best guided by high clinical suspicion. Test results should be interpreted with careful consideration of collection methods before pursuing imaging tests for localization or referring for endocrinologic evaluation.

PPGLs are rare neuroendocrine tumors, with an estimated incidence of 2 to 8 per million.<sup>1</sup> These catecholamine-secreting chromaffin cell tumors are mostly benign<sup>2</sup> but can manifest as metastatic disease in 15% to 17% of cases.<sup>1</sup> Pheochromocytomas arise from chromaffin cells of the adrenal medulla, and paragangliomas arise from extra-adrenal chromaffin cells of sympathetic or parasympathetic origin. The prevalence of PPGLs in patients presenting with hypertension in the outpatient setting is 0.1% to 0.6%.<sup>1,3</sup> However, PPGLs can be asymptomatic and discovered incidentally on imaging. Of these incidentalomas, 80% to 85% are pheochromocytomas, and 15% to 20% are paragangliomas.<sup>1,3</sup> While the parasympathetic nervous system of the head and neck can also give rise to paragangliomas, tumors in this location do not produce vasoactive amines.<sup>1</sup>

## ■ CLINICAL PRESENTATION

Clinical features are key in diagnosing PPGLs.<sup>2</sup> The kaleidoscope of clinical presentations is dominated by signs and symptoms that indicate an overactive sympathetic autonomic nervous system (Table 1).<sup>3,4</sup>

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Palpitations, hyperhidrosis, and headaches form the classic triad of symptoms with a combined specificity of 93.8%,<sup>5</sup> but there are distinguishing factors. For example, palpitations, hyperhidrosis, tremors, pallor, and nausea are the most frequently reported symptoms in patients with PPGLs, with one or more occurring in 85% of patients, and their presence may help distinguish patients with PPGLs from those without PPGLs.<sup>4</sup> Despite the typical symptoms occurring in 85% of patients, incidentalomas noted on computed tomography and genetic case-detection testing lead to up to 62% of diagnoses.<sup>6</sup>

## ■ CONSEQUENCES OF CATECHOLAMINES

Catecholamines—including the “fight or flight” hormones epinephrine, norepinephrine, and dopamine—are secreted in response to stress. In healthy people, catecholamine levels after myocardial infarction may be 10 to 20 times higher than at baseline.<sup>2,7</sup> Hypertension, a key characteristic of PPGLs, is precipitated by high catecholamine levels. Norepinephrine and epinephrine increase cardiac output through beta-receptor activity and increase peripheral vascular resistance through alpha-receptor activity. Paroxysmal release of catecholamines results in mostly episodic hypertension, with some patients normotensive between episodes and others experiencing sustained hypertension.<sup>3</sup>

Dopamine production targets D1 and D2 receptors. D1 receptor activation results in renal vasodilation, and D2 activation inhibits norepinephrine

secretion from sympathetic nerve terminals, which has a negative inotropic effect on the heart. This explains why some patients with dopamine-secreting PPGLs present only with hypotension.<sup>8,9</sup> Orthostatic hypotension in a patient with a history of hypertension is a good clinical clue for PPGLs.<sup>3</sup> The overall balance of vasoconstrictive vs vasodilatory effects of the unique hormonal cocktail produced by the tumor determines the tumor's clinical behavior.

### ■ INITIAL BIOCHEMICAL TESTING: FOCUS ON SENSITIVITY

A missed diagnosis of PPGLs can have devastating cardiovascular consequences, including myocardial infarction, cardiac arrhythmias, heart failure due to toxic cardiomyopathy, and pulmonary edema. The initial biochemical testing methods should therefore focus on maximizing sensitivity.

Biochemical testing for pheochromocytoma is indicated in patients who have symptoms of catecholamine excess, an adrenal incidentaloma, or a hereditary predisposition to development of PPGLs.<sup>9</sup>

In contrast to episodic catecholamine release, the products of catecholamine metabolism are constantly released from PPGLs into the circulation. Metabolic products of catecholamines have longer plasma half-lives and are therefore easier to measure. Hence, plasma free metanephrines or 24-hour urinary fractionated metanephrines should be the initial investigative tests to rule out PPGLs.<sup>2,9</sup> Levels of dopamine and its metabolite plasma 3-methoxytyramine can help establish the biochemical subtype of PPGL but are not essential for initial screening.<sup>2</sup>

The diagnostic sensitivity of plasma free metanephrines is above 96% and the specificity is about 89%. The sensitivity of 24-hour urinary fractionated metanephrines is 86% and specificity is above 69%.<sup>2</sup> The sensitivities and specificities reported in the literature vary depending on the assays used. Plasma tests using liquid chromatography with tandem mass spectrometry afford higher sensitivity and specificity than immunoassays.<sup>2</sup> Mass spectrometry methods employed in urine testing are also more sensitive and specific than other techniques.<sup>2</sup>

Some studies have claimed to demonstrate that measuring plasma free metanephrines has a higher specificity than 24-hour urinary fractionated metanephrines,<sup>2</sup> but robust, direct comparisons using the gold standard of mass spectrometry to establish this are lacking. Therefore, the Endocrine Society and the North American Neuroendocrine Tumor Society

TABLE 1

### Symptoms of pheochromocytomas and paragangliomas

Most frequent	Most specific (classic triad)	Less frequent
Palpitations	Palpitations	Anxiety or panic
Hyperhidrosis	Hyperhidrosis	Weight loss
Tremors	Headaches	Fatigue
Pallor		Constipation
Nausea		

Based on information in references 3 and 4.

guidelines recommend initial screening with either plasma free metanephrines or urinary fractionated metanephrines.<sup>2,9</sup>

### ■ HOW THE SAMPLE IS COLLECTED IS KEY

For accurate results, the blood sample for plasma free metanephrines must be collected by an indwelling catheter placed 30 minutes prior to the draw, and the patient must be in a supine position for the full 30 minutes. A sample collected under these conditions can be a powerful tool for diagnosing PPGLs, with newer studies reporting a false-positive rate of less than 3% with proper collection, and superiority over 24-hour urine collection.<sup>10</sup>

Testing of plasma free metanephrines is preferred over urine fractionated metanephrines in patients with renal dysfunction, but many laboratory collection sites do not have time, expertise, or resources to follow the protocol required for the blood draw. Therefore, 24-hour urine collection may be a more accurate, although time-consuming, option. Emerging studies have noted that the sensitivity and specificity of spot urine samples correlate well with those of 24-hour samples, but at present the evidence is insufficient to recommend adopting this strategy in routine clinical practice.<sup>2,11</sup>

Vanillylmandelic acid has poor sensitivity and is not indicated in the initial biochemical workup for possible PPGLs.<sup>12</sup>

### ■ DIAGNOSTIC INTERPRETATION

A 3-fold to 4-fold rise above the upper limit of normal for plasma free metanephrines or urinary fractionated metanephrines is unlikely to be a false-positive result. Metanephrine levels within the reference range are

**TABLE 2**  
**Medications associated with false-positive screening tests**

Class	Name
Antihypertensive	Beta-blocker (labetalol, sotalol)
	Alpha-2 agonist (alpha-methyldopa)
	Alpha-2 antagonist (phenoxybenzamine)
	Alpha, beta-1, beta-2 agonist (ephedrine)
	Calcium channel blocker (dihydropyridines)
Stimulant	Caffeine
	Nicotine
	Amphetamine
	Cocaine
Anxiolytic	Buspirinone
Analgesic	Acetaminophen
Anti-inflammatory	Sulfasalazine
Antidepressant	Tricyclic antidepressants
	Monoamine oxidase inhibitors
Dopamine agonist	Levodopa

Based on information in references 3 and 4.

usually sufficient to exclude PPGLs. But importantly, very small tumors (< 1 cm) or dopamine-secreting tumors can result in false-negative results.<sup>2</sup>

Fasting blood levels of plasma 3-methoxytyramine should be measured to evaluate for dopamine-secreting PPGLs if initial metanephrine testing is negative but the index of clinical suspicion for PPGL remains high.<sup>2</sup>

**■ EQUIVOCAL RESULTS: WHAT IS NEXT?**

An equivocal test result (ie, metanephrine elevation to less than 3 times the upper limit of reference range) indicates a need for further workup and questions:

- **Was the blood or urine screening sample collected appropriately?** Caffeinated beverages, alcohol intake, smoking, and intense physical activity can cause false-positive results and should

be avoided at least 24 hours prior to test collection.<sup>1</sup> Several medications (Table 2)<sup>3,4</sup> can also skew the results if not withheld before the sample is drawn. Acetaminophen should ideally be held for 5 days before sample collection. Given that the false-positive rate is not very high with antihypertensive medications, these can be continued at the time of test collection unless a repeat test is being performed for confirmation of a prior equivocal test.<sup>13</sup> If the patient is taking monoamine oxidase inhibitors, stimulants, or tricyclic antidepressants, the medication should be stopped at least 2 weeks before biochemical testing for PPGLs.<sup>14</sup>

- **Was the patient under physiologic stress at the time of collection?** Screening tests are likely to be falsely positive during critical illness. In this setting, the test should be repeated when clinical stability is achieved.
- **Are the results still equivocal?** A clonidine suppression test can be considered. This test, shown to be highly specific,<sup>2,9</sup> involves measurement of baseline serum normetanephrine levels followed by clonidine administration with a repeat draw and measurement 3 hours later. If serum normetanephrine levels are elevated or decrease by less than 40%, PPGL is likely. Clonidine, an alpha-receptor agonist, inhibits norepinephrine release in patients without autonomous production of catecholamines but not in patients with PPGLs.

If the patient has a low pretest probability of having PPGLs, then a screening test can be repeated in 6 months to assess the trend. This would help identify a small tumor that may be enlarging over time.

**■ TAKE-HOME POINTS**

The rationale for timely diagnosis of PPGLs relies on a high index of suspicion and awareness of clinical features. Appropriate collection methods, testing that prioritizes high sensitivity, and careful review of findings will support the diagnostic process. ■

**■ DISCLOSURES**

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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## Q: Fundic gland polyps: Should my patient stop taking PPIs?

**A:** Fundic gland polyps (FGPs) associated with proton pump inhibitors (PPIs) are generally considered benign, and patients without high-risk features (ie, more than 20 FGPs or polyp size greater than 1 cm) can be advised to continue taking the PPI if there is a clear indication for its use.

It is estimated that 1 in 10 patients in the United States takes a PPI.<sup>1</sup> Long-term PPI use can promote development of FGPs in the stomach because the decrease in stomach acidity leads to increased production of gastrin. Gastrin has trophic effects that lead to parietal cell and enterochromaffin-like cell hyperplasia and the formation of fundic gland cysts and polyps.<sup>2,3</sup> The number and size of FGPs is proportionate to the dose and duration of PPI therapy.<sup>2,4</sup>

### ■ SPORADIC AND SYNDROMIC TYPES

There are 2 types of FGPs—sporadic and syndromic—and when encountering FGPs, the most important principle is to distinguish the two (Table 1).<sup>5–8</sup> Sporadic FGPs are associated with PPIs. Syndromic FGPs occur with a background of familial adenomatous polyposis (FAP), including classic FAP, attenuated FAP, gastric adenocarcinoma and proximal polyposis of the stomach, and MUTYH-associated polyposis.<sup>9,10</sup>

Sporadic or PPI-associated FGPs exhibit activating beta-catenin gene mutations and rarely show dysplasia.<sup>11,12</sup> In contrast, syndromic or FAP-associated FGPs arise through somatic second-hit mutations of the adenomatous polyposis coli gene. They frequently demonstrate dysplasia, leading to a much higher risk of gastric cancer than PPI-associated FGPs.<sup>6,13</sup> However, these mutations are not routinely checked in histology.

Case reports have described dysplasia in patients with sporadic FGPs who take a PPI, but the true

risk of carcinoma in patients with PPI-associated FGPs is unclear.<sup>14</sup> PPI-associated FGPs have not been linked to an increased risk of malignant transformation compared with the risk in the general population.<sup>14,15</sup> While the risk of dysplasia increases with polyp size in FAP-associated FGPs, a study of 132 large (> 1-cm) sporadic FGPs with a median follow-up of 3.2 years reported a rate of dysplasia of 2.6 cases per 1,000-person years of follow-up and no carcinoma.<sup>16</sup> This study may have been limited by its short follow-up period, as reports of cancer with sporadic FGPs do exist.<sup>15</sup>

In the rare cases of sporadic FGPs with carcinomas, most are small polyps with a mean size of 5.4 mm, suggesting that even polyp size may not predict malignancy risk.<sup>14</sup>

### ■ CASE 1: FUNDIC GLAND POLYPS, NO DYSPLASIA

*A 65-year-old woman underwent esophagogastroduodenoscopy for surveillance of a history of Barrett esophagus without dysplasia. In addition to short-segment Barrett esophagus, 12 sessile polyps 4 to 6 mm in size were found in the body of her stomach. Biopsy results showed fundic gland polyps, negative for dysplasia. The patient has taken omeprazole 20 mg daily for many years. Should she stop using omeprazole?*

Benign FGPs are typically small (< 1 cm) sessile polyps with a smooth contour found in the body of the stomach.<sup>7</sup> When upper gastrointestinal endoscopy reveals fewer than 20 gastric polyps with the characteristic appearance of FGPs in the gastric body, biopsy is unnecessary. If the endoscopic appearance has atypical characteristics such as irregular surface, redness, erosion, or depression, the polyp should be resected, as these features have been associated with dysplasia and carcinoma.<sup>14</sup> Polypectomy is also recommended when the size is greater than 1 cm or the

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**TABLE 1**  
**Sporadic and syndromic fundic gland polyps compared**

Feature	Sporadic fundic gland polyps	Syndromic (FAP-associated) fundic gland polyps
Number	< 20	≥ 20, often hundreds <sup>8</sup>
Location	Body of the stomach	Mostly in the body of the stomach, but can also be seen in the antrum
Presence of dysplasia	Rare	In 25%–40% <sup>5</sup>
Age	Older; average age 40	Under age 40
Sex	More common in females than males	Incidence similar in both sexes <sup>6</sup>
Other EGD findings	None known	Concurrent duodenal adenomas can be seen <sup>7</sup>

EGD = esophagogastroduodenoscopy; FAP = familial adenomatous polyposis

Based on information in references 5–8.

location is antral to assess for other causes such as hyperplastic gastric polyps.<sup>7,17</sup>

The incidence of sporadic FGPs appears to be inversely correlated with *Helicobacter pylori* infection.<sup>3</sup> In the absence of other indications such as dyspepsia and hyperplastic polyps, testing for *H pylori* in the setting of FGPs is unnecessary.

