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Lancaster General Hospital

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Fold twice in each direction before tearing.

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See page 125 for an update from the Lancaster Medical Heritage Museum.

FROM THE EDITOR'S DESK

A Compelling Read for the Road Ahead

Corey D. Fogleman, MD, FAAFP
Editor in Chief

"Serve the patient, first and foremost, but also serve the clinician."

– Ted Tristan, MD, Founder, Tristan Radiology Associates, Harrisburg, PA[1]

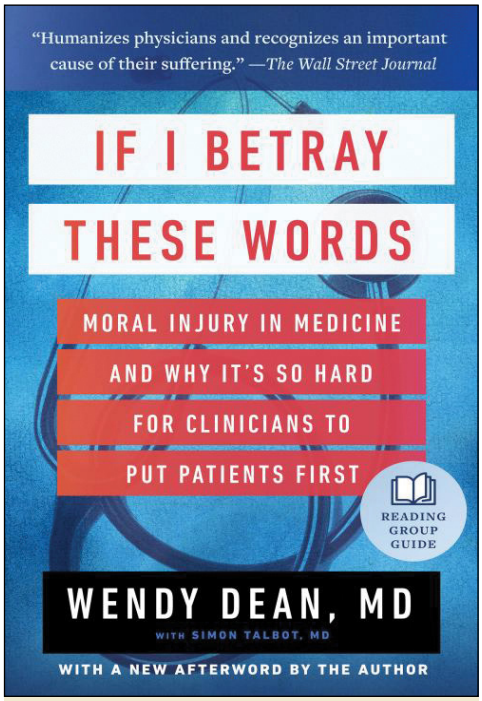
In 2006, Shervin Dean, MD, shortly out of residency, joined the Tristan Radiology group. Six months later, the Deficit Reduction Act of 2005 reduced funding for radiological procedures and testing. Attempts to align Tristan with the very business-minded Pinnacle Health and then UPMC left the Tristan team feeling that they were compromising patient care and their own accountability.

As a result, the group eventually dissolved in favor of a joint venture in which the employees of Tristan would work with Penn State Health as Community Medical Group employees. In the words of Wendy Dean, MD, a psychiatrist and former emergency physician – and Shervin's spouse – they finally felt they could "focus ... on doing good."[1]

In 2018, Dr. Wendy Dean, along with Simon Talbot, MD, appropriated the term "moral injury." The term had previously been used to describe the wounds warriors incur on the battlefield when they are unable to help their brothers- and sisters-in-arms.[2] The most ominous threat is when leaders force their teams to betray core beliefs.

Veterans of war describe this threat as a crisis-of-confidence in their own virtue as well as the good within all they encounter.[3] Threats to their values may be as dire as any wartime threats to their lives, and, even when diagnosed as "post-traumatic stress disorder," moral injury may jeopardize veterans' ability to serve. This is a despair that who they are may be compromised in a Faustian and irreparable way. Among veterans, innovative approaches include encouraging work in charity, and in the end, some may need to redefine what it means to be a soldier.[3]

In the profession of medicine, Drs. Dean and Talbot believe, we are as much at risk in our hospitals and clinics. Moral injury, they argue, is a term just as appropriate to the loss of control many clinicians feel when our systems threaten our values. In 2023 they expanded their original postulate and closely examined the very compelling trials and tribulations of several individuals and health systems in their book, *If I Betray These Words.*



By Wendy Dean, MD, with Simon Talbot, MD
Lebanon, NH, Steerforth Press, 2023,
304 p, 29.00 hardcover

The book contains a cast of characters that will be familiar to many of us who have lived and practiced in Pennsylvania over the past 10 years. In this page-turner, they hold up the solemn oath we each take, to stake our lives to "care for anyone who suffers, [be they] prince or slave." As binding now as when Hippocrates first modeled this ethic, we are more conflicted than were the ancients. Our allegiances are multifaceted – to our families and communities as well as our systems, and to layers of government bureaucracy.

Further, we may be beholden to what non-experts counsel regarding fluoride or vaccines and to insurance companies demanding prior authorization. In short, we are at risk for "cuts to the soul," similar to our veterans.

Drs. Dean and Talbot suggest there is hope and lay out a prescription to help us renew and strengthen our covenant. To begin, each of us must revisit the core values that compelled us to study medicine, including the commitment to charity and the pursuit of scholarship that inspired us. There also tends to be less moral injury when clinicians have a seat at the leadership table and when clinician well-being is tracked as a metric for which leadership is held accountable. Thus, the authors implore that physicians must be involved in decision-making at every level and that leaders must remain committed to the physical, mental, and spiritual health of all stakeholders — to the patients, as well as the staff and clinicians who work for them.

"In this page-turner, [the authors] hold up the solemn oath we each take, to stake our lives to 'care for anyone who suffers, [be they] prince or slave.' As binding now as when Hippocrates first modeled this ethic, we are more conflicted than were the ancients."

At the same time, it remains reassuring to see our leaders in the trenches. "Go to the Gemba" is a Lean principle that many of us practice, and Drs. Dean and Talbot aim to motivate leaders to continue to spend time on the wards and in the clinics, to see things at the field level.

Policy wise, we should be encouraging Congress to put limits on consolidation, to protect rural communities — a concern that seems urgent and close to home, with recent financial turmoil that has led to loss of access at nearby Crozer Health.[4] Further, insurance and billing reform could go a long way toward relieving practitioner distress, especially if it includes ending the ridiculous practice of prior authorization.

Health care professionals are trained to put the needs of our patients first, to practice virtuously and in an evidence-based fashion. Our systems should give us the wherewithal, time, and space to do just that.

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Editor in Chief Corey Fogleman, MD, put out a call last year for narrative medicine articles. "Rereading and rewriting about what we encounter forces us to emphasize and economize, to pair some ideas and pare others," *he wrote.*

Your stories might address staff experiences, patient experiences, or anything else that might be educational for our readers. For more information and to submit your story ideas, please scan the QR code at right or visit our website at JLGH.org.

Preventing Death by Firearm in Lancaster County

An LG Health Initiative

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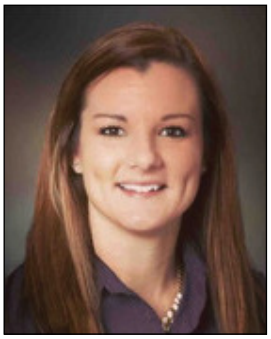
Pringle


Fenimore

A 19-year-old male had no prior history of mental health problems. When he arrived at college, he had challenges structuring his time and managing relationships. After a semester of sporadic attendance, he received several failing grades and was unable to return. His parents remained supportive, but after an argument with his girlfriend, he died by suicide with firearm. He used a gun in the home that was stored in a "secret" yet unlocked location.

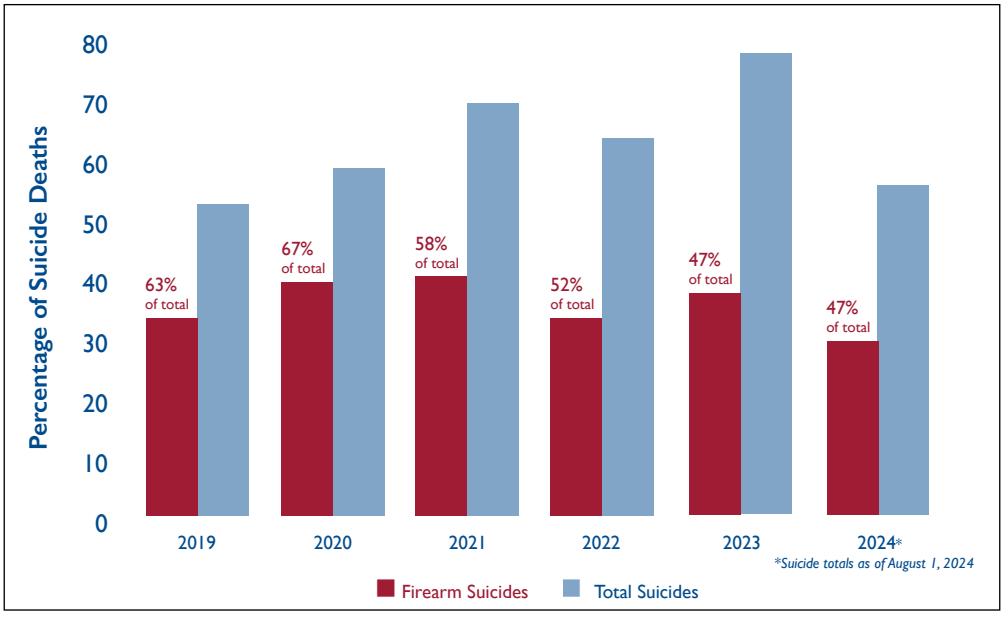

Fig. 1. Firearm suicide vs. total suicides (all ages) in Lancaster County. *Data sourced from the Pennsylvania Department of Health Bureau of Family Health and the Lancaster County Child Death Review.*

BACKGROUND

As health care providers, we know how devastating firearm deaths are for families and communities. While gun-related mortality has become more common, we will never become numb to it; instead, we grieve each loss acutely. Many of us remain frustrated and unsure how to prevent further deaths.

Over the last decade we have focused on improving mental health care and reducing stigma. The advent of telehealth and online counseling has made therapy more accessible, and many school systems now have anti-bullying policies, mental health support, and parent education. Evidence suggests these initiatives are making a difference. One recent study showed that fewer adults worry about retaliation in the workplace if they take time off to seek mental health care, and the percentage of kids who report being bullied at school is decreasing.[1,2] But there is more to do to prevent deaths due to firearm.

Preventing death by firearm should be understood as a public health opportunity much like other measures to prevent motor vehicle accidents and prevent lead poisoning. Health care providers can make a difference by asking their patients about firearms, offering information on safe storage, and educating about the link between firearms in the house and suicide. With proper training and a prevention approach, this important topic can be addressed comfortably.

EVIDENCE REVIEW

Firearms have become a leading killer of people ages 18 to 24 years in the United States[3]; Lancaster County is no exception. In 2023 there were 37 suicides

by firearm in Lancaster County. Most firearm deaths each year are suicides, and firearms are the most common method used for suicide.[3]

Reports reveal that 82% of firearm suicides in the United States were completed using a family member's gun.[4] What's more, easy access to weapons is a threat to the community because 77% of school shooters in the United States also use a family member's gun.[5] Gun sales have steadily increased since 2010, and it is estimated that 4.6 million children in the United States live in a home with a loaded, unlocked, firearm.[6] Thus, safe storage and/or removal of firearms may help prevent these tragedies.

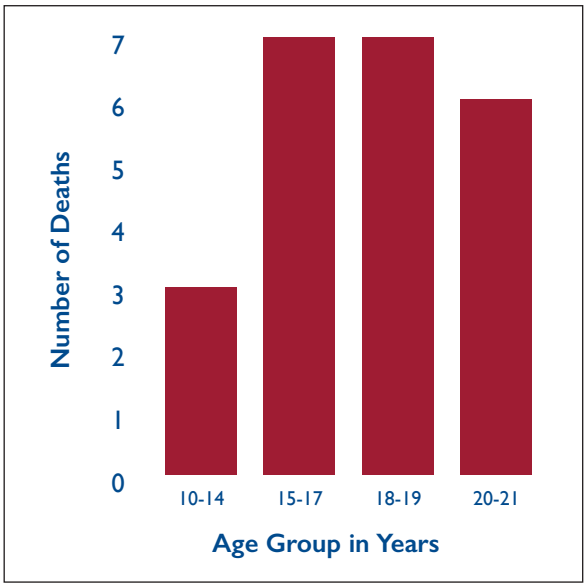

Fig. 2. Number of firearm suicide deaths per age group in Lancaster County (2015-2023). *Data sourced from the Pennsylvania Department of Health Bureau of Family Health and the Lancaster County Child Death Review.*