There are no guidelines regarding follow-up of sporadic FGPs. In general, for patients with sporadic FGPs in whom syndromic FGPs are ruled out, PPI therapy can be continued at the lowest effective dose for as long as indicated. However, PPI cessation should be considered if there are more than 20 polyps or polyps larger than 1 cm, especially if there are so many polyps as to give a carpeting appearance.<sup>7,8,14</sup> Polyps should be examined carefully with white light and narrow-band imaging. Those larger than 1 cm or with atypical endoscopic features should be resected completely. Several studies suggest that if dysplasia is found in sporadic FGPs, progression to gastric cancer occurs slowly, if at all, and repeat endoscopy 1 to 3 years after polypectomy is reasonable.<sup>18,19</sup> Evidence demonstrates regression of FGPs if PPIs are stopped, even if they were large in size, and endoscopic follow-up to confirm regression is unnecessary.<sup>7,8</sup>

**Resolution of case**

The FGPs seen in this 65-year-old patient have typical characteristics of sporadic FGPs (< 20 in number, < 1 cm in size, with sessile appearance and located in the gastric body), without any high-risk features, and thus do not need polypectomy or specific follow-up. The patient can continue PPI therapy and surveillance esophagogastroduodenoscopy as indicated for Barrett esophagus.

**■ CASE 2: YOUNG MAN WITH ‘CARPETING’ AND UNKNOWN FAMILY HISTORY**

*A 32-year-old man underwent esophagogastroduodenoscopy for evaluation of iron deficiency anemia. Innumerable polyps were found carpeting the fundus of his stomach. Biopsies showed FGPs with low-grade dysplasia. The patient had recently started taking omeprazole for treatment of gastroesophageal reflux disease. He was adopted and his family history is unknown. Should he stop his PPI?*

Any of these risk factors raises suspicion for an underlying FAP syndrome:

- The number of gastric polyps exceeds 20
- The patient is younger than 40
- Polyps are present in the antrum
- Dysplasia is seen on polyp biopsy
- There is concurrent duodenal adenoma.

If possible, a detailed family history of cancer, especially colon or other gastrointestinal tract neoplasm, should be sought. Colonoscopy is indicated to evaluate for colonic polyps or neoplasms. Genetic evaluation should be considered in young patients with carpeting of polyps or if there is a family history of cancer. If the diagnosis of FAP is confirmed, the patient should be managed accordingly as described in guidelines.<sup>5,8</sup>

**Resolution of case**

This patient has multiple factors (age < 40, large number of polyps with dysplasia) concerning for syndromic FGPs. He should undergo colonoscopy and be referred for genetic evaluation. If an inherited polyposis syndrome is diagnosed, the development of his FGPs is unlikely associated with PPI use, and the patient can continue to use PPIs to manage his reflux disease. In fact, acid suppression may protect against dysplasia in syndromic FGPs.<sup>20</sup> On the other hand, if

**TABLE 2**  
**Indications for long-term use of proton pump inhibitors**

Definitive (> 8 weeks)	Conditional
Barrett esophagus (unrelated to GERD symptoms or esophagitis)	PPI-responsive, endoscopy-negative reflux disease with recurrence on PPI cessation
Erosive esophagitis Los Angeles classification grade C/D	PPI-responsive functional dyspepsia with recurrence on PPI cessation
Esophageal stricture due to GERD	PPI-responsive upper-airway symptoms with recurrence on PPI cessation
NSAID/antiplatelet users with increased risk of ulcers and bleeding	Refractory steatorrhea in chronic pancreatic insufficiency with enzyme replacement
Eosinophilic esophagitis	Secondary prevention of peptic ulcers without concomitant antiplatelet drugs
Pathological hypersecretory conditions (Zollinger-Ellison syndrome)	
Prevention of progression of idiopathic pulmonary fibrosis	

GERD = gastroesophageal reflux disease; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitors

Based on information in references 21 and 22.

a diagnosis of an inherited polyposis syndrome cannot be made, the patient should be advised to stop PPIs and manage his reflux disease with lifestyle modification or a histamine-2 blocker. Whether or not he has syndromic FGPs, this patient should undergo surveillance esophagogastroduodenoscopy to follow up on the low-grade dysplasia.

**■ BOTTOM LINE: NUMBER AND SIZE OF POLYPS, NEED FOR PPI**

If syndromic FGPs are ruled out and the patient is taking a PPI, we recommend considering PPI cessation if there are 20 or more FGPs or polyp size is larger than 1 cm. Polyps that are larger than 1 cm or atypical should be resected to evaluate for dysplasia and rule out other types of gastric polyps, but endoscopic surveillance is

not needed if no atypical features are found.

With increasing use of PPIs and increasing incidence of PPI-associated FGPs, updated evidence is needed to elucidate the natural history of these polyps and identify risk factors for malignant transformation. Regardless of the presence of any gastric polyp, a review of the indications for chronic PPI use is warranted for all patients taking a PPI for longer than 8 weeks (Table 2).<sup>21,22</sup> Inappropriate PPI use should be discontinued to minimize the adverse effects, including FGPs associated with long-term PPI use. ■

**■ DISCLOSURES**

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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# The cost of ‘free’: Advising patients about sponsored genetic testing

**I**N RECENT YEARS, we have witnessed sponsored genetic testing providing an alternative to out-of-pocket or insurance-billed tests through partnerships between genetic laboratories and biopharmaceutical companies. Available through many laboratories, sponsored genetic testing can be attractive to both patient and clinician in appearing free, but close scrutiny reveals hidden nonfinancial disadvantages that could create ethical challenges for both clinician and patient in our opinion. We break down benefits and drawbacks of sponsored genetic testing for clinicians to use in helping patients make informed decisions.

Sponsored genetic testing must be ordered through a healthcare provider and involves the distribution of genetic data among four possible primary stakeholders: the referring clinician, the patient, a genetic testing laboratory, and a third-party biopharmaceutical or biotech company, with the sponsoring biopharmaceutical or biotech company covering the financial cost. Direct-to-consumer testing is transparent in that it is a consumer-business relationship with costs up front.

## ■ ADVANTAGES AND DISADVANTAGES

Sponsored genetic testing is available for many disorders, including epilepsy, skeletal dysplasia, and cardiomyopathies.<sup>1-4</sup> Sponsoring companies may use resulting data to recruit patients for clinical trials, make providers and patients aware of new therapies, or develop new tests for diagnosing genetic diseases.

It may be tempting to conflate sponsored genetic testing with free genetic testing. Our experience has been that sponsored genetic testing is not free. Rather, when patients opt to have their genetic tests paid by the sponsoring company, the laboratory conducts the test and reports the results to the ordering clinician, typically sharing either de-identified or in some cases

identifiable results with the sponsoring third party. Data-sharing has significant implications, and being aware of these is important for patient and provider. Currently, there is little guidance for clinicians who are faced with helping patients determine whether sponsored genetic testing is appropriate for them.

In our experience, the benefits of sponsored genetic testing include expanding access to genetic testing and providing opportunity for patients to participate in research. Despite market trends toward lower pricing for out-of-pocket testing and broader insurance coverage, patients seeking genetic testing still face financial barriers.<sup>5</sup> Sponsored genetic testing may be more or equally affordable for patients who could not otherwise access genetic testing, allowing patients access to information regarding disease risks and diagnoses. However, sponsored genetic testing is not the only affordable option. Many laboratories have alternative options for low-cost or no-cost testing that do not involve a third-party sponsor and have financial assistance programs (based on a sliding income-based scale) and laboratory billing policies (such as no balance-billing for those with Medicaid).<sup>6</sup>

Even with the benefits of sponsored genetic testing, clarification regarding potential disadvantages is crucial for addressing practical and ethical issues in best patient care. Ethical issues relevant to clinicians, professional societies, laboratories, and sponsors of sponsored genetic testing involve informed consent and autonomy, confidentiality and privacy, data sharing, equity, assessing clinical appropriateness of breadth of genes tested on sponsored genetic testing panels, access to and clarification of results, and future engagement with laboratory and sponsors.<sup>7-9</sup>

Although professional societies and organizations have published resources regarding many aspects of genetic testing,<sup>10</sup> none address the unique concerns regarding advan-

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tages and disadvantages of sponsored genetic testing.<sup>11</sup> This poses challenges for those lacking familiarity with the nuances of sponsored genetic testing. Laboratories that partner with sponsoring biopharmaceutical companies may promote sponsored genetic testing to healthcare providers, many of whom have limited familiarity with the ethical nuances of genetic testing and counseling, and to patient advocacy organizations for rare diseases through sponsored content and advertisement on public-facing websites (eg, journal articles, Statnews.com). While some sponsored genetic testing offers patients the opportunity to receive sponsored genetic counseling, access to genetic counselors is not guaranteed and varies from program to program. Additionally, the sponsoring laboratories that provide access to genetic counselors and physicians via telehealth may have a financial relationship with the aforementioned sponsors, raising concerns about potential conflicts of interest.

### ■ USE OF DATA

One consideration for enhancing transparency around sponsored genetic testing is clarifying how data will be used. Although sponsored genetic testing may not involve payment, when a clinician and patient pursue sponsored genetic testing, both are still engaging in a transactional exchange with the laboratory and sponsoring company. Specifically, patients are exchanging data for the cost of the genetic test. While insurance companies do not have access to results of insurance-paid genetic testing, patients who pursue sponsored genetic testing risk losing control over their data. In other words, one risk of sponsored genetic testing may involve access to de-identified or, in some instances, identifiable data, which are shared with the paying (sponsoring) company.

To date, there are no qualitative studies specifically exploring patient attitudes toward sharing their information with a third-party sponsoring laboratory. Current literature shows that participants have concerns about privacy and confidentiality regarding de-identified genetic biobank research.<sup>12,13</sup> Likewise, a 2018 study<sup>13</sup> on participant views of risks and benefits of general data sharing found that approximately 8% or 61 of 771 expressed serious concerns about access to their data, and less than 8% or 1 in about 12 respondents felt that the potential negative consequences outweighed the benefits. Participant concerns included data theft, data used for marketing, and data sharing decreasing enrollment in clinical trials.<sup>13</sup> Extrapolating from this 2018 study, those with concerns about the risks of data sharing may be in the

minority, but their views provide insight that can be used to make data sharing a more transparent process.

In our experience, while some sponsored genetic testing programs provide easy-to-access websites with detailed information on use of data, some programs are unclear about what data will be shared in exchange for sponsored genetic testing. At times, sponsored genetic testing privacy policies can be vague or use legal language that may be obscuring, leading to several questions, such as the following:

- What is meant by de-identified data?
- If sufficient genetic information obtained from a clinical test is shared, is an individual's information then identifiable?
- Could the de-identified data be used for research and development of treatments beyond the targeted genetic test?
- How will data be secured?
- With whom will data be shared (including third parties beyond the laboratory and sponsoring company) and for how long?
- What data will be shared?
- How will data be used?
- Will any data be identifiable?

Additionally, if clinicians order sponsored genetic testing, they should consider the implications for their own practice and for their hospital systems.<sup>14</sup> We have found that while patient data are often (although not always) de-identified, both the laboratory and sponsoring entity may collect the contact information of prescribing healthcare professionals. In turn, per the typical sponsored genetic testing requisitions form, prescribing clinicians may later be asked to recruit patients to participate in a registry or clinical trial. Some laboratories and sponsors offering sponsored genetic testing specify that ordering clinicians and patients are not under obligation to the sponsoring company or laboratory, but others are vague about the relationship between providers and third parties. This consideration may already be part of a clinician's risk-benefit calculation, given prior experience with pharmaceutical companies that use prescribing data for marketing and soliciting patients for clinical trials.

### ■ INTERPRETING TEST RESULTS

Concerns about sponsored genetic testing and data also emerge regarding test results that will be shared with the patient.<sup>14</sup> The scope of genes targeted in sponsored genetic testing may reflect the sponsoring company's goals and not necessarily those of the patient and clinician. The broad nature of sponsored

genetic testing panels can be beneficial in many cases, especially when a patient is found to have a medically actionable incidental finding and the ordering provider knows how to interpret the medically actionable findings. Consider, for example, a patient with hypertrophic cardiomyopathy who decides to undergo sponsored genetic testing, which is typically a 30-gene panel. The sponsored genetic testing panel can include genes associated with all forms of hereditary cardiomyopathy or arrhythmia. Instead of finding a variant that caused the hypertrophic cardiomyopathy, the sponsored genetic testing may produce results that lead to a diagnosis of long-QT syndrome, which would otherwise have gone undiagnosed and for which there is a straightforward lifesaving intervention.

Conversely, broader panel testing can result in higher rates of variants of uncertain significance, which are prone to misinterpretation.<sup>14</sup> These results may be considered a benefit or drawback, depending on patient perspective, or may be overwhelming and distressing to patients, especially for individuals who actively wish to not know incidental findings. With broad genetic testing (such as clinical exome or genome sequencing), reporting of secondary findings and patient wishes to have them shared may be presented as an option (“opt in” or “opt out”) during the informed consent process.<sup>15</sup> With sponsored genetic testing, secondary findings and opting out of the results of secondary findings may not be an explicit part of the informed consent process.

An example involves a cardiologist intending to test for suspected cardiac transthyretin amyloidosis using sponsored genetic testing with a 100+ gene neuropathy and cardiomyopathy panel that may include testing for autosomal recessive childhood-onset conditions not clinically indicated. Although the testing may return a result that rules out hereditary amyloidosis, the broad nature of sponsored genetic testing may also yield an unexpected result identifying the patient as an adult carrier for an autosomal recessive childhood-onset metabolic condition. While the patient would be informed by the cardiologist that they did not have hereditary amyloidosis, the other findings, including the autosomal recessive childhood-onset metabolic condition, may not be discussed by the cardiologist having not prepared the patient for potential results from the 100+ sponsored genetic testing panel. Without proper counseling, the patient may learn about the unexpected findings (that have an impact on reproductive decision-making) from the results report, which could lead to distress.

When incidental findings are possible and fall outside the scope of the ordering clinician, such clinicians should be prepared not only to facilitate an informed decision prior to testing, but also to ensure the patient has access to adequate posttest counseling. The previous example underscores that access to genetic counseling must occur alongside wide-ranging genetic testing. In making an informed decision to pursue sponsored genetic testing, patients should be made aware of all results a sponsored genetic testing may yield, and a clear plan should be established between provider and patient about how to approach unexpected findings.

### ■ GENETIC COUNSELING

Sponsored genetic testing may vary regarding access to genetic counseling. Some programs may offer posttest genetic counseling free of charge, but the service is not standard and may only be available for patients who meet certain criteria. Sponsored genetic testing that offers access to free genetic counseling may eliminate some of the burden on clinicians with little training regarding genetics who have concerns about results that extend beyond their expertise. However, for most sponsored genetic testing, the burden of pretest counseling regarding uncertain or unintended results falls on the clinician. While pretest counseling is an essential duty of the provider, consistent guidance from professional societies and transparency from sponsors of sponsored genetic testing could alleviate some of the burden placed on providers.

### ■ INFORMED CONSENT

Currently, there is no standard informed-consent process for sponsored genetic testing, and the level of information varies across sponsored genetic testing offerings. Often it seems that sponsored genetic testing involves a blanket consent that centers on the rights of the laboratory to disclose information to third parties. The third parties are not always clearly defined, nor is it clear how third parties are vetted by the laboratory. In some ways, the flow of data resulting from sponsored genetic testing is similar to a biobank, but with less transparency about what qualifies a third party to become a sponsor (other than financial capability).<sup>16,17</sup> A defined informed-consent process, beyond a company-provided website, brochure, or form, may help clinicians meet the clinical obligation to each patient’s unique medical needs. Without a disclosure statement describing potential future uses, patients do not know whether a company can sell their data to

other companies, or what happens to data if companies become insolvent. Existing academic literature on informed consent and data sharing can provide useful guidance for developing an informed-consent process for sponsored genetic testing.<sup>18–20</sup>

General healthcare providers as well as patients need better educational resources provided by relatively neutral experts to complement the informed-consent process. Additional resources to support informed decision-making by patients should be generated by medical institutions, professional societies, or trusted sources like the US Centers for Disease Control and Prevention and the National Institutes of Health, and made available on their respective websites. Such resources may take the form of frequently asked questions (FAQs) on webpages addressing the basics of sponsored genetic testing that providers can use to facilitate conversations with their patients. Handouts with sponsored genetic testing provider FAQs and patient FAQs are available in the online version of this article.

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**THE BOTTOM LINE**

Many of these issues will resonate previous debates about data, biobanking, electronic health records, and commercial genetic testing.<sup>21,22</sup> Although sponsored genetic testing may help enhance access to genetic testing for many and provide researchers with data to develop new therapies, a lack of resources about the disadvantages of sponsored genetic testing for patients and providers who do not specialize in genetics poses challenges for informed use. In lieu of position statements or policy statements from specialty societies and other organizations, we offer these statements for consideration to help practitioners who may be interested in ordering sponsored genetic testing for their patients.

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## REVIEW

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# Colovesical fistula in men with chronic urinary tract infection: A diagnostic challenge

## ABSTRACT

Although uncommon, colovesical fistula creates significant morbidity, and many patients wait months to receive a correct diagnosis and treatment. Most cases are in older men who have diverticular disease, Crohn disease, cancer, or iatrogenic injury, and some of these associations may have occurred in the patient's distant past and may not be immediately apparent. Since the incidence of diverticulitis in elderly patients is increasing and, in a separate trend, more patients are undergoing bladder instrumentation, we need to suspect this diagnosis when evaluating any patient with urinary tract infection, especially a man with prolonged symptoms refractory to conventional treatments.

## KEY POINTS

Colovesical fistula is challenging to diagnose, as the signs and symptoms can resemble those of simple urinary tract infection.

There is currently no consensus on how best to diagnose colovesical fistula.

Urinalysis and urine culture offer no specific clues about anatomy and demonstrate only bacteriuria in more than 85% of cases.

The optimal treatment is surgery, but a medical approach is acceptable in patients who are too sick or frail to undergo surgery.

COLOVESICAL FISTULA IS BY FAR the most common of the four types of enterovesical fistula (colovesical, rectovesical, ileovesical, and appendicovesical). First noticed by Rufus of Ephesus in CE 200, it was described officially by Cripps in 1888.<sup>1,2</sup> It has been estimated to be responsible for 1 in 3,000 surgical admissions, typically occurring in men in their sixth or seventh decade.<sup>1,2</sup>

Colovesical fistula is a diagnostic challenge. Although it is an enteral disorder, the symptoms and signs mimic those of ordinary urinary tract infection.<sup>2-5</sup> In addition, it is relatively rare, making large studies difficult, and thus there is no consensus on the best workup test or pathway.<sup>1</sup> All of these factors contribute to delayed diagnosis and prolonged suffering.<sup>4-6</sup>

Here, we review the etiology, clinical presentation, diagnosis, and management of colonic fistula and propose a diagnostic approach.

## ■ DIVERTICULAR DISEASE CAUSES MOST CASES

The most common conditions that cause colovesical fistula in men are diverticular disease (responsible for 65% to 79% of cases in various series), malignancy (10%–20%), Crohn disease (5%–7%), and iatrogenic injury.<sup>1-3,7-9</sup>

**Diverticular disease.** The risk of developing a colovesical fistula in patients with diverticular disease is 1% to 4%.<sup>2,3,6,8</sup> The mechanism is thought to be direct extension of a ruptured diverticulum or erosion of a peridiverticular abscess into the bladder. Peridi-

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verticular phlegmon and abscesses are risk factors for future fistula formation.<sup>2,3,5</sup>

**Malignancy.** Advanced colon cancer and bladder cancer are the most common malignant causes of colovesical fistula. Less-common causes include urogenital malignancies and lymphomas.<sup>1,2</sup> External-beam radiation to the bowel can induce endarteritis obliterans leading to necrosis and mucosal breakdown, which can contribute to fistula formation.

**Crohn disease.** About 2% of patients with Crohn disease develop colovesical fistula, most commonly iliovesical.<sup>1,4,5</sup> Regional enteritis with transmural inflammation may result in adhesion of the inflamed section of the bowel to the bladder, followed by erosion with fistulization.<sup>1,4,5,6,10</sup>

**Iatrogenic surgical injury** is an uncommon cause of colovesical fistula but may be increasing in absolute numbers as more men undergo surgery in this part of the body. Colorectal, diverticular, and urologic surgery are some of the more common procedures associated with colovesical fistula.

**Direct trauma** such as a penetrating injury to the abdomen or pelvis is an uncommon cause of colovesical fistula.<sup>1</sup>

### ■ A MIMIC OF SIMPLE URINARY TRACT INFECTION

Although the cause of colovesical fistula is usually enteral, many patients present with urologic complaints.<sup>1,2,8,9</sup> They can have long-term symptoms of recurrent urinary tract infection or asymptomatic bacteriuria, sometimes lasting months.<sup>10,11</sup>

The hallmark of any enterovesical fistula is Gouverneur syndrome, characterized by suprapubic pain, frequency, dysuria, and tenesmus.<sup>1,7</sup> Symptoms can come from the gastrointestinal or urinary tract, but mostly from the latter.

Pneumaturia and fecaluria are pathognomonic and common.<sup>1,2,5,9</sup>

Abdominal pain is also common. It is not directly from the fistula, but is usually a late manifestation associated with Crohn disease with abdominal mass and abscess.<sup>1</sup>

Frequency, urgency, and suprapubic pain are present in almost all cases but are indistinguishable from symptoms of regular urinary tract infection.<sup>1,6</sup>

### ■ DIAGNOSIS IS A CHALLENGE

The diagnosis of colovesical fistula is clinical and a challenge for any clinician irrespective of training or specialty. There is no consensus on a diagnostic gold standard,<sup>1</sup> and this disease is most commonly diag-

nosed through various tortuous, unusual, and sometimes unconventional clinical procedures.<sup>8</sup> In most cases, the diagnosis is delayed or an afterthought.<sup>1,10</sup>

### History

Normally, bacteria in the bladder get there by way of the urethra, and men, who have a longer urethra than women, are less vulnerable to urinary tract infection. Therefore, urinary tract infection in a male patient, especially recurrent infection, should raise suspicion for an underlying cause such as fistula. If urinary tract infection or bacteriuria recurs in any patient, a concerted effort is needed to identify an underlying cause. Important things to ask about in the history should include the following:

- A history of instrumentation in the urogenital or gastrointestinal tract
- A history of inflammatory bowel disease, external-beam radiation, or internal brachytherapy
- How the patient recognized that he has urinary tract infection (eg, tenesmus, suprapubic pain)
- Pneumaturia (Is your urine frothy? Are there bubbles in your urine stream?)
- Fecaluria (Do you notice particles or cloudiness in your urine? Do you tend to push out cloudy urine during or after a bowel movement?)

Although a patient may not have paid attention to these symptoms before, asking may prompt him to look closer the next time he has urinary symptoms.

### Physical examination

Common physical findings are fever, abdominal tenderness, and abdominal mass, although many patients have none of these.<sup>12</sup> A more advanced examination should be done when this diagnosis is strongly suspected.

### Laboratory testing

Some patients have anemia and leukocytosis.<sup>12</sup> However, the laboratory approach usually relies on urinalysis, as blood test results tend to be within normal limits or nonspecific.<sup>5</sup> Further, urinalysis and urine culture from midstream samples offer no specific clues, although they demonstrate significant bacteriuria in more than 85% of cases.<sup>2</sup>

The type of bacteria isolated may raise suspicion for various disease processes. Most urinary tract infections associated with colovesical fistula are caused by gram-negative bacteria, most often *Escherichia coli*. However, *E coli* is native to both the gastrointestinal and genitourinary tracts, and therefore if it is present in the urine it may have come from the gut—or not. Urinalysis by itself does not delineate the anatomy of the tract.<sup>1,2,12</sup>

Gram-positive bacteriuria, on the other hand, should always be evaluated critically. If *Staphylococcus aureus* (a gram-positive organism) is isolated in the urine, systemic bacteremia needs to be ruled out: in 2 series, the prevalence of bacteremia in patients with *S aureus* bacteriuria was 13%<sup>13</sup> and 26.9%.<sup>14</sup> If streptococci (another group of gram-positive organisms) are isolated in a man's urine, an eroding malignancy and systemic bacteremia need to be ruled out.<sup>15</sup> If the streptococci are enterococci, systemic bacteremia still needs to be ruled out, but the suspicion of colovesical fistula increases exponentially.

### Special tests and imaging

If the clinical history and laboratory findings raise suspicion for colovesical fistula, numerous tests and imaging studies can be used to confirm it. However, their reliability varies.<sup>1,2</sup>

**The poppy seed test** involves feeding the patient 50 g of poppy seeds mixed with a beverage, yogurt, or something similar, and then examining the urine 48 hours later to see if these (relatively indigestible) seeds are coming out by that route. Kwon et al,<sup>16</sup> in a series of 20 patients who ultimately underwent surgery and were found to have colovesical fistula, reported that this test was positive in all 20 patients (100%), whereas computed tomography yielded positive results in only 14 (70%).

**Activated charcoal** can also be ingested by mouth. If it is seen in the urine within 24 hours, this is considered diagnostic, with a reported sensitivity of 100%.<sup>2,5</sup>

**Methylene blue test.** Gynecologists who treat women with suspected vesicovaginal fistula often do a digital vaginal examination with a soft white gauze on the clinician's gloved finger while a diluted solution of methylene blue in saline is infused into the bladder through a urinary catheter. If the gauze turns blue, there is a fistula.<sup>2,10</sup> Similarly, gastroenterologists looking for colovesical fistula can infuse a tinted fluid such as methylene blue, with or without hydrogen peroxide, into the colon during sigmoidoscopy or colonoscopy. A blue tint in the urinary catheter indicates a fistula, and a diagnosis can be made.

However, Deshmukh et al<sup>17</sup> found that methylene blue can be absorbed by the rectal mucosa and excreted by the kidneys and was therefore unreliable for confirming colovesical fistula. Indocyanine green can be used instead, with high specificity.<sup>2,8,17,18</sup>

Although these tests are inexpensive and easy to perform, they do not locate the fistula, and they may be unreliable.<sup>1,5,16</sup>

**Cystoscopy** has been regarded as the best diag-

nostic test for colovesical fistula. Woods et al,<sup>19</sup> in a series of 53 patients with colovesical fistula, reported that they could directly visualize the fistula on cystoscopy in 24 (46%). However, they could see suggestive signs such as localized bullous edema with erythema or ulcer in 80% to 100% of the patients. Sou et al,<sup>18</sup> using indocyanine green with cystoscopy, found the fistula in 11 (92%) of 12 patients.

Cystoscopy has thus been suggested as a first-line investigation.<sup>2,6,9,10,18,19</sup> However, Golabek et al,<sup>1</sup> in a review of 70 studies, found that cystoscopy yielded nonspecific findings, failing to identify colovesical fistula in 54% to 65% of cases.

**Proctoscopy and colonoscopy** have been suggested for every case of colovesical fistula. These procedures have a low detection rate, usually no more than 55%, but since 10% to 15% of cases of colovesical fistula are secondary to malignancy, endoscopy is still regarded as an essential part of the workup.<sup>5,10</sup>

**Plain abdominal radiography** is not helpful in diagnosing colovesical fistula, as the finding of air-fluid levels is not consistent with this diagnosis.<sup>1,9,19</sup>

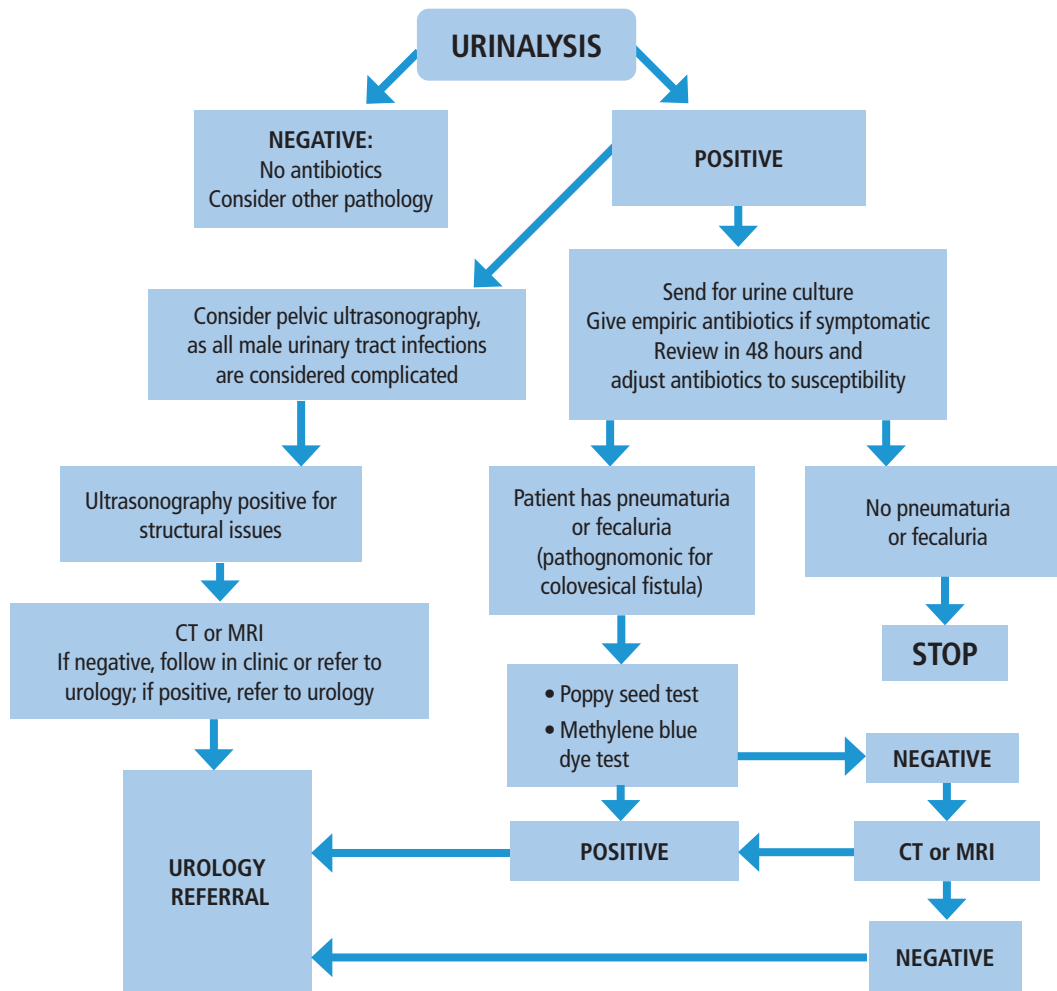
**Radiography with barium enema** has a low diagnostic sensitivity of about 30%.<sup>1</sup>