Limiting access to lethal means, like firearms, can play a significant role in decreasing the risk of suicide. Having a gun in the home, having a gun loaded, and having a gun unlocked are all associated with increased risk for firearm suicide.[7] The Children's Hospital of Philadelphia reports that in homes where there is an unlocked firearm, there is 4-10 times higher risk of suicide.[8]

With a firearm, once the trigger is pulled, there's no turning back; suicide by firearm has a 90% completion rate, making it the quickest and most lethal method of suicide. Easy access to a loaded gun takes away the chance for second thoughts and seeking help, whereas other methods of self-harm often require planning and time, during which many will seek help and thus avoid harm.[9,10]

Evidence suggests that information about safety from trusted health care providers is effective to spark change and compliance. A 2008 study found that brief counseling on safe firearm storage with the distribution of a cable gun lock during routine well-child evaluations yielded a substantial increase in safe storage behavior.[11] A 2016 meta-analysis found that distributing a free locking device was a critical ingredient for compliance.[12]

PROTOCOL

The Lancaster County Child Death Review Committee reviewed data noting that local trends follow national trends (see Fig. 1 on page 99 and Fig. 2 at left). Because there were few measures in place to promote firearm safety, members of the committee began searching for prevention opportunities. This led to the formation of alliances with community partners and a search for program funding.

In January 2024, Penn Medicine Lancaster General Hospital was awarded a grant from the Pennsylvania Department of Health's Bureau of Health Promotion and Risk Reduction to fund the distribution of no-cost gun locks and biometric safes, firearm safety classes, and provider support/education in Lancaster County. See Figs. 3 and 4 at right for information and images of these safe storage options.

The initiative included methods to push out firearm safety messages to the public in general, as well as to specific audiences such as parents and gun owners. The grant is for two years with the option to extend, and the team is being mindful about ways to make these initiatives permanent.

To strengthen the impact, we partnered with two vital organizations:

1. Mental Health America is a national organization with a local chapter whose mission is to promote mental health, as well as prevent and treat mental illness. The goal of this partnership focuses on preventing suicides by firearm through family and provider education and support.
2. The Sheriff's Association of Lancaster County will provide the grant partners with firearm education expertise; specifically, members will act as firearm instructors to teach safety classes. The Lancaster County Sheriff's Office, in addition to other participating police departments, will serve as a public resource to promote the use of gun locks.

These partnerships make this grant unique among firearm safety initiatives by bringing together primary care providers, mental health providers, and law enforcement as educators to prevent firearm deaths. The

Fig. 3. Page 1 of firearm safety brochure to be distributed with cable locks and biometric gun safes.

Fig. 4. Page 2 of firearm safety brochure to be distributed with cable locks and biometric gun safes.

grant will fund several initiatives designed to reach specific populations.

Health care providers who work in primary care, behavioral health, the emergency department, and trauma surgery will be offered education regarding firearm deaths and safety. This may include talking points about guns to debunk frequently disseminated misinformation and will provide guidance about how to remain politically neutral when discussing firearm ownership and safety. In addition, providers will be

given gun locks, along with educational materials regarding proper firearm storage and death prevention, which they can in turn distribute to patients.

Marketing campaigns will be funded across Lancaster County to reach the general population. This may include putting up billboards, setting up media events, and distributing coasters and posters to be placed in bars and pubs. These aspects of the initiative will keep the focus on firearm safety and suicide prevention.

Law enforcement in precincts throughout Lancaster County will be offered mental health first-aid classes, during which they will be provided talking points about firearm safety and suicide prevention. Alongside any gun lock or safe distributed by law enforcement, mental health resources and information on suicide prevention will be distributed.

METRICS

For the duration of the grant period — July 1, 2024, through June 30, 2026 — success will be measured using several metrics:

- Number of health care providers exposed to firearm safety education.
- Number of gun locks and gun safes distributed.
- Number of attendees in firearm safety classes taught by law enforcement.

CONCLUSION

The first safe firearm storage class was conducted in October 2024 with more than 40 attendees from various zip codes in the county. In addition to a biometric gun safe, each attendee was offered the brochure shown in Figs. 3 and 4 on page 101 and additional materials detailing signs of mental health crisis and available mental health resources.

We are hopeful that this initiative, augmenting existing resources and implementing interventions tailored to specific Lancaster County needs, will yield fewer deaths by firearm and save lives here in Lancaster County. If your practice would like to participate by having firearm safety materials and gun locks to distribute, please email the authors.

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ADDITIONAL RESOURCES

Lancaster County Safe Firearm Storage Initiative
mhalancaster.org/suicide-prevention-coalition/gun-lock-project/

Gun Violence: Safe Storage — NAMI
nami.org/Advocacy/Policy-Priorities/Stopping-Harmful-Practices/Gun-Violence-Safe-Storage

Firearm Access Is a Risk Factor for Suicide — Harvard University
means-matter.hsph.harvard.edu/means-matter/risk

Personal Firearms: Programs that Promote Safe Storage and Research on Their Effectiveness
gao.gov/products/gao-17-665

When This Hospital Gave Gun Locks to Families in Crisis, More People Secured Their Firearms — Cincinnati Children's Research Horizons
scienceblog.cincinnatichildrens.org/when-this-hospital-gave-gun-locks-to-families-in-crisis-more-people-secured-their-firearms/

Stigma, Prejudice, and Discrimination Against People with Mental Illness — American Psychiatric Association
psychiatry.org/patients-families/stigma-and-discrimination

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A Guide to Pre-Exposure Prophylaxis (PrEP) and Non-Occupational Post-Exposure Prophylaxis (nPEP) for the Primary Care Physician

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Carr Reese

Sex is a normal part of life. However, health care practitioners often neglect discussions about sexual health.[1] Without such discussions, clinicians cannot adequately assess patients' risk of sexually transmitted infections (STIs) or offer human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) or non-occupational post-exposure prophylaxis (nPEP) to appropriate candidates.