**Cystography** similarly may show contrast outside of the bladder, marking a crescentic defect on the upper margin of the bladder representing a perivesical abscess. Like other plain imaging studies, it has a low detection rate of 20% to 30%.<sup>1,5,12</sup>

**The Bourne test** is radiographic evaluation of radiodense particles from a 24-hour urine collection after barium enema. It confirms colovesical fistula in up to 90% of cases. However, with advances in computed tomography, its role is decreasing.<sup>1,2,12,20</sup>

**Computed tomography** has become the test of choice for diagnosing colovesical fistula, recommended by the American College of Radiology as the first-line imaging test in suspected cases.<sup>5</sup> It is widely available and noninvasive and provides explicit information not only about the location of the fistula but also about any surrounding inflammation, stricture, or malignancy, and is thus an aid to finding the underlying cause. It generates results quickly and has a diagnostic accuracy for colovesical fistula of up to 100%.<sup>5</sup>

The typical findings of colovesical fistula on computed tomography are air or contrast medium in the bladder and perivesical stranding with possible phlegmon or abscess nearby and adjacent thickened loops of bowel. However, other sources of air or contrast medium in the bladder that can present similarly and thus must be ruled out include recent urinary instrumentation or, in patients with diabetes, urinary tract



**Figure 1.** Our approach to male patients age 50 and older who have a first episode of suspected urinary tract infection.

CT = computed tomography; MRI = magnetic resonance imaging

infection with gas-forming organisms. A scan done with oral contrast that is then observed trickling into the bladder can help in both diagnosing a fistula and finding its location.<sup>1,2,5,11,12</sup>

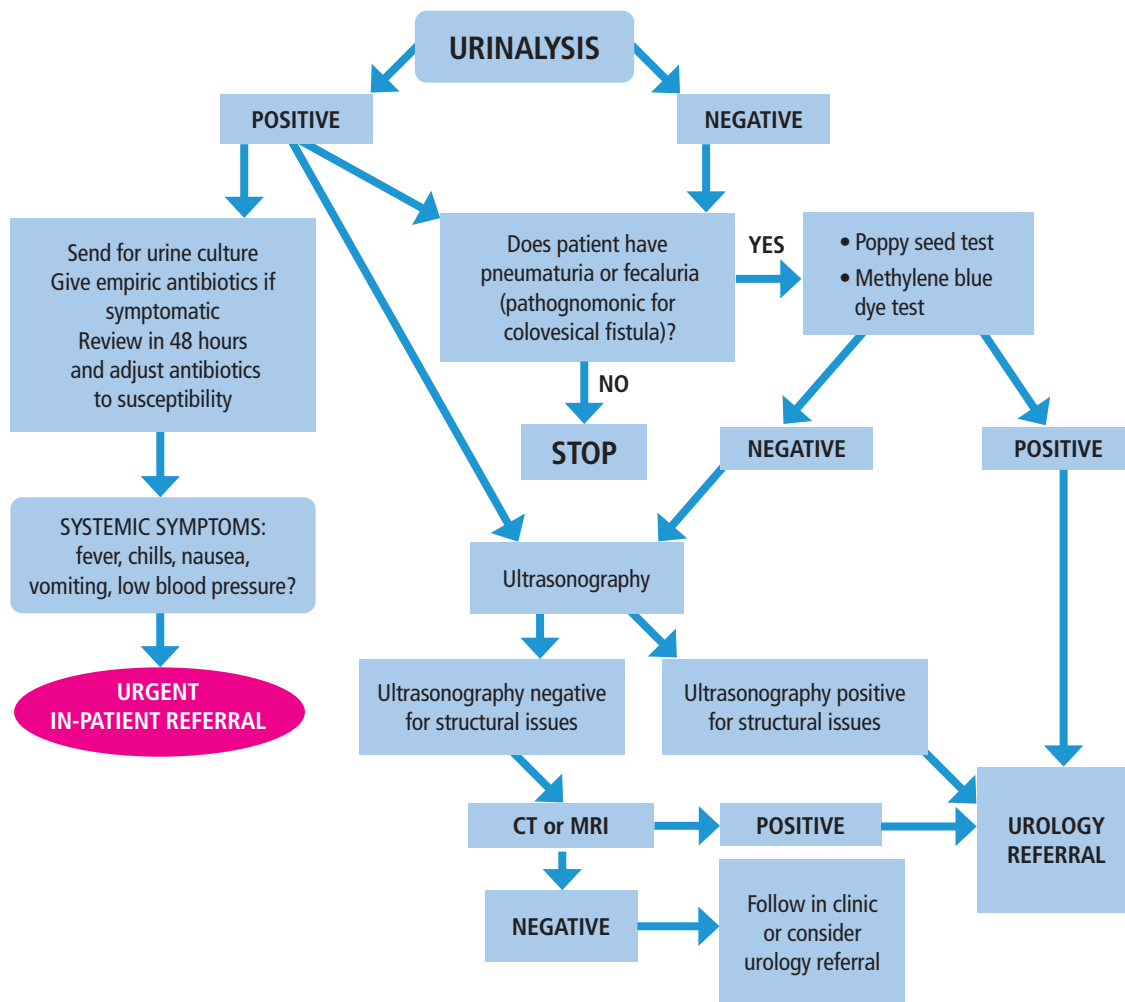
**Magnetic resonance imaging** is a good alternative. It has high intrinsic soft-tissue resolution, which provides a better view of the fistula tract whether the communication is filled with air or fluid. It has sensitivity and specificity of up to 100%.<sup>5</sup> Using intravenous gadolinium contrast improves the resolution and the accuracy of detecting bladder fistula. However, it is expensive and not available in every hospital, limiting its wider use.<sup>1,5,12</sup>

Currently, the European Association of Urology,<sup>21</sup> American Association of Family Practice,<sup>22</sup> and Infec-

tious Disease Society of America<sup>23</sup> do not recommend routinely performing cystoscopy or imaging in the diagnostic workup of recurrent urinary tract infection unless there is a high suspicion for renal calculi, outflow obstruction, interstitial cystitis, or urothelial cancer. When using imaging studies, the emphasis has been on minimizing radiation exposure.<sup>22</sup> Documentation of the reason for the chosen imaging approach should include reasons beyond “recurrent UTI.”

**Ultrasonography** has therefore become the preferred imaging study in evaluating recurrent urinary tract infection. Golabek et al<sup>1</sup> reported the usefulness of ultrasonography, and in some small series the detection rate of colovesical fistula has been up to 100%.<sup>1,24</sup> With ultrasonography, the hallmark diag-





**Figure 2.** Our approach to male patients age 50 and older who have recurrent episodes of suspected urinary tract infection.

CT = computed tomography; MRI = magnetic resonance imaging

nostic sign is air in the bladder, although this is not specific. Applying abdominal pressure can enhance the yield by revealing the “beak sign” at the connection of the peristaltic bowel lumen with the urinary bladder.<sup>1,21-23</sup> An innovative approach is to perform retrograde cystography and ultrasonography while the bladder is being filled with fluid. However, this has limited utility since most colovesical fistulas are unidirectional and flow from the colon into the bladder, as the bladder is more compliant than the colon.<sup>2,5,25</sup>

### Our approach

In view of the considerations we have discussed, herein we propose our own approach.

The first time a patient has a suspected urinary tract infection (**Figure 1**), urinalysis is the initial test.

If the results of urinalysis are positive and the patient has typical symptoms of urinary tract infection and no pathognomonic symptoms, he can be treated empirically with antibiotics while awaiting culture results and considering ultrasonography. If the results are negative but pathognomonic symptoms of pneumaturia or fecaluria are present, we can consider a poppy seed test or methylene blue test. Computed tomography or magnetic resonance imaging can be used if these tests have negative results but the patient still has pathognomonic symptoms.

For patients with recurrent urinary tract infection (**Figure 2**), urinalysis and ultrasonography can be considered initially. If the patient has positive results on ultrasonography or pathognomonic symptoms,

then we consider a poppy seed test or methylene blue test, followed by computed tomography or magnetic resonance imaging of the abdomen and pelvis with contrast if the result is not definitive. Refer the patient to a urologist if colovesical fistula is definitively diagnosed or if the patient continues to have symptoms with an indeterminate diagnosis.

### ■ SURGERY IS USUALLY REQUIRED

Although the best treatment for colovesical fistula can be debated, the definitive treatment is surgery.<sup>1,3,5,11,26</sup> Endoscopic, open, and laparoscopic approaches have all been reported, and the choice depends on the underlying pathology, site of the bowel lesion, and the patient's preoperative condition.<sup>1</sup>

Also open to discussion is whether to do the surgery all at once or over several stages. In a single-stage approach, the aim is to resect the primary lesion with anastomosis while also correcting the bladder defect. In a 2-stage approach, a diverting colostomy or Hartmann pouch is created after primary resection and anastomosis, which is then closed in a second procedure. Some perform a 3-stage operation to close the stoma.<sup>1,10</sup> Lavery<sup>9</sup> reported that most patients benefit from single-stage surgery.

Colovesical fistula can be managed conservatively in patients who are poor surgical candidates, those with minimal symptoms (particularly those with Crohn disease), or those who frankly refuse surgery.<sup>1,8,10,27</sup> Golabek et al<sup>1</sup> and Solkar et al<sup>8</sup> reported that conservative therapy with a trial of bowel rest, total parenteral nutrition, antibiotics, steroids, immu-

nomodulatory drugs, and urethral catheter drainage led to similar disease-specific mortality rates as with surgical treatment. However, others have reported significantly more deaths related to progression of malignant disease and septicemia: Garcea et al<sup>26</sup> reviewed previous studies, which showed that up to 75% of patients with colovesical fistula who did not undergo surgery died of septic complications.

Historically, surgical management has been recommended to minimize risks of uremia or septicemia.<sup>8</sup> However, surgery is not without complications. Solkar et al<sup>8</sup> and Woods et al<sup>19</sup> reported surgical morbidity rates of 4% and 45% and mortality rates of 0% and 30% in 2 small series. Technological advances and safer anesthesia and postoperative care have significantly reduced overall mortality rates in surgery of the colon in patients presenting with complications.<sup>3</sup> Over time, surgery is essential to prevent recurrence and give the best overall benefit.<sup>1,26</sup>

Before surgery, endoscopy is recommended to rule out underlying malignancy.<sup>9</sup>

The outcome of colovesical fistula management is usually excellent, and recurrence after surgery is uncommon if the tissues are healthy and the underlying disease is not progressive.<sup>1</sup> ■

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### ■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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# To repeat or not to repeat? Measuring bone mineral density during anti-resorptive therapy or a drug holiday

## ABSTRACT

An initial bone mineral density (BMD) measurement is used to diagnose osteoporosis and decide whether patients need treatment, but the utility of repeating this test in those on treatment or on a drug holiday (ie, during a pause in bisphosphonate treatment) is controversial. Here, we present evidence for and against the use of BMD monitoring in patients receiving antiresorptive therapy or on a drug holiday, and give our recommendations, arguing against a one-size-fits-all approach.

## KEY POINTS

Recommendations for using BMD to make treatment decisions must be predicated on the availability of accurate, precise densitometry to minimize measurement error.

We recommend against measuring BMD again for patients already taking highly potent antiresorptive agents such as denosumab. However, we do suggest it for patients on less-potent antiresorptive agents. Changing to other, more-potent agents should be considered only if there is convincing bone loss, ie, if there is bone loss at more than 1 site or over more than 1 testing interval, or if there is bone loss and the patient's levels of markers of bone turnover are not low (suppressed).

Further study is needed to assess the utility of repeating BMD measurement in those on treatment or on a drug holiday.

**D**UAL-ENERGY X-RAY absorptiometry gives an estimate of bone mineral density (BMD) by measuring the differential attenuation of high-energy vs low-energy x-ray beams by mineralized bone matrix. Even though it does not tell us anything about thickness of the bone or its microarchitecture, and even though there is overlap in BMD between people who have fractures and those who do not,<sup>1</sup> BMD is a strong predictor of fractures.<sup>2-4</sup>

A meta-analysis<sup>2</sup> in 1996 indicated that a reduction in BMD of 1 standard deviation was associated with an increased risk of fracture, and the association was similar to the risk of stroke predicted by a 1-standard-deviation increase in blood pressure and better than the risk of cardiovascular disease predicted by a 1-standard-deviation increase in cholesterol levels. A more recent study<sup>3</sup> suggested that each standard-deviation decrease in femoral neck BMD was associated with an approximately 3-fold increased risk of hip fracture in both men and women.

In view of these associations, BMD is used to diagnose osteoporosis,<sup>5</sup> to monitor response to treatment,<sup>6-8</sup> and to monitor for bone loss in patients not on treatment.<sup>9</sup>

However, while the utility of an initial BMD reading in assessing fracture risk is well established, the value of repeating it has been the subject of much debate. One reason proposed for measuring BMD again in patients on treatment is to verify whether the BMD is stable or increasing. For patients on a bisphos-

phonate drug holiday (ie, a pause in treatment after completing a course of the drug), the main reason proposed for measuring BMD again is to determine if it is time to resume treatment.

Guidelines from the Endocrine Society,<sup>10</sup> the American Association of Clinical Endocrinologists,<sup>11</sup> and the International Society of Clinical Densitometry<sup>12</sup> recommend repeating BMD measurements during treatment and during the drug holiday, while guidelines from the American College of Physicians<sup>13</sup> recommend not monitoring BMD after starting treatment. This dissonance of views has been confusing, highlighting the need for an objective measure for clinicians to use to follow patients during and after treatment.

### Improvement in BMD on treatment strongly predicts reduction in fracture risk on treatment

Here, we present the evidence for and against monitoring BMD during treatment and during a drug holiday, we argue against using a one-size-fits-all approach, and we propose deciding on the basis of which drug the patient is receiving or has received and whether a stronger drug is available.

#### ■ PATIENTS RECEIVING TREATMENT FOR OSTEOPOROSIS

Following up BMD measurements during treatment for osteoporosis makes sense only if the changes in BMD tell us whether the treatment is lowering the patient's risk of fracture. If fracture risk were no different in those losing BMD compared with those gaining BMD on treatment for osteoporosis, it would make no sense to repeat the measurement.

While some early studies suggested that the increases in BMD during raloxifene treatment explained only a very small proportion of the reduction in fracture risk,<sup>14</sup> most studies found that increases in BMD during treatment strongly predicted the reduction in fracture risk.<sup>15,16</sup>

Bouxsein et al<sup>17</sup> performed a meta-regression analysis of 38 randomized controlled trials of 19 different treatments and concluded that increases in BMD during treatment strongly predicted lessening in fracture risk. The  $r^2$  values, or variance in fracture risk predicted by changes in BMD, were about 0.5, showing that about 50% of the improvement in fracture risk was accounted for by the change in BMD, and these associations were highly statistically significant.<sup>17</sup>

Therefore, despite the initial controversy, we consider this issue settled: improvement in BMD on treatment strongly predicts reduction in fracture risk on treatment.

#### Arguments against testing

If it is clear that improvements in BMD during treatment are meaningful, how then can one argue against monitoring BMD during treatment?

The main argument against it is that almost everyone receiving treatment has stable or improving BMD, and in the rest, most of the bone loss detected during treatment is actually due to measurement error, even when the bone loss reported exceeds the expected measurement error based on precision studies.<sup>18</sup>

Bell et al<sup>19</sup> analyzed data from the Fracture Intervention Trial, which compared alendronate (specifically the name-brand Fosamax, which may be relevant—see “Arguments for testing,” below) vs placebo, and found that 97.5% of participants receiving active therapy gained BMD at the hip.

Cummings et al<sup>20</sup> reanalyzed the same data and found that the group of patients who lost BMD while taking alendronate gained it back the next year, suggesting that they never truly lost BMD in the first place.

These 2 studies suggest that most people do not lose BMD while taking alendronate, and that when we find what looks like bone loss, it is usually measurement error that will regress to the mean and go back up the next year. So, while it is best to gain BMD on treatment, and it could be concerning to lose BMD on treatment, true bone loss on treatment is rare, and the bone loss that we do detect is usually not true bone loss.

#### Arguments for testing

This argument against monitoring BMD during treatment was rebutted in an editorial by Watts et al,<sup>21</sup> who make several important points:

First, the data in the studies of Bell et al<sup>19</sup> and Cummings et al<sup>20</sup> were derived from a randomized controlled trial, from which patients were excluded if they had secondary risk factors for osteoporosis and in which the patients were highly adherent to taking their medications. This highly selected patient population is very different from that encountered in clinical practice, making generalization difficult. Dowd et al,<sup>22</sup> for example, found that of 120 patients with osteoporosis seen in their clinic, only 3.3% to 20.8% would have qualified for inclusion in randomized controlled trials of anti-osteoporosis medications.

The main reasons for exclusion were comorbidities, prior treatment for osteoporosis, and secondary osteoporosis.<sup>22</sup>

Furthermore, the analysis by Bell et al<sup>19</sup> used data from the Fracture Intervention Trial, in which any participants losing significant BMD at the lumbar spine or total hip (> 8% over 1 year, > 10% over 2 years, and > 12% over 3 years) were excluded from the analysis, making it difficult to extrapolate these results to patients encountered in clinical practice.<sup>20,21</sup>

Moreover, the patients in the Fracture Intervention Trial received name-brand Fosamax. Generic formulations may not be as effective: 40% to 50% lesser gains in BMD were seen when generic formulations of alendronate were used compared with the brand-name preparation.<sup>23</sup> In vitro studies found that different generic preparations differed in how fast they disintegrate, which may at least partially explain these findings.<sup>24,25</sup>

Furthermore, not all anti-osteoporosis drugs are equivalent. Alendronate preserved BMD more effectively than ibandronate,<sup>26</sup> risedronate,<sup>27</sup> and raloxifene<sup>28</sup> in head-to-head trials, so even if most patients taking alendronate do not lose BMD, the same cannot be said for less-potent drugs.

### How much observed bone loss is real?

The questions then remain, how often do patients lose bone during treatment for osteoporosis and, of the observed bone loss, how much is real and how much is measurement error? Given the limitations in directly extrapolating from randomized controlled trials, let us examine real-world data regarding the utility of repeating BMD measurements in those taking anti-osteoporosis medications.

Kline et al<sup>29</sup> retrospectively analyzed data from 1,369 women in Manitoba, Canada, who had at least 3 serial BMD measurements. Most (79.7%) of these women were taking bisphosphonates, and they had undergone repeat BMD testing at approximately 3-year intervals from baseline. Only 1.4% showed BMD losses at both treatment intervals.<sup>29</sup>

The large sample size, exclusion of those switching therapies, use of a province-wide centralized BMD program, and the high medication adherence rate (> 85%) were notable strengths of the study. Given that only 1.4% of participants lost BMD at both intervals, the study authors questioned the utility of repeating BMD measurement for postmenopausal women who were highly adherent to antiresorptive therapies.<sup>29</sup>

However, another way of looking at these data is that while only 1.4% of participants lost BMD at

both intervals, among the 6.5% of participants who lost BMD at the lumbar spine in the first interval, 62.5% were determined to have loss of BMD at that site on long-term follow-up, while among the 13.4% of women who lost BMD in the first interval at the total hip region, 72.4% were determined to have loss of BMD on long-term follow-up.<sup>29</sup>

### Our recommendations

We estimate that two-thirds to three-quarters of the bone loss seen in patients receiving antiresorptives is real, while the remainder perhaps is “noise.” The likelihood of experiencing real bone loss is likely higher in those taking less-potent antiresorptives and in those not adherent to therapy. If one accepts the premise that bone loss on treatment is concerning and not uncommon, and if more-potent antiresorptives such as denosumab are available,<sup>30</sup> following BMD on treatment seems a reasonable and defensible strategy.

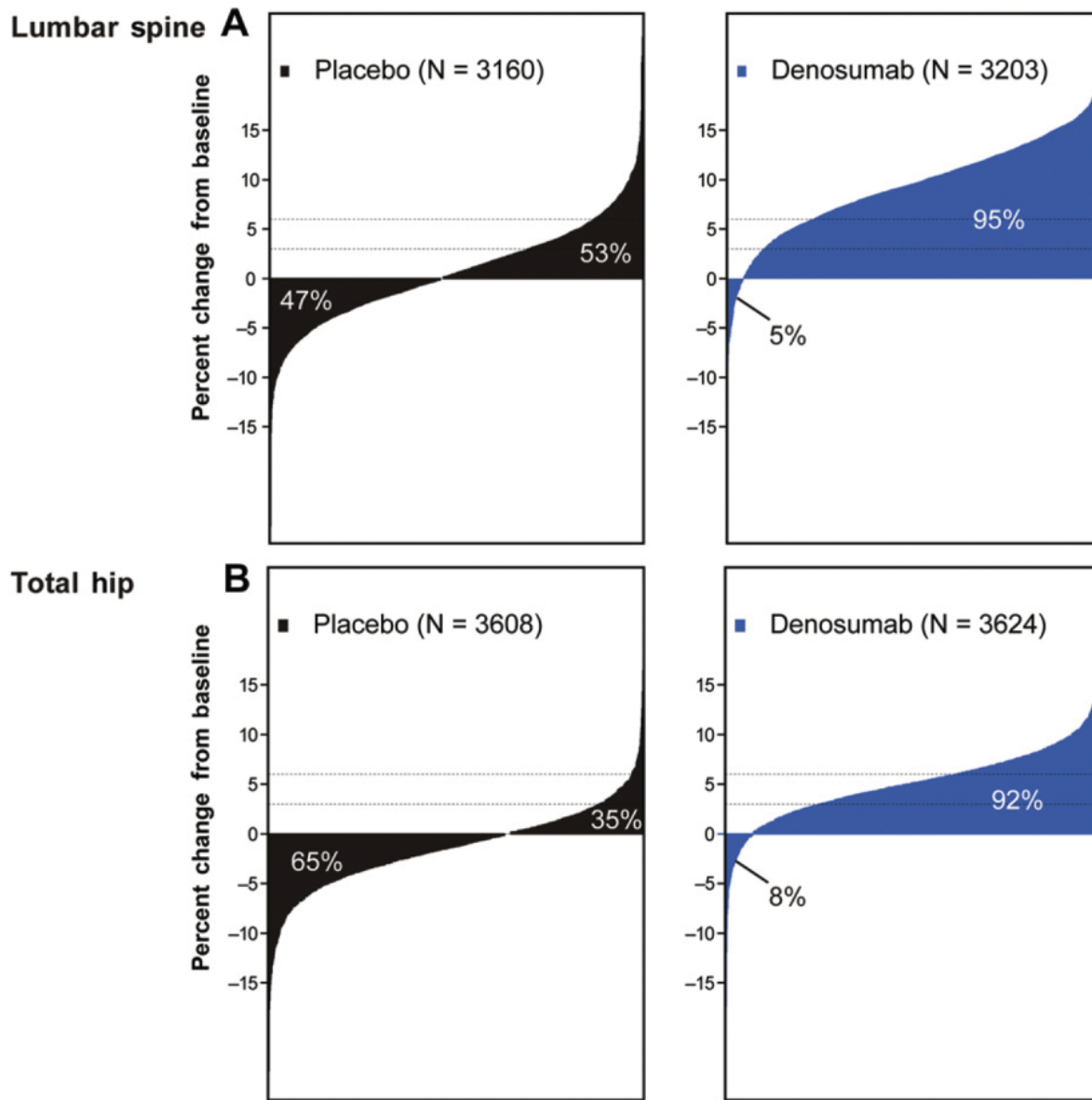
The following are our recommendations:

Densitometry must be of high quality to be worthwhile.<sup>18</sup> If the densitometry that is available is not of high quality, most of the bone loss that is discovered will be measurement error, and follow-up BMD measurements during treatment cannot be recommended. Best practices for bone densitometry have been published by the International Society for Clinical Densitometry Guidance.<sup>18</sup>

Few patients lose BMD while taking highly potent agents. In a number of studies,<sup>26-31</sup> a substantial minority of patients lost BMD during treatment, but the more potent the antiresorptive, the less likely that patients will lose BMD.

Denosumab is more potent than alendronate in its effects on BMD and bone turnover,<sup>30</sup> and few patients being treated with denosumab had significant bone loss in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study (**Figure 1**).<sup>31</sup> For this reason, we are inclined to accept the logic that argues against serial densitometry in patients receiving denosumab.<sup>19</sup> Bone loss is unlikely with this drug, and even if we did find bone loss in patients on denosumab, what alternative do we have that is more effective? In this case, the patient is already receiving the most potent antiresorptive. If we found bone loss in a patient taking a less potent drug, we could switch to a more potent drug, but if we find bone loss in a patient taking a more potent drug, where do we go from there?

True bone loss must be distinguished from measurement error. Although some bone loss during treatment is real, some is clearly due to measurement



**Figure 1.** Waterfall plots demonstrating the percent changes in bone mineral density on treatment with denosumab vs placebo at the lumbar spine (A) and total hip (B) over 36 months in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months study. While many patients in the placebo group lost bone mineral density, few in the denosumab group did. Almost none of the participants on denosumab lost a significant amount of bone mineral density (> 5%) over 36 months.

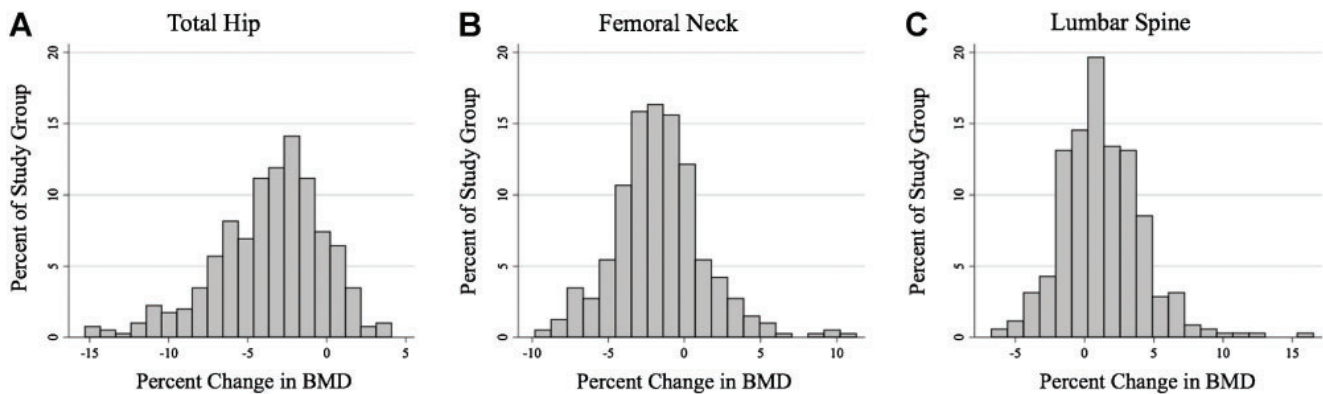
Reprinted from Bolognese MA, Tegljbjærg CS, Zanchetta JR, et al. Denosumab significantly increases DXA BMD at both trabecular and cortical sites: results from the FREEDOM study. *J Clin Densitom* 2013; 16(2):147–153. doi:10.1016/j.jocd.2012.02.006 with permission from Elsevier.

error.<sup>20,29</sup> If we do perform serial densitometry on treatment, how is the clinician to know if the observed bone loss on treatment is real or due to measurement error? Switching all patients losing BMD on alendronate to denosumab when only a fraction of them are really losing BMD is not recommended. Switching

treatments is recommended only if the observed bone loss is convincing.