PrEP and nPEP are tools used to combat the acquisition of HIV with the goal of ending the HIV epidemic. Yet prescribing rates remain low, in part because clinicians remain unfamiliar with the clinical guidelines.[2] In this article, we review taking a comprehensive sexual history and summarize the guidelines for prescribing and monitoring PrEP and nPEP. We aim to help clinicians gain the familiarity and confidence needed to prescribe PrEP and nPEP to appropriate candidates.

TAKING A SEXUAL HISTORY

Taking a brief, targeted sexual history is recommended for all adult and adolescent patients as part of ongoing primary care.[3] Barriers such as time constraints and clinician and patient discomfort can hinder collection of comprehensive sexual histories.[1] However, the sexual history provides an important opportunity to discuss behavioral risks and mitigation strategies, and to determine appropriate STI screening.[1]

Despite the importance of taking a comprehensive sexual history, only 56% of surveyed primary care physicians feel adequately trained to take a sexual history. Moreover, only 58% reported asking about sexual activity at routine visits.[1]

Clinicians also exhibit bias when taking sexual histories. For example, clinicians take sexual histories at higher rates in female and Black patients, those on Medical Assistance, and those presenting for STI-related concerns.[4] Conversely, clinicians take fewer sexual histories in older adults, although 54% of adults aged 65-80 years in romantic relationships report being sexually active.[4,5] Additionally, younger clinicians take fewer sexual histories in older patients, compared to their older colleagues. Relying on demographics alone in risk stratification can lead to missed opportunities for care or, conversely, the over-medicalization of normal behavior.

As the prevalence of STIs reaches historic highs in the United States, the importance of a framework for routinely obtaining comprehensive sexual histories cannot be overstated.[3] The Centers for Disease Control and Prevention (CDC) recommends utilizing the "Five Ps" as a standardized strategy for eliciting key information about patients' sexual histories. These include information about patients' partners, practices, protection from STIs, history of STIs, and prevention of pregnancy.[3] The Five Ps help keep a comprehensive sexual history simple and organized. (Refer to the Fall 2023 *JLGH* article, "Updates in the Treatment of Sexually Transmitted Diseases," for a more detailed discussion about the Five Ps.[6])

PRE-EXPOSURE PROPHYLAXIS

A comprehensive sexual history helps identify patients at increased risk of acquiring HIV who may benefit from PrEP. The U.S. Preventive Services Task Force (USPSTF) recommends clinicians offer PrEP to all sexually active adults and adolescents at substantial risk of acquiring HIV (see Fig. 1 on page 104).[7]

The USPSTF also recommends clinicians offer PrEP to people who have injected drugs (PWID) in the past six months and share injection equipment.[7] Not only does PrEP mitigate the risk of HIV transmission,

Individuals who have had vaginal or anal sex in the past 6 months AND any of the following:
≥ One sexual partner(s) with unknown HIV status and inconsistent condom use
HIV+ partner with unknown or detectable viral load
A recent bacterial sexually transmitted infection (STI) in the past 6 months
OR the following alone:
People who have injected drugs (PWID) in the past 6 months and share injection drug equipment

Fig. 1. Identifying substantial risk for HIV acquisition. *Source: USPSTF.*[7]

but a PrEP office visit provides an opportunity to discuss patients' mental health, provide referrals to behavioral health specialists or drug treatment centers, and offer medications for opioid use disorder.[8]

Initiation

For patients who are interested in starting or restarting PrEP and meet the eligibility criteria, the first step is to rule out a current HIV infection through laboratory testing and a review of systems.[8] The appropriate HIV laboratory test to rule out current infection depends on whether a patient has recently taken antiretroviral medications.[8]

Antiretrovirals used for PrEP can suppress early viral replication, which can delay development and detection of antibodies to HIV (seroconversion). Thus, if exposed to oral antiretrovirals in the past three months or injectable antiretrovirals within the past 12 months, it is important to obtain both an HIV antigen/antibody (Ag/Ab) test *and* an HIV viral load (HIV RNA).[8]

In contrast, for individuals without recent exposure to antiretroviral therapy, a combination HIV Ag/Ab test is sufficient. Clinicians can use the algorithms in Figs. 2 and 3 from the CDC's 2021 PrEP clinical practice guideline to confidently determine the HIV status of a patient interested in PrEP.[8]

The detection of acute HIV prior to starting PrEP is crucial to prevent the development of drug-resistant virus strains; PrEP is sufficient to prevent but not treat HIV, and clinical trials reveal drug-resistant virus can emerge in individuals who start PrEP with unrecognized acute HIV infection.[8-10] Acute infections may not be picked up by HIV screening tests during the window period. The window period refers to the time between potential exposure to HIV and the point when tests can reliably detect the virus or the body's response to it.

The duration of the window period varies depending on the type of test used, with viral load (RNA) capable of detecting infection earlier than Ag/Ab tests (10 to 33 days versus 18 to 45 days after exposure, respectively).[11] If patients report symptoms of acute HIV, further history (e.g., recent exposures) should be elicited prior to prescribing PrEP. Common symptoms of acute infection include fever, fatigue, myalgia, skin rash, headache, pharyngitis, cervical adenopathy, arthralgia, night sweats, and diarrhea.[12]

Clinicians should test all individuals starting PrEP for syphilis, gonorrhea, and chlamydia based on sites of sexual activity (oropharyngeal, urine/endocervical, and/or rectal). Reduced renal function impacts medication selection, so a serum creatine needs to be measured.

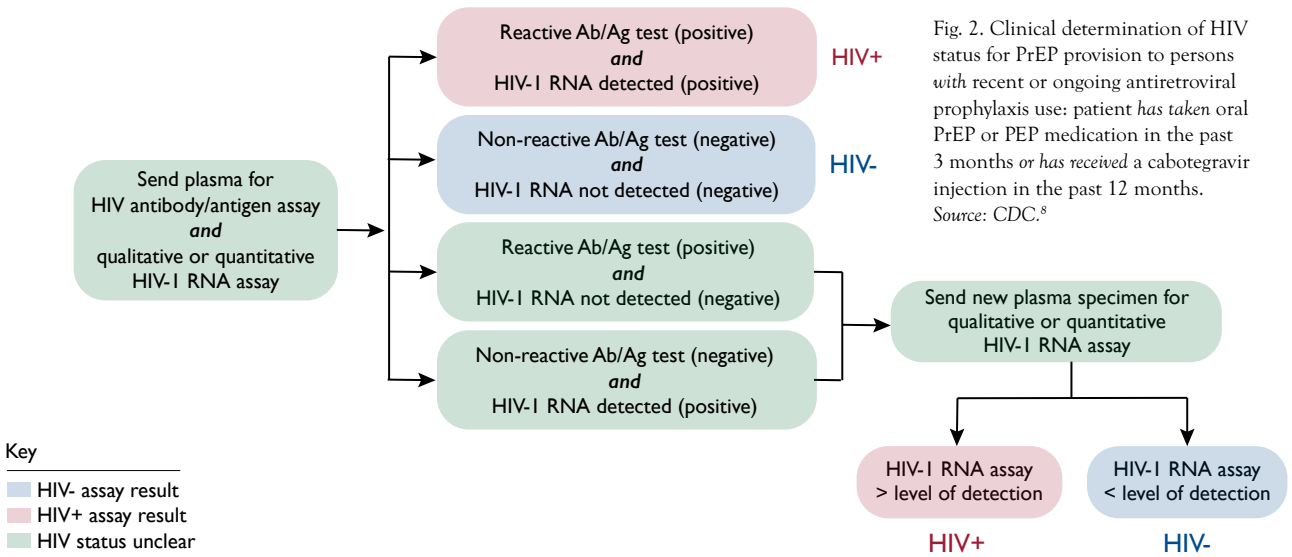

Fig. 2. Clinical determination of HIV status for PrEP provision to persons *with* recent or ongoing antiretroviral prophylaxis use: patient *has taken* oral PrEP or PEP medication in the past 3 months *or has received* a cabotegravir injection in the past 12 months. *Source: CDC.*[8]

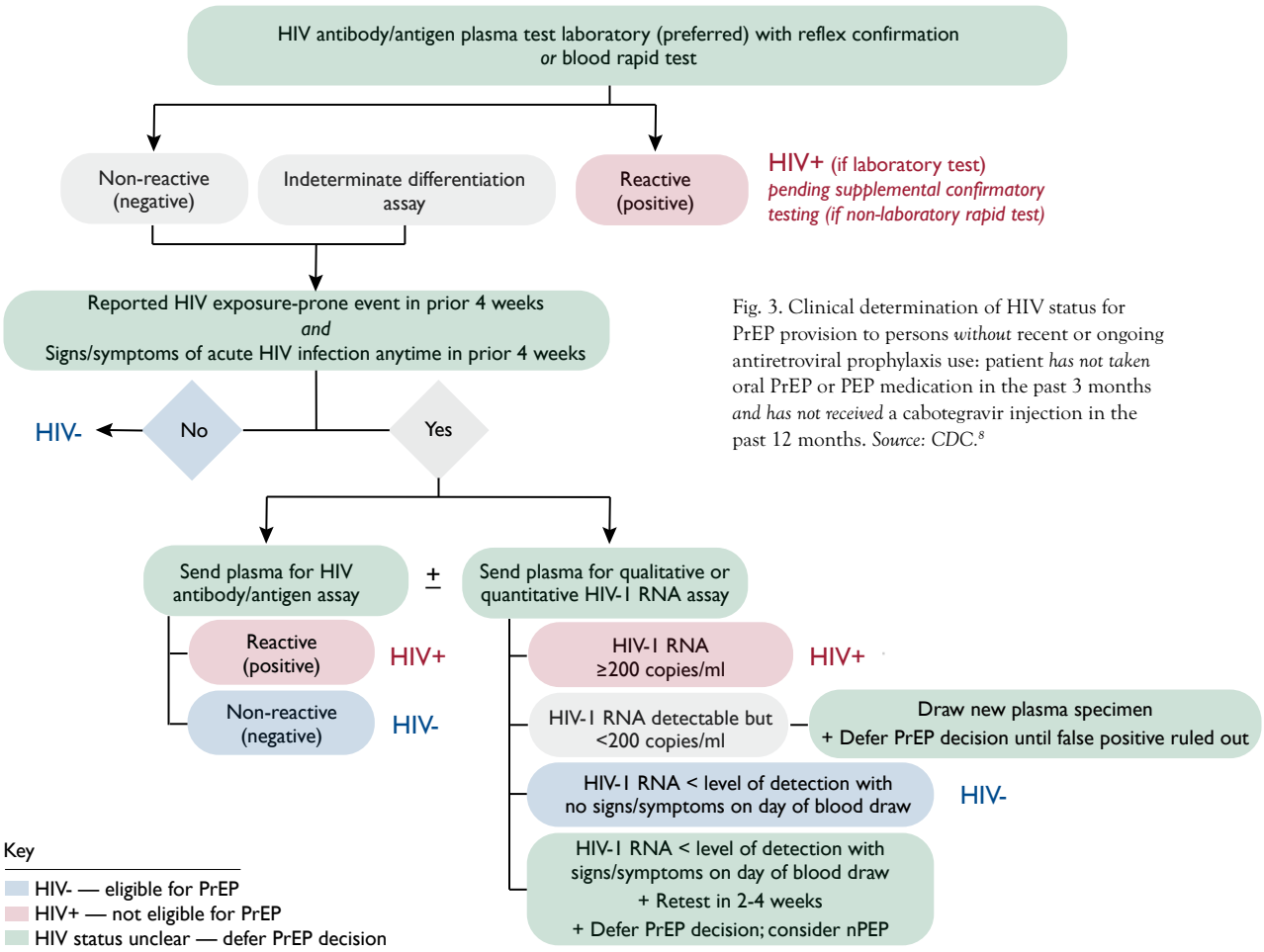

Fig. 3. Clinical determination of HIV status for PrEP provision to persons *without* recent or ongoing antiretroviral prophylaxis use: patient *has not taken* oral PrEP or PEP medication in the past 3 months *and has not received* a cabotegravir injection in the past 12 months. *Source: CDC.*[8]