Convincing bone loss would be bone loss at more than 1 site or over more than 1 interval, or bone loss associated with elevated markers of bone turnover such as cross-linked C-telopeptide of type-1 colla-





**Figure 2.** Changes in total hip bone mineral density (BMD) 5 years after completing a 5-year course of treatment with alendronate in the long-term extension of the Fracture Intervention Trial. Many patients had no significant hip bone loss, but a substantial minority had more than 5% bone loss, and an even smaller minority had more than 10% bone loss.

Reprinted from McNabb BL, Vittinghoff E, Schwartz AV, et al. BMD changes and predictors of increased bone loss in postmenopausal women after a 5-year course of alendronate. *J Bone Miner Res* 2013; 28(6):1319–1327. doi:10.1002/jbmr.1864 with permission from John Wiley and Sons.

gen (CTx) greater than 300 pg/mL.<sup>32</sup> If a patient on treatment loses BMD at 1 site over 1 interval with a low CTx, we would presume that the bone loss might be due to measurement error, and we would continue the current treatment and continue to monitor. This recommendation is similar to that made by the International Osteoporosis Foundation on inadequate response to osteoporosis treatment.<sup>33</sup>

### ■ PATIENTS ON A DRUG HOLIDAY

A drug holiday is appropriate only for patients who have completed a course of bisphosphonate treatment, since bisphosphonates such as alendronate and zoledronate are known to continue to protect for years after a course is completed. A holiday is not suggested after a course of estrogen, raloxifene, denosumab, or anabolic treatments, since patients will lose BMD after stopping these agents.

The concept of a drug holiday after bisphosphonate treatment is based on the idea that after a course of bisphosphonates, BMD remains fairly stable and bone turnover is substantially depressed for years, though the duration of stability varies based on the half-life and potency of the bisphosphonate used.

Bone et al<sup>34</sup> found that in patients who had completed 5 years of alendronate treatment, spine BMD remained stable and mean hip BMD decreased by 1.8% over the subsequent 5 years. While mean urine cross-linked N-telopeptide of type 1 collagen had been suppressed to 70% below

baseline on treatment and rose during the drug holiday, it remained suppressed to about 50% below baseline. Turnover was more suppressed without any hip BMD loss in those who continued alendronate out to 10 years.<sup>34</sup>

A larger study of 5 vs 10 years of treatment with alendronate<sup>35</sup> and a study of 3 vs 6 years of zoledronate<sup>36</sup> yielded similar findings. These 2 studies also demonstrated a lower risk of fractures with the longer course of bisphosphonates, which came at the cost of the risk of overtreatment syndromes such as atypical femoral fractures, which start to rise in incidence to about 1 in 1,000 per year with longer duration of therapy.<sup>37,38</sup>

These studies provide the evidence for letting patients with osteoporosis suspend bisphosphonate treatment after completing a course of treatment, after which they can continue to enjoy some protection for some time. Of note, there are no data that patients can enjoy protection after stopping a course of ibandronate or risedronate, though it is common practice to give them a drug holiday as well to avoid the potential for overtreatment syndromes such as osteonecrosis of the jaw or atypical femoral fractures.<sup>11</sup>

### How should patients be followed during the drug holiday?

Since improvement in BMD during treatment correlates with a reduction in fracture risk, it seems likely that loss of BMD during the drug holiday would correlate with an increase in fracture risk. But how often do we see significant bone loss during the drug holiday?

McNabb et al<sup>39</sup> reported that of 406 patients who took alendronate for 5 years and then had 5 years of follow-up off alendronate in the long-term extension of the Fracture Intervention Trial, 29% had more than a 5% reduction in mean hip BMD, and some had a reduction of more than 10% (Figure 2).<sup>39</sup> Based on this analysis, if we are concerned about bone loss during a drug holiday, there is a substantial minority of patients losing BMD during the drug holiday who could be identified with serial densitometry and then undergo another course of treatment.

### Arguments for and against testing

The main argument against serial densitometry during the drug holiday was made by Bauer et al.<sup>40</sup> Analyzing the same cohort of participants followed off alendronate for 5 years, they reported that the tertile of hip BMD loss at 1 year did not predict the risk of fracture during the drug holiday, but age and T-score at the time of discontinuation of alendronate did. They concluded that changes in BMD off treatment with alendronate are not predictive of fracture risk, and monitoring BMD during the drug holiday is not warranted.<sup>40</sup>

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### We can get meaningful information from monitoring, but only if we have high-quality bone densitometry available

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While Bauer et al make a cogent point, they reported that while 1-year changes in hip BMD did not predict fracture risk during the drug holiday, 2-year changes did.<sup>40</sup> We must consider as well that there is always some measurement error around each measurement of BMD, so that the annual bone loss determined at a 1-year interval may have more noise than annual bone loss determined at a 2- or 3-year interval. This point harkens back to the discussion above about “convincing” bone loss: it is very likely that bone loss at 2 sites, or bone loss at 1 site over multiple measurements, or bone loss at 1 site with clearly increasing CTx predicts fracture more than does isolated bone loss at 1 site.

In addition, fracture risk is largely determined by the T-score at the time one enters a drug holiday. But if a patient is on a drug holiday, a determination has already been made based on fracture risk and duration of treatment that it was time to start the drug holiday. The real question we are confronted with when a patient is on a drug holiday is whether the protection from the prior course is wearing off. If the protection is

wearing off, then it is necessary to give more treatment to prevent further bone loss, and it should be safe from the perspective of overtreatment syndromes such as osteonecrosis of the jaw to resume treatment. So the challenge is not how best to predict fractures during the drug holiday, but rather to determine when there is evidence for dissipation of protection based on serial measurements of BMD and measurements of turnover.

In practice, do patients do better with all this monitoring during the drug holiday, or would they do just as well if we pick a fixed duration of drug holiday (3 or 5 years), after which they would resume treatment? This question has unfortunately never been directly studied. The closest information we have available is through follow-up of patients starting a drug holiday, suggesting that bone loss is common on a drug holiday following treatment with risedronate and less common but not rare following alendronate or zoledronate treatment.<sup>39,41</sup> Therefore, BMD may be monitored at a shorter time interval during a drug holiday after taking risedronate compared with that for alendronate or zoledronate.

Until a dedicated randomized study is done to inform the utility of monitoring, the clinician needs to choose an approach that makes sense. If the clinician would like to make this decision based on the imperfect monitoring tools we have, that is reasonable. If the clinician is unconvinced that we can get clear and meaningful guidance from monitoring, at the beginning of the drug holiday the clinician should choose how long the holiday should be, after which treatment should be resumed. Our opinion, and that of many osteoporosis organizations<sup>11,12,18</sup> is that we can get meaningful information from monitoring, but only if we have high-quality bone densitometry available.

### Our recommendations

We believe that the duration of the drug holiday should depend on how likely it is that the patient is losing BMD. Again, we argue against a one-size-fits-all approach and make the following recommendations regarding repeating BMD while on a drug holiday:

**Rationale for repeating BMD: Does the patient need to resume treatment?** The rationale for repeating BMD on a drug holiday should be to determine when the effect of bisphosphonate treatment is dissipating and the patient is a candidate for more treatment. Availability of high-quality bone densitometry is a precondition to repeating BMD.

**Testing interval depends on the agent used.** Given the data regarding loss of BMD while on drug holiday,

and taking into account the relative duration of effect of individual agents, we believe that BMD should be repeated in 1 year after pausing risedronate, and 2 to 3 years after pausing alendronate or zoledronate. This recommendation is similar to that by the task force by the American Society for Bone and Mineral Research on managing osteoporosis for those on drug holidays.<sup>42</sup>

**Resume treatment if necessary.** We recommend resuming treatment if there is convincing evidence for dissipation of the effect of treatment, as demonstrated by convincing bone loss at more than 1 site, or over more than 1 interval, or that associated with nonsuppressed markers of bone turnover such as CTx.

**Some patients can resume without testing.** Patients who have already had a long drug holiday and patients whose drug holiday began after a course of risedronate might be candidates for restarting treatment with any sign of bone loss, while patients who had been on alendronate or zoledronate and have had a less than 5-year drug holiday might not be candidates for restarting until we see more convincing bone loss.

## ■ NO CLEAR ANSWER

There is no clear answer to the question of how patients with osteoporosis should be followed while on treatment and during a drug holiday. Changes

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in BMD during these periods are likely meaningful but are confounded by measurement error. For this reason, some clinicians will choose to treat with an agent for a specified duration, and then stop treatment for a drug holiday for a period of time. A perfectly reasonable alternative that we and many specialty societies recommend is to follow patients while on treatment to assure stability of BMD, and during the drug holiday to determine when to resume treatment.<sup>11,12</sup>

Again, monitoring BMD is reasonable only if high-quality densitometry is available.

Furthermore, monitoring BMD on treatment makes sense if more-potent treatments are available, and makes less sense if the patient is already taking a highly potent treatment and deterioration of BMD is not likely to change treatment. Further study is needed to assess the utility of repeating densitometry as a measure of treatment adequacy in patients on treatment and drug holiday on specific antiresorptive agents. ■

## ■ DISCLOSURES

Dr. Khan has disclosed teaching and speaking for Amgen, Boehringer Ingelheim, Eli Lilly Canada, IPSEN, Janssen, and NovoNordisk Canada, and working as advisor or review panel participant for Eli Lilly Canada. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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# Update on current contraceptive options: A case-based discussion of efficacy, eligibility, and use

## ABSTRACT

With high rates of unintended pregnancy in the United States, it is crucial for clinicians to be well-informed about the full spectrum of contraceptive options to improve reproductive autonomy. We review new contraceptive options including a nonhormonal intravaginal gel, hormonal contraceptives in the form of new pills, patches, and vaginal rings, and combined hormonal contraceptives that contain new estrogens as alternatives to ethinyl estradiol. We review updated prescribing methods for several established hormonal contraceptives such as depot medroxyprogesterone acetate, which is now available for subcutaneous self-injection. Additional choices of available contraceptive methods have important clinical implications that may remove unnecessary barriers to contraceptive use.

## KEY POINTS

Certain long-acting reversible contraceptive methods can prevent pregnancy beyond the approved duration of use. However, this does not allow for extending the duration of use for lowest-dose progestin intrauterine devices.

Intravaginal contraceptive gel offers a nonhormonal contraceptive alternative.

Contraceptives with longer approved durations of use or that do not require frequent access to healthcare professionals can improve adherence and outcomes.

**D**ESPITE WIDELY AVAILABLE contraceptive methods, the percentage of unintended pregnancies in the United States remains stagnant at 45%, higher than in many industrialized nations, with many of these pregnancies in individuals of low socioeconomic status and subpar access to healthcare.<sup>1</sup> Several new contraceptive methods have become available in the last few years, and clinicians should be able to counsel on the full spectrum of options, as patient satisfaction with the method will improve adherence. Particularly now, with reproductive autonomy being discussed in many states, there is a need for action to ensure that every patient receives their preferred safe and effective contraceptive. In addition to preventing pregnancy, contraceptives often are used for symptom management in medical conditions including acne, hirsutism, dysmenorrhea, heavy menstrual bleeding, menstrual migraine, and perimenstrual mood disorders.

Herein, we discuss several new hormonal and nonhormonal contraceptive options. Please note that this article is focused on cis-gender women who have sex with men. The term “she” in this paper refers to those assigned female sex at birth.

## ■ NONHORMONAL CONTRACEPTIVE INTRAVAGINAL GEL

*A 47-year-old with latex allergy presents to the office. She is interested in contraception, but does not want anything that contains hormones.*

Until recently, nonhormonal contracep-

tive options were limited to the copper intrauterine device (IUD), condoms (male and female), diaphragm, cervical cap, and spermicides.<sup>2-4</sup> The use of a copper IUD requires a procedure and may lead to increased menstrual bleeding and cramping.<sup>5,6</sup> Barrier methods are user-dependent, may impact spontaneity, have varying effectiveness, and variable unintended pregnancy rates per year of use (eg, 18% to 28% for spermicide).<sup>2-4</sup> Most barrier methods require an office visit for optimal fitting and need to be used with spermicides, which may be associated with irritative vaginal or urinary symptoms.<sup>3</sup>

A new barrier method intravaginal gel (Phexxi; lactic acid 1.8%/citric acid 1%/potassium bitartrate 0.4%) is inserted within 1 hour prior to intercourse. The gel maintains the physiologically acidic pH of the vagina to inhibit sperm motility, and the viscosity offers a barrier to sperm over the cervix.<sup>4</sup> A new applicator needs to be used with each act of intercourse.

The AMPOWER study was a multicenter, single-arm, open-label, phase 3 study of 1,384 women, of which 1,114 were included in the primary efficacy analysis.<sup>7</sup> In this study, the intravaginal gel demonstrated 86.3% contraceptive efficacy with typical use (as opposed to preliminary studies submitted to the US Food and Drug Administration [FDA] that suggested 93% efficacy with perfect use over 7 cycles).<sup>7-9</sup> When using contraceptive methods with lesser efficacy, an advanced prescription for an emergency contraceptive pill (such as ulipristal acetate) is recommended, especially if pregnancy prevention is an important goal for the patient.

The most common adverse events have been reported to be vaginal burning (18%) and itching (14.5%).<sup>9</sup> Similar to other barrier methods, an association with cystitis, pyelonephritis, and urinary tract infections have been reported, perhaps due to the shift in pH of the genitourinary system.<sup>9,10</sup>

Intravaginal gel is an option for patients desiring nonhormonal birth control (owing to preference or medical contraindication), wanting an on-demand option, or those who have allergies to other barrier methods such as latex condoms or spermicide. This method is particularly unique because it is on-demand and similar to condoms but not partner-dependent. It can also be used postpartum, post-miscarriage, or post-abortion. In addition, some women who are encouraged to use two methods of contraception (ie, when on a medication that will induce liver enzymes or has teratogenic potential) can use this method with a shorter-acting method such as birth control pills. This is a reasonable contraceptive option for women

in the late menopause transition, where the chance of unintended pregnancy is decreased (though still possible). Those who need a highly reliable method to prevent pregnancy should be counseled on the use of more effective methods.

### ■ INTRAVAGINAL RING

*A 28-year-old shift-worker notes difficulties remembering her birth control pills. She is interested in an option that does not require daily use. You suggest an IUD or arm implant, but she wants to avoid a procedure. What method would you recommend?*

Despite the variety of available contraceptive options, imperfect adherence remains an issue that decreases effectiveness. Nearly 48% of unintended pregnancies occur in women who use contraception.<sup>11,12</sup> Most American women use short-acting hormonal contraceptives or combined oral contraceptives (COC), even though the chance of unintended pregnancy is significantly lower for an IUD and implant.<sup>5,6</sup> Expanding the available non-oral formulations of short-acting hormonal contraceptives is crucial to ensure that women who do not desire a procedure or daily oral regimen have adequate efficacious options.