Hepatitis B and C testing should be conducted, as co-infection with HIV is not uncommon due to shared routes of transmission.[8] Hepatitis B screening is of particular importance as some medications used for PrEP (tenofovir and emtricitabine) are also used to treat hepatitis B.[8] These medications suppress hepatitis B viral replication, but do not cure infection, and pose a risk of a hepatitis flare upon PrEP discontinuation.[8]

Medication Options for PrEP

The Food and Drug Administration (FDA) approved tenofovir disoproxil fumarate (300 mg/day)/emtricitabine (200 mg/day) (Truvada®) as the first oral PrEP medication for adults in 2012. In 2018, approval was expanded to include adolescents weighing at least 35 kg.[13] It is highly efficacious in preventing HIV in all populations.[14] Headache, abdominal pain, and decreased weight are common side effects.[15-17]

The long-term safety concerns with this medicine include decreased bone mineral density and mildly decreased kidney function, thus it should not be initiated if the creatinine clearance (CrCl) <60 mL/min. Recent studies demonstrate that these changes are usually reversible after medication cessation.[18] Tenofovir disoproxil fumarate/emtricitabine is available in generic form.

In 2019, the FDA approved tenofovir alafenamide (25 mg/day)/emtricitabine (200 mg/day) (Descovy®) for PrEP.[19] It has similar efficacy to tenofovir disoproxil fumarate/emtricitabine and is safer to use in those with renal dysfunction. It can be initiated with a CrCl ≥30 mL/min.[14] Mild increases in low-density lipoprotein (LDL) and weight have been observed with use of this medication.[16] Tenofovir alafenamide is only approved as PrEP for men who have sex with men (MSM) and transgender women (TGW).[16] Common side effects include diarrhea, nausea, and mild weight gain.[16,20] There is no generic formulation available.

Cabotegravir (600 mg/injection) (Apretude®), the first injectable PrEP medication, was approved by the FDA in 2021.[21] It is an excellent option for individuals who struggle with taking daily pills, as injection is

only needed every two months for maintenance.[21] Additionally, it is a good choice for those who are intolerant of oral regimens or who have more severe kidney disease as it can be used with a CrCl <30 mL/min.[16]

Cabotegravir is the most effective form of PrEP, likely attributable to patients' lack of compliance with prescribed oral medications.[22] However, cabotegravir has a "long tail" of up to 12 months, meaning it can remain in the body at detectable, but not necessarily therapeutic, levels for long periods of time.[23] This long tail can breed drug resistance in patients who miss doses or who discontinue the medication but have ongoing risk.[24,25] There is no generic formulation available.

All regimens have demonstrated efficacy and safety, and the choice depends on individual patient factors.[16] See Table 1 for a side-by-side comparison of PrEP medications.

PrEP Protective Efficacy

Although there is no consensus on the drug concentrations in different body tissues associated with protection from HIV acquisition, pharmacokinetics studies have assessed the relationship of PrEP dosing frequency to HIV protective efficacy.[26-28] These studies suggest the rectal or vaginal mucosa concentrations of tenofovir disoproxil fumarate +/- emtricitabine that correlate with HIV protectivity.[26-28]

In one study, tenofovir concentrations were found to be significantly higher in the rectal mucosa with fewer weekly doses compared with the female genital tract.[27] This finding suggests patients who have a female genital tract need greater compliance to achieve protectivity.[27] In another study of tenofovir concentrations in MSM, HIV risk reduction was estimated to be 76% for patients taking two doses per week, 96% for patients taking four doses per week, and 99% for patients taking seven doses per week.[28] Thus, perfect compliance is likely not necessary to confer protection in MSM, but increased compliance rates confer more protectivity.[26,28] Similar pharmacokinetics data are not currently available for tenofovir alafenamide or cabotegravir.[8]

CDC guidance states that oral PrEP reaches maximum protection from HIV for receptive anal sex (bottoming) after about seven days of daily use.[29] For receptive vaginal sex and injection drug use, oral PrEP reaches maximum protection at about 21 days of daily use.[29] There are no sufficient data available on the time required for oral or injection PrEP to reach maximum protection for insertive anal sex (topping) or insertive vaginal sex.[29]

On Demand or 2-1-1 PrEP

For MSM and TGW, there is an alternative to a daily dosing regimen. The 2-1-1 or "on-demand" dosing regimen involves taking two tablets of tenofovir disoproxil fumarate/emtricitabine 2-24 hours before anticipated sexual activity, followed by one tablet daily for the next two days (see Fig. 4).[30] This method aims to provide HIV protection during times of increased risk, with the benefit of reducing the total number of pills taken compared to daily PrEP.

Individuals who benefit most from the 2-1-1 dosing strategy are those who have infrequent, but some-

Table 1. Comparison of Medications Used for PrEP

	Tenofovir disoproxil fumarate	Tenofovir alafenamide	Cabotegravir
Who can use?	All exposures, including sexual and injection drug use	Sexual exposures in cisgender men, TGW, and adolescents weighing ≥35 kg	Sexual exposures in all adults and adolescents weighing ≥35 kg
Exclusions	Approved in all populations; should not use with CrCl <60 mL/min	Not approved for those exposed through receptive vaginal sex or PWID; should not use with CrCl <30 mL/min	Not approved for PWID
Safety concerns	Potential decrease in renal function and bone mineral density	Small increase in LDL	Long medication tail
Side effects	Headache, abdominal pain, and decreased weight are common side effects	Diarrhea, nausea, headache, fatigue, abdominal discomfort, mild weight gain	Mild weight gain Mild injection site reaction, usually improves with time
Dosing	Daily or on demand	Daily only	Optional 30-day oral lead-in, followed by first injection First two injections given 4 weeks apart; thereafter, dosed every 2 months
Used to treat hepatitis B?	Yes	Yes	No
Generic available?	Yes	No	No

TGW = transgender women; CrCl = creatinine clearance; PWID = persons who inject drugs; LDL = low-density lipoprotein

Adapted from Vail et al.[16]

what planned, sexual activity or who have challenges with daily medication adherence. It does require a high level of engagement and awareness of potential sexual activity to ensure efficacy. Two large randomized clinical trials, IPERGAY and Prevenir, have demonstrated protective efficacy with the 2-1-1 dosing regimen.[31-33] When administered as instructed, tenofovir disoproxil fumarate/emtricitabine had a relative reduction of 86% in the risk of HIV-1 infection in the population studied.[31] Although on-demand dosing is not FDA approved at this time, the International Antiviral Society-USA endorses it as an optional dosing method.[34]

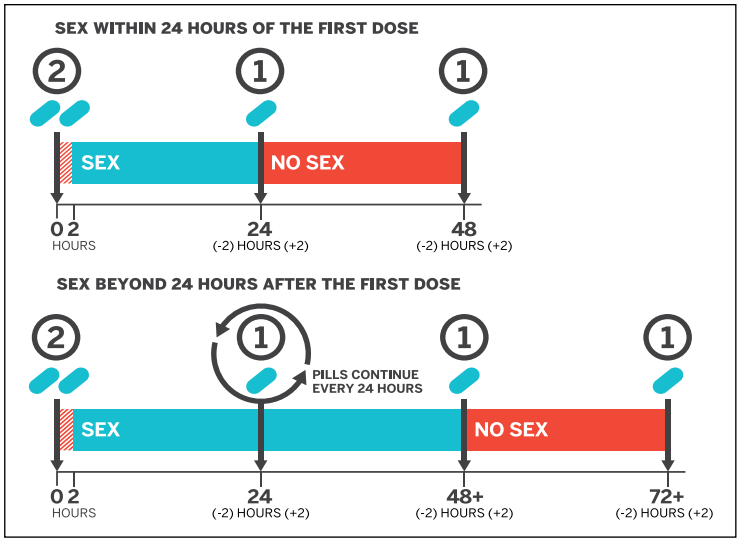

Fig. 4. Visual representation of the PrEP 2-1-1 dosing. *Source: San Francisco AIDS Foundation.*[30] *Used with permission.*

Same-Day PrEP Initiation

Most patients can start PrEP the same day as their appointment, while their labs are in process. A 2019 study demonstrated same-day prescribing is both safe and convenient.[35] Almost 80% of same-day start study participants came to at least one follow-up appointment, and 100% reported they liked having the option for a same-day start.[35]

Shortening the time to initiate PrEP is useful for patients with time constraints, significant barriers to returning to clinic, or those at high risk for HIV acquisition between visits.[8] Candidates for same-day starts should have access to a clinic with the following capabilities:

- Immediately able to draw necessary lab tests.
- Can assist uninsured or underinsured patients in obtaining health insurance or copayment assistance.
- Can provide rapid follow-up contact for patients whose laboratory test results indicate HIV infection or renal dysfunction.
- Can provide scheduled follow-up care appointments.
- Have clinicians available to dispense or prescribe oral PrEP medication.

However, same-day PrEP initiation is not appropriate for everyone. Patients who are ambivalent about starting PrEP, unable to undergo necessary laboratory testing, exhibit signs of acute HIV infection, have a history of renal disease, lack insurance or payment means for medication, or do not have reliable contact information for follow-up are not suitable candidates.[8]

PrEP Monitoring

Patients taking oral PrEP should follow-up every three months.[8] At these visits, clinicians should conduct repeat HIV screening, assess medication compliance, and continue to discuss additional risk-reduction strategies.[8] It should be noted that taking PrEP is an incredibly important risk-reduction strategy for which patients should be commended.

Repeat STI screening should be conducted for MSM and TGW every three months, and every six months for all sexually active individuals on PrEP.[8] Clinicians should check serum creatinine — every six months for individuals aged ≥50 years or with a CrCl <90 mL/min, and every 12 months for individuals aged <50 years with a CrCl >90 mL/min.[8] For individuals on tenofovir alafenamide, a yearly lipid panel is recommended.[8] See Table 2 on page 108 for a full laboratory monitoring schedule.

All patients receiving injectable cabotegravir for PrEP should return one month after their first injection for repeat HIV viral load testing. Starting after the second injection, patients should return every two months for repeat HIV viral load testing and cabotegravir injection. Unlike oral PrEP, patients receiving injection therapy do not need routine creatinine, lipids, and hepatitis serologies monitoring unless these values have previously been noted to be abnormal. Screen for bacterial STIs per Table 2 on page 108.[8]

NON-OCCUPATIONAL POST-EXPOSURE PROPHYLAXIS

Occupational post-exposure prophylaxis (PEP) emerged in the 1990s as a safe and effective intervention for preventing HIV acquisition in health care workers exposed to HIV-contaminated blood or body fluids. It reduced transmission rates in one study by as much as 81%.[36,37]

Table 2. Timing of PrEP-Associated Laboratory Tests[8]