A new 13-cycle combined vaginal ring containing 150 µg segesterone acetate and 13 µg ethinyl estradiol provides one year of birth control using the same ring without being discarded (Annovera),<sup>13</sup> unlike other vaginal contraceptive rings (eg, NuvaRing, EluRyng) that have a different type of progestin and are intended for only 1 month of use at a time. Similar to other vaginal rings, Annovera is placed inside the vagina for 21 days by the patient, then removed for 7 days to allow menses.<sup>13-15</sup>

The initial phase 3 trials included two multicenter, multinational studies of 3,052 women, with 999 completing 13 cycles of use with Annovera.<sup>16</sup> Effectiveness in pregnancy prevention was noted to be 97.3% when used as recommended, comparable to perfect use of COCs.<sup>13,14</sup>

Complete expulsions occurred in the studies in 7% of cycles, although these were mainly in the initial cycle.<sup>16</sup> No backup contraception is needed if the intravaginal ring is reinserted within 2 hours of expulsion.<sup>17</sup> This may not be an appropriate method for those with difficulty or pain using the vaginal ring, such as those with arthritis of the hands, pelvic floor dysfunction, vaginismus, preference to avoid intravaginal placement, or other limitations for correct use.

This method is a good choice for those who want longer-acting, reversible contraception that is not a pill, injection, or procedure, especially in patients struggling to adhere to a daily pill or with limited access to healthcare. The segesterone acetate and ethinyl estradiol ring has not been studied for continuous use (no placebo break), though it is used this way in clinical practice. A modeling study using pharmacokinetics data from 37 women suggested that serum levels of estrogen and progestin after 364 days of hypothetical continuous use would be appropriate for pregnancy prevention,<sup>15</sup> but evidence from clinical trials to support continuous use is currently unavailable.

**PROGESTIN-ONLY PILL**

*A 35-year-old needs contraception and would like to regulate her cycles. She has a history of lower extremity venous thromboembolism following intensive care unit hospitalization for viral pericarditis. She wants to avoid procedures or injections and prefers oral pills. She has tried a progestin-only pill in the past, does not recall its name, but does remember frequent breakthrough bleeding with that method.*

Before 2019, the only progestin-only pill (POP) available in the US would have been 0.35-mg daily norethindrone, available in multiple generic names. Because it does not contain estrogen, a POP can be used in women with a history of arterial or venous thrombosis and those considered to be at high risk for these conditions (ie, uncontrolled hypertension, tobacco use, antiphospholipid syndrome, migraine with aura, etc.).<sup>5,6</sup> Given that there are only a few contraindications to its use (such as active hormone-dependent breast cancer treatment), a POP can be offered as a “quick start” method to any woman who is sure that she is not pregnant and as a bridge for more effective methods requiring a procedure at a future time.

With traditional POPs, patients need to follow rigid daily timing as missed pills lessen effectiveness.<sup>18</sup> Traditional POPs are different from estrogen-containing contraceptives in a variety of ways. They inhibit ovulation only in about 50% to 70% of user cycles.<sup>6,18</sup> Thus, this method also prevents pregnancy with other mechanisms of action, such as impacting cervical mucus.<sup>18,19</sup> Norethindrone-only pills also have a shorter half-life than COCs.<sup>18</sup> Consequently, a POP user must adhere to a consistent pill schedule, with a maximum delay of 3 hours in dosing compared to 12 to 24 hours with a COC.<sup>18,19</sup> Women who are more

than 3 hours late taking their norethindrone POP are encouraged to use additional backup contraception.<sup>18</sup>

The new 4-mg drospirenone POP, a derivative of spironolactone, acts as an antiminerocorticoid with antiandrogenic properties,<sup>18,19</sup> with activity similar to 25-mg spironolactone. Therefore, it is likely to be beneficial in those with acne, hirsutism, or tendency toward fluid retention. Although it has not been directly compared to norethindrone POPs, the 4-mg dose for drospirenone was determined based on effective suppression of ovulation for up to 24 hours following a missed or delayed dose.<sup>18</sup>

Norethindrone POP is taken daily, without any placebo breaks. Thus, variable bleeding can occur, as can lighter regular bleeding, amenorrhea, or irregular spotting. Drospirenone is taken in a 24-active pill/4-placebo-pill formulation to induce a regularly scheduled withdrawal bleed as opposed to traditional POPs taken continuously.<sup>19,20</sup>

As with all progestin-only methods, unscheduled or prolonged bleeding is common. It typically occurs in the first 6 months, between cycles 2 to 4, with declining frequency over time, and an eventually greater percentage of participants reporting lighter cycles or amenorrhea at a year or beyond.<sup>19,21,22</sup> Based on a multicenter, noncomparative trial, the 4-mg drospirenone “24/4-day regimen” reduced unscheduled bleeding over time; participants reported 90% of bleeding days as light or moderate, with only 4.2% of participants stopping the study due to irregular bleeding.<sup>19,21,22</sup> Prior to prescribing, appropriate counseling of expected bleeding patterns over the first year is likely to help with patient adherence and satisfaction with the method.

Similar to traditional POPs, drospirenone has a desirable safety profile.<sup>19,21,22,23</sup> In a study of over 700 participants from 41 European sites, treated for one year, no one experienced cardiovascular events, thromboses, or hyperkalemia, despite participants having at least one cardiovascular risk factor.<sup>19</sup> Drospirenone 3 mg is available in a COC together with ethinyl estradiol doses of 20 or 30 µg (with additional FDA approval to treat premenopausal dysphoric disorder).<sup>23</sup> Despite the higher dose of 4-mg drospirenone in the progestin-only formulation, plasma concentrations of drospirenone at a steady state have been shown to be higher after use of 3-mg drospirenone combined with ethinyl estradiol.<sup>23</sup> However, this difference is unlikely to have significant clinical implications for most individuals.

Given its effectiveness in ovulatory suppression, predictable bleeding pattern, and favorable side

effect profile, a 24/4-day regimen of 4-mg drospirenone would be an excellent option for women with contraindications to estrogen-containing hormonal contraceptives.

### NEWER ESTROGEN OPTIONS

*A frustrated 38-year-old visits the office for a birth control follow-up. She has tried multiple COCs with different progestin types, yet each caused her to develop a diffuse rash. She is adamant about not placing an intravaginal ring, arm implant, or intrauterine device. Are there any other options?*

Most COCs contain ethinyl estradiol, a synthetic hormone with a long half-life, which helps with stability of dosing for effectiveness and bleeding control. Oral intake of ethinyl estradiol impacts the production of various liver proteins involved in coagulation, fibrinolysis, and hypertension, thus contributing to its commonly known thrombosis risk. Also, ethinyl estradiol is highly potent compared to more natural analogs of estradiol, which has led to a lowering of ethinyl estradiol doses over the years to improve the safety profile of hormonal contraceptives.<sup>24</sup> Although most women tolerate ethinyl estradiol-containing pills very well, for those who are intolerant, there were few alternative estrogen-containing contraceptive options until recently. In 2010, the FDA approved COCs containing estradiol valerate, followed by the recent approval of estetrol in 2021, expanding the number of options for those intolerant to the estrogen component of the pill.

Estradiol valerate is available in a quadriphasic formulation (US trade name Natazia), which decreases estrogen from 3 mg to 1 mg and increases the progestin (dienogest) from 1 mg to 4 mg, both over the course of the monthly regimen. Estradiol valerate is a synthetic prototype of natural 17 beta-estradiol, being rapidly metabolized to estradiol after oral intake.<sup>25-27</sup> Two mg of estradiol valerate has the impact of 10 µg of ethinyl estradiol, qualifying this contraceptive as very low-dose.<sup>27</sup> Dienogest is a progestin with a 17-cyanomethyl group, causing its strongly progestogenic and weakly antiandrogenic activity.<sup>25</sup> Two inert (placebo) pills complete the pack for the last 2 days to allow for a shortened withdrawal bleed.<sup>26-28</sup> Comparable to triphasic pills, the 26 active pills contain tapering doses of the active drugs in attempt to mimic the natural menstrual cycle.<sup>26-28</sup> Although both estrogen and progestin components are newer to the US market, this particular progestin has been used in Europe since the 1990s.

Natazia was the first quadriphasic dosing regimen used to treat heavy menstrual bleeding.<sup>26,27</sup> A multicenter, double-blind, randomized, placebo-controlled phase III study conducted in Europe and the Asia Pacific demonstrated the effectiveness of the estradiol valerate-dienogest combination in significantly reducing menstrual bleeding and improving productivity and daily activities in women's lives.<sup>26</sup> Though most COCs can treat heavy menstrual bleeding, this formulation has higher rates of amenorrhea compared with typical COCs, with amenorrhea occurring in 19% to 24% of women, making it potentially useful for those plagued with persistent breakthrough bleeding using other regimens.<sup>26,27</sup> Also, estradiol valerate caused a significantly milder effect on metabolic parameters than ethinyl estradiol.<sup>25-29</sup>

Estetrol 14.2 mg is a novel estrogen combined with 3-mg drospirenone (US trade name Nextstellis, 2021). Estetrol is marketed as a "natural estrogen" because it is produced by the fetal liver during pregnancy and acts selectively in tissues (impacts alpha receptors), showing mixed estrogen agonist and antagonist activity.<sup>30</sup> Clinically, it has been shown to have minimal impact on the synthesis of coagulation factors, hepatic metabolism, triglycerides, and breast stimulation.<sup>24,30</sup> Owing to these differences, estetrol cannot be translated into an equivalent dose of ethinyl estradiol that applies to all tissues. However, contraceptive efficacy of estetrol with drospirenone has been shown to be similar to other marketed ethinyl estradiol-estetrol with drospirenone containing COCs. Estetrol has been marketed as more environmentally friendly due to less accumulation of estrogen metabolites in the urine, with the hopes that it will be less likely to pollute water supplies.<sup>31</sup> However, further study is needed to assess which of these factors, if any, will be of clinical significance.

Nextstellis is monophasic (all pills have consistent hormone dosing), available with 24 active pills and 4 days of placebo, leading to an optimum withdrawal bleeding pattern (typically, the fewer placebo days, the shorter the expected bleeding).<sup>24,30</sup> Studies have suggested lower venous thromboembolism (VTE) incidence compared to traditional COCs,<sup>24,30</sup> but there is need for more extensive studies (in real-world settings, in larger groups) to give a more accurate population estimate of VTE incidence. The additional absolute increase in the risk of venous thrombosis with the use of all estrogen-containing contraceptives (when compared to baseline population rates of VTE) is about 1 of 1,000 or less, in the rare category of risk, and well below the thrombosis risks of unintended



pregnancy.<sup>5,32</sup> Thus, large populations need to be studied to assess thrombosis risk in otherwise healthy women during reproductive age.

The side effect profiles of these newer estrogens are similar to all other classes of combined hormonal contraceptives and may include mood changes, irregular bleeding, nausea, headache, and breast tenderness. Newer estrogen options might be beneficial in those with intolerance to multiple COCs, both in terms of symptoms and bleeding irregularities, and may be the desired option for those with cardiometabolic risk factors such as elevated triglycerides, pending further study. Estradiol valerate, in particular, could be a highly efficacious hormonal contraceptive for women with menorrhagia.

### ■ TRANSDERMAL OPTIONS

*A 23-year-old needs birth control that will provide predictable cyclical bleeding and help her acne, but does not want to be required to remember pills. She has read that birth control patches increase the risks of blood clots more than other formulations and asks for your advice.*

The delivery of hormonal contraceptives has evolved since the birth control pill was first introduced in the 1960s, now including oral, transdermal, subcutaneous implant, intrauterine, and intravaginal options. Transdermal delivery of hormones helps address poor adherence and fluctuation of hormones due to pharmacokinetic variations of serum hormonal levels associated with COCs.<sup>33–36</sup>

Similar to a bandage, a small adhesive patch is placed on the lower abdomen, buttocks, upper arm, or upper torso (excluding the breast), worn continuously for 1 week, and is removed and replaced immediately by a new patch weekly for 3 weeks, followed by a patch-free week when the menstruation occurs. Alternatively, a new patch can be placed weekly without any breaks for continuous use. However, pharmacokinetic studies have suggested a gradual rise in serum ethinyl estradiol over time after 12 weeks of continuous use, thus long-term safety of patch use without placebo breaks is not clear.<sup>33–36</sup> The patch is designed to stay in place while bathing, swimming, or exercising, but users should not apply lotion or oil near the patch site. Like all transdermal medications, allergic reactions to the adhesive are possible.

The first patch containing 35 µg ethinyl estradiol and the progestin norelgestromin was FDA approved in 2001 within the United States and internationally (initial trade name Ortho Evra, now Xulane). Once applied to the skin, a steady state is reached within

48 hours of application and maintained consistently until removal; like forms of hormonal contraceptives, the contraceptive effectiveness begins after 1 week of use.<sup>6</sup> Several clinical trials indicate that the contraceptive patch is as effective as COCs and may lead to better adherence.<sup>34–50</sup> However, this first generation of patches led to higher exposure of serum ethinyl estradiol, similar to a 50-µg COC,<sup>36</sup> leading to conflicting reports about whether rates of VTE were increased compared with COCs.<sup>37</sup> Some of these studies found no associated increase in VTE risk compared with low-dose comparators.<sup>38–40</sup> While another found comparable VTE risks to levonorgestrel-containing pills (a progestin that typically shows lower relative risks of VTE among COCs) but could not exclude additional risk for older women.<sup>41</sup> In contrast, several studies suggested that the norelgestromin-ethinyl estradiol patch magnifies relative risk for VTE compared with norelgestromin or levonorgestrel-containing pills by 2-fold.<sup>42–44</sup> However, there were limitations to several of these studies, including that the 95% confidence intervals (CIs) crossed one in most analyses and had no adjustment for possible confounding variables.<sup>36</sup> Thus, the FDA Advisory Board concluded that though there may be an increased relative risk for VTE with the norelgestromin-ethinyl estradiol patch compared with some birth control pills, the absolute risk is still considered lower.<sup>45</sup>

A new transdermal patch containing 30-µg ethinyl estradiol and 120-µg levonorgestrel daily dosing (Twirla; FDA-approved 2020) was designed to address the need for a lower-dose contraceptive patch and delivers daily hormone exposure compared with similarly dosed pills.<sup>35</sup> Twirla is well tolerated, with reported lower rates of detachment and site irritation than the norelgestromin-ethinyl estradiol patch.<sup>34,35</sup> Based on evidence from five clinical trials, the norelgestromin-containing patch has a VTE frequency of 53 per 100,000 women (95% CI 1–294).<sup>34</sup> Though direct head-to-head studies are not available between the 2 patches, studies of the levonorgestrel-containing patch are estimated to have a VTE frequency of 32 per 100,000 women (95% CI 1–176).<sup>34</sup>

Norelgestromin patch users typically had less breakthrough bleeding and spotting than COCs at cycle 13.<sup>45</sup> However, users of this patch were also more likely to report breast discomfort, dysmenorrhea, nausea, and vomiting.<sup>29,40,41</sup> Users of the novel levonorgestrel patch were less likely to experience nausea and infrequently reported headaches and fatigue when compared to COC users.<sup>34,47,48</sup> Again, it should be noted that studies directly comparing side

effects of the 2 patches are not available.

Based on limited evidence, there is concern of a higher risk for contraceptive failure in transdermal contraceptive users who have a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>.<sup>35</sup> Thus, relying on a hormonal contraceptive patch as the sole method to prevent pregnancy in women with a BMI  $\geq 30$  kg/m<sup>2</sup> is not recommended, especially when pregnancy prevention is a high priority.

Transdermal hormonal contraceptives are advantageous for individuals having difficulty with remembering a daily pill. Healthy women in their teens and 20s at low risk for VTE may still be candidates for norelgestromin patches, especially if higher doses are preferred for cycle control, improving acne (which tends to be treated best with higher estrogen-containing options), or combined with medications that may interact to decrease hormone levels. However, additional transdermal options with a lower estrogen dose will be useful in clinical practice.

### ■ SELF-ADMINISTERED DEPOT MEDROXYPROGESTERONE ACETATE

Depot medroxyprogesterone acetate (DMPA) users represented 2% of US women aged 15 to 49 between 2017 and 2019.<sup>51</sup> DMPA-intramuscular 150-mg injections have historically required an office visit, which can pose additional barriers to staying consistent with a patient's preferred contraceptive method. Following their review, the Centers for Disease Control and Prevention and World Health Organization recommended self-administered 104-mg subcutaneous (SC) DMPA.<sup>50</sup> This formulation can be injected at home by the patient, which empowers self-care and removes barriers such as frequent in-person visits to a clinic. It is a user-controlled method with the potential to improve contraceptive access and reproductive autonomy.<sup>49</sup>

Currently, the FDA label states DMPA-SC is only to be administered by clinicians. Nonetheless, following a shared decision between clinician and patient, an FDA-approved drug may be prescribed for off-label use, not excluding self-administration when medically needed. In clinical practice, many patients are encouraged to self-inject at home, and self-administered DMPA-SC has been shown to have a higher continuation rate than provider-administered DMPA.<sup>49,51</sup> One study reported that 97% of patients found DMPA-SC easy to administer and reported an 87% satisfaction rate, which was higher than provider-administration at 12 months of follow-up.<sup>51</sup> In a US study conducted during the COVID-19 pandemic,

37% of contacted DMPA-intramuscular patients were interested in self-administration of DMPA-SC, with 58% of those interested individuals transitioning to self-administration, reported to be similar to provider administration, and the safety profile was not different, though more injection site reactions have been reported in the self-administered group.<sup>52</sup> Barriers to self-administration include a preference for an in-person visit, fear of needles, incorrect administration, and insurance coverage.<sup>49</sup>

The recommendation for self-administered initiation, follow-up, and reinjection interval is the same as when provider administered. Repeat DMPA injections should be provided every 3 months and may be given up to 2 weeks late without requiring backup contraceptive protection.<sup>53</sup> Patients should receive instruction for self-administration and sharps disposal. These individuals should have access to follow-up care along with the opportunity to switch to provider-administration or another contraceptive method if desired.

### ■ USE OF LONG-ACTING CONTRACEPTIVE DEVICES BEYOND FDA-APPROVED DURATION OF USE

Long-acting reversible contraceptives (LARCs) have become an increasingly popular contraceptive choice because of their high degree of efficacy and safety profiles that include efficacy at preventing pregnancy, ability to be used for several years, limiting patient effort and thus user error, and offering rapid return to fertility. A prospective cohort study of over 9,000 women with normal weight and BMI  $> 30$  kg/m<sup>2</sup> received the LARC of their choice (an IUD or arm implant) and observed a failure rate of less than 1 per 100-woman years without any difference according to BMI category.<sup>53-55</sup>

When long-term pregnancy prevention is priority, LARC may be the optimal contraceptive choice. Recently, research has shown that several commonly used LARC methods maintain efficacy 1 to 2 years after the FDA-approved duration of use (**Table 1**).<sup>5,6,53,56</sup>

#### Subdermal implant

Nexplanon is a small polymer rod impregnated with the progestin etonogestrel. During a simple office procedure, this implant is placed subdermally in the non-dominant upper arm. While FDA-approved for only 3 years for contraception, emerging data have shown efficacy maintained for up to 5 years. An open-label, multicenter, randomized trial demonstrated that etonogestrel implants had a 5-year cumulative pregnancy rate of 0.6 per 100 women-years

**TABLE 1**  
**Comparison of commonly used LARCs, all with > 99% efficacy<sup>a</sup>**

Brand	LARC type	Progestogen, dose	Size, mm	FDA-approved duration of use	Data-supported duration of use	Bleeding patterns	Amenorrhea according to package insert	Other clinical pearls
Mirena	Levonorgestrel-IUD	52 mg	32 x 32	8 years	8 years	More likely to have significantly decreased menstrual bleeding and pain, especially after 1 year of use Progestin-only methods may be associated with irregular bleeding and spotting	1 year: 20% 5 years: 40%	Approved for treatment of heavy menstrual bleeding Can be used as emergency contraception <sup>56</sup>
Liletta	Levonorgestrel-IUD	52 mg	32 x 32	8 years	8 years		1 year: 19% 5 years: 40%	More affordable for patients with limited insurance coverage
Kyleena	Levonorgestrel-IUD	19.5 mg	28 x 30	5 years	5 years		1 year: 12% 5 years: 23%	Smaller size may be more suitable to nulliparous patients or those with anatomically smaller uterus
Skyla	Levonorgestrel-IUD	13.5 mg	28 x 30	3 years	3 years		1 year: 6% 3 years: 12%	
Paragard	Copper IUD	Hormone-free	32 x 36	10 years	12 years	Possible increased amount and duration of menstrual bleeding	No causal relationship established	Can be used as emergency contraception Best for highly effective contraception that is hormone free (ie, after breast cancer) When used during age of mid-late 30s, can provide contraception into menopause transition
Nexplanon	Subdermal etonogestrel implant	68 mg	2 x 40	3 years	5 years	Unpredictable bleeding pattern, though lightens over time for most	2 years: 20%	Does not require a pelvic examination Easy to learn procedure, training via drug company as opposed to clinician

<sup>a</sup>All the contraceptives are the most-effective contraceptive methods; safe in breastfeeding; no long-term effects on fertility, fertility is immediate following discontinuation; safe for women who cannot or prefer not to take estrogen.

FDA = US Food and Drug Administration; IUD = intrauterine device; LARC = long-acting reversible contraceptives

Based on data from references 5, 6, 53, and 56.

[n = 204; 95% CI, 0.2–1.8].<sup>57</sup> In contrast, the chance of unintended pregnancy at the end of 1 year is 6% to 9% with typical use of patient-controlled methods such as pills, rings, patches, and DMPA injections.<sup>6</sup> Thus, even when used two years beyond the removal date, it is likely that contraceptive efficacy is considerably better than those of the short-term reversible methods.

In our experience, it is reasonable for a clinician to have a shared-decision-making conversation regarding the option to leave the device for 4 or 5 years or

replace it at year 3. Of note, there is insufficient data regarding the efficacy of the etonogestrel implant in extended use in patients with a BMI ≥ 30 kg/m<sup>2</sup>, as obesity has been shown to decrease serum levels of progestin.<sup>5,6</sup> Additionally, given that the progestin dosage decreases over time, some patients who opt for extended use may experience increased irregular bleeding. Before choosing this option, clinicians must discuss with patients to ensure a complete understanding of potential adverse effects.

**Intrauterine devices**

The highest dose (52 mg) levonorgestrel-releasing IUDs have the longest FDA-approved duration of use of the progestin IUDs available in the United States. Since 2022, both Mirena and Liletta are now FDA-approved for 8 years of use based on updated studies showing effectiveness beyond their originally approved duration of use (had been 5 years). The lower-dose hormonal IUDs (Skyla and Kyleena) should not be used beyond their FDA-approved duration of use due to lack of data.

Studies suggest that the nonhormonal copper IUD (Paragard) remains a highly effective contraceptive at least until 12 years of use.<sup>58</sup> In 1997, the World Health Organization and United Nations conducted a large, randomized, multicenter trial that determined the cumulative 12-year intrauterine pregnancy rate was 1.9 per 100 person-years (standard error, 0.6,  $P < 0.001$ ), which is similar to all sterilization methods.<sup>58</sup>

**KEY MESSAGES**

Now, more than any other time in recent US history, it is crucial for all clinicians to be well-informed about the full spectrum of contraceptive options. Shared

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decision-making between each patient and clinician is recommended to choose the best option, recognizing that the risks of any contraceptive are always less than the risks of unintended pregnancy. Though a growing body of evidence supports the safety of expanding the duration of LARC use, individuals should never be coerced into keeping the device longer than what they prefer. The bleeding profiles and contraceptive efficacy may be impacted negatively with a greater duration of use, and for some women, their highest priority may be the best possible protection from unintended pregnancy. Although increasing nonprocedural options with new pills, patches, and rings are important for patient choice, financial barriers to using these newer (and often more expensive) products remain a real challenge. We urge clinicians to advocate on behalf of their patients for various contraceptive options to be made available and affordable to all women who need them. ■

**DISCLOSURES**

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## Stay Current With These Objectives

Wednesday Optional Workshop	2-Day Course	Saturday Optional Workshops
<ul style="list-style-type: none"> <li>• Building a Point-of-Care Ultrasound Program</li> <li>• Describe the components of successful point-of-care ultrasound programs</li> <li>• Summarize process for image acquisition, machine utilization, and IT configuration</li> <li>• Describe the importance of a training, quality improvement, and credentialing</li> <li>• List components of billing and coding for various ultrasound exams</li> </ul>	<ul style="list-style-type: none"> <li>• Summarize the basic science and diagnostic use of ultrasound imaging</li> <li>• Describe the protocols, evaluation, and best use of echocardiography in critically ill patients</li> <li>• Review the role of ultrasound in a focused assessment with sonography in trauma (FAST) exam to assess for free fluid in the abdomen or around the heart</li> <li>• Summarize the basics of using ultrasound to assess lungs</li> <li>• Describe the most effective diagnostic use of ultrasound to assess for vascular abnormalities including aortic pathology and deep venous thrombosis</li> <li>• Practice the evaluation of shock and respiratory failure with point-of-care echocardiography</li> <li>• Demonstrate competence in ultrasound guidance for needle placement and peripheral intravenous access, arterial line access, and midline access</li> <li>• Demonstrate the best use of ultrasound for paracentesis, thoracentesis, and arthrocentesis</li> <li>• Describe the fundamentals of tunneling technique and the tunneled CVC kit</li> <li>• List the indications, complications, and aftercare related to insertion of a tunneled central venous catheter (CVC)</li> <li>• Demonstrate competence in central venous access including materials, ultrasound landmarks, and needle placement</li> </ul>	<p><b>Airway Management in the Critically Ill Patient</b></p> <ul style="list-style-type: none"> <li>• Summarize the Cleveland Clinic Airway Management protocol and algorithm for critically ill patients</li> <li>• Apply airway management tools to secure the airway</li> <li>• Demonstrate application of the airway management protocol</li> <li>• Choose the best strategy to manage the airway in critically ill patients</li> </ul> <p><b>Pediatric Simulations and Ultrasound</b></p> <ul style="list-style-type: none"> <li>• Detail the causes of hypoxemia in the critically ill neonate</li> <li>• Effectively manage undifferentiated shock in the neonate and infant</li> <li>• Describe tips and tricks for vascular access in the pediatric population</li> </ul> <p><b>Hemodynamic Assessment of the Critically Ill Patient</b></p> <ul style="list-style-type: none"> <li>• Identify the hemodynamically compromised patient</li> <li>• Describe the 3 components of the Rapid Ultrasound for Shock and Hypotension (RUSH) exam: Pump, Tank, Pipes</li> <li>• Utilize the Rapid Ultrasound for Shock and Hypotension (RUSH) exam protocol</li> <li>• Explain the ultrasound findings seen in the 4 types of distributive shock</li> </ul>

## Who Should Attend

This workshop is designed for physicians, physician assistants, and nurse practitioners in emergency medicine, internal medicine, hospital medicine, critical care, cardiology, general surgery, pediatrics, pulmonology, anesthesiology, and radiology.

Register Today! [ccfcme.org/GoUltra](https://ccfcme.org/GoUltra)

This activity is approved for AMA PRA Category 1 Credit™, ANCC Contact Hours, and AAPA Category 1 CME Credits.

## How to earn *AMA PRA Category 1 Credit*<sup>™</sup> and ABIM MOC points

### *AMA/PRA Category 1 Credit*<sup>™</sup>

To read articles as CME activities and claim credit, go to [www.cjcm.org](http://www.cjcm.org), click on the “CME/MOC” menu, and then “Articles.” Find the articles that you want to read as CME activities and click on the appropriate links. After reading an article, click on the link to complete the activity. You will be asked to log in to your MyCME account (or to create an account). Upon logging in, select “CME,” complete the activity evaluation, and print your certificate.

Call 216-444-2661 or e-mail [ccjm@ccf.org](mailto:ccjm@ccf.org) with questions.

## Maintenance of Certification (MOC) Points

All *Cleveland Clinic Journal of Medicine* CME activities are eligible for ABIM MOC points. Physicians may claim MOC points in addition to CME credit.

Follow the instructions for completing and claiming credit for CME activities.

When you log into your MyCME account, select “CME & MOC” and enter your ABIM identification number and your date of birth. The system will store this information after you enter it the first time.

Complete the quiz and evaluation and print your CME certificate.

## March 2023 CME/MOC activity

Estimated time to complete the activity: up to 1 hour

### Update on current contraceptive options: A case-based discussion of efficacy, eligibility, and use

Release date: March 1, 2023

Expiration date: February 28, 2024

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In support of improving patient care, Cleveland Clinic Center for Continuing Education is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Cleveland Clinic Center for Continuing Education designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit*<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Participants claiming CME credit from this activity may submit the credit hours to the American Osteopathic Association for Category 2 credit.

### AMERICAN BOARD OF INTERNAL MEDICINE (ABIM):

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

**Please Note:** To receive MOC you must select the MOC option during the online credit claiming process and complete the required steps. ABIM MOC points will be reported within 30 days of claiming credit.