Oral PrEP-Associated Laboratory Tests

Test	Screening/Baseline Visit	Q3 months	Q6 months	Q12 months	When Stopping PrEP
HIV test	X	X			X
eCrCl	X		If age ≥50 or eCrCl <90 ml/min at PrEP initiation	If age <50 or eCrCl ≥90 ml/min at PrEP initiation	X
Syphilis	X	MSM/TGW	X		MSM/TGW
Gonorrhea	X	MSM/TGW	X		MSM/TGW
Chlamydia	X	MSM/TGW	X		MSM/TGW
Lipid panel (F/TAF)	X			X	
Hep B serology	X				
Hep C serology	MSM, TGW, and PWID only			MSM, TGW, and PWID only	

Injectable PrEP-Associated Laboratory Tests

Test	Initiation Visit	1 month visit	Q2 months	Q4 months	Q6 months	Q12 months	When Stopping CAB
HIV*	X	X	X	X	X	X	X
Syphilis	X			MSM/TGW only	Heterosexually active women and men only		MSM/TGW only
Gonorrhea	X			MSM/TGW only	Heterosexually active women and men only	X	MSM/TGW only
Chlamydia	X			MSM/TGW only	MSM/TGW only	Heterosexually active women and men only	MSM/TGW only

X = all PrEP patients; eCrCl = estimated creatinine clearance; MSM = men who have sex with men; TGW = transgender women; F/TAF = emtricitabine and tenofovir alafenamide; PWID = persons who inject drugs
** HIV-1 RNA assay*

However, it is important to note that no prospective randomized placebo controlled clinical trials exist to evaluate the efficacy of *non*-occupational PEP (antiretroviral therapy use after HIV exposure through sexual contact or injection drug use). Instead, recommendations for nPEP are extrapolated from observational and animal studies.[37,38]

Candidacy for nPEP

Prompt evaluation of individuals potentially exposed to HIV is paramount. The 2016 CDC and Department of Health and Human Services nPEP Guidelines[38] recommend offering nPEP to individuals who meet all the following:

- Patient has had exposure with substantial risk for HIV acquisition (defined in Fig. 5).
- Patient presents to care within 72 hours of the exposure.
- Known source individual is HIV positive.

If the source individual's HIV status is unknown, nPEP can be offered on a case-by-case basis.[38]

Locally, the Penn Medicine Lancaster General Health Emergency Department has three-day supplies of nPEP medications to give to patients, who can then follow-up for the rest of their medication and testing with their primary care clinician, or if that is not possible, with the STI clinic at LGHP Comprehensive Care. nPEP is not recommended for negligible risk exposures (defined in Fig. 5) or if the patient presents >72 hours after the exposure.[38]

Laboratory Evaluation

The CDC recommends clinicians check baseline labs from both the source and exposed individuals prior to prescribing nPEP. Laboratory evaluation should include tests for HIV antigen/antibody, hepatitis B serologies (surface antigen, surface antibody, and core antibody), hepatitis C serology (hepatitis C antibody), and STI screening (gonorrhea, chlamydia, syphilis).[38] For exposed individuals, obtain serum creatinine, liver function tests, and a pregnancy test for anyone with childbearing potential.

If the source individual is known to be HIV positive, obtain a viral load and genotype.[38] Clinicians should repeat labs at the four- to six-week, three-month, and six-month marks to monitor for delayed seroconversion. See Table 3 on page 110 for full testing recommendations from the CDC.

Medication Options for nPEP

Strong evidence identifying an optimal combination of antiretroviral medication for nPEP is lacking. Consequently, CDC-recommended nPEP regimens are based on expert opinion and observation of drug efficacy, tolerance, and adherence.[37,38]

The CDC recommends a three-drug regimen be utilized because it maximizes viral suppression and confers greater protection from drug-resistant virus.[38] The preferred three-drug regimen for adults and adolescents aged ≥13 years consists of a 28-day course of tenofovir disoproxil fumarate (300 mg/day) + emtricitabine (200 mg/day) + either raltegravir (400 mg twice daily) or dolutegravir (50 mg/day).[38] Dolutegravir has the benefit of daily dosing, whereas raltegravir is dosed twice daily, which may present a challenge for some patients. Common side effects of this regimen include nausea, vomiting, diarrhea, fatigue, headaches, and insomnia.[38]

The preferred regimen cannot be used with CrCl <60 mL/min due to safety concerns with the tenofovir disoproxil fumarate component. The alternative regimen recommended by the CDC for individuals with impaired renal function is renally dosed zidovudine and lamivudine + either raltegravir or dolutegravir (dosing as above).[38] However, it is important to note that newer medications with better safety profiles and tolerability have become available since the CDC nPEP guidelines were published in 2016.

Tenofovir alafenamide (25 mg/day)/emtricitabine (200 mg/day) (Descovy®) was approved by the FDA for PrEP less than six months before the nPEP guidelines were published. Many clinicians now prescribe Descovy® in place of tenofovir disoproxil fumarate/emtricitabine (Truvada®) in the preferred 28-day nPEP regimen, as it can be used to a CrCl ≥30 mL/min.[39,40]

Growing evidence further suggests that the single-tablet regimen of tenofovir alafenamide (25 mg/day) + emtricitabine (200 mg/day) + bictegravir (50 mg/day) (Biktarvy®) is an effective and more tolerable option for nPEP than older agents.[41,42] Consequently, some clinicians have begun offering it for this purpose for the standard 28-day course. However, it is important to note that Biktarvy® and tenofovir alafenamide are not currently FDA approved for nPEP.

Further research is needed to explore and evaluate new medications for nPEP to ensure their safety, efficacy, and tolerability in preventing HIV infection.

Duration

Exposed individuals should continue nPEP until the source patient's HIV status is confirmed. If negative, they can stop the medication.

If the source patient is known or found to have HIV and has a detectable or unknown viral load, the exposed individual should continue nPEP for a 28-day course.[43]

FINANCIAL COVERAGE FOR PrEP AND nPEP

When PrEP first became available, its high cost (approximately $1,800 per month) limited access to only a fraction of eligible individuals.[44] However, in 2019, the USPSTF granted PrEP a grade A recommendation, meaning it is strongly recommended to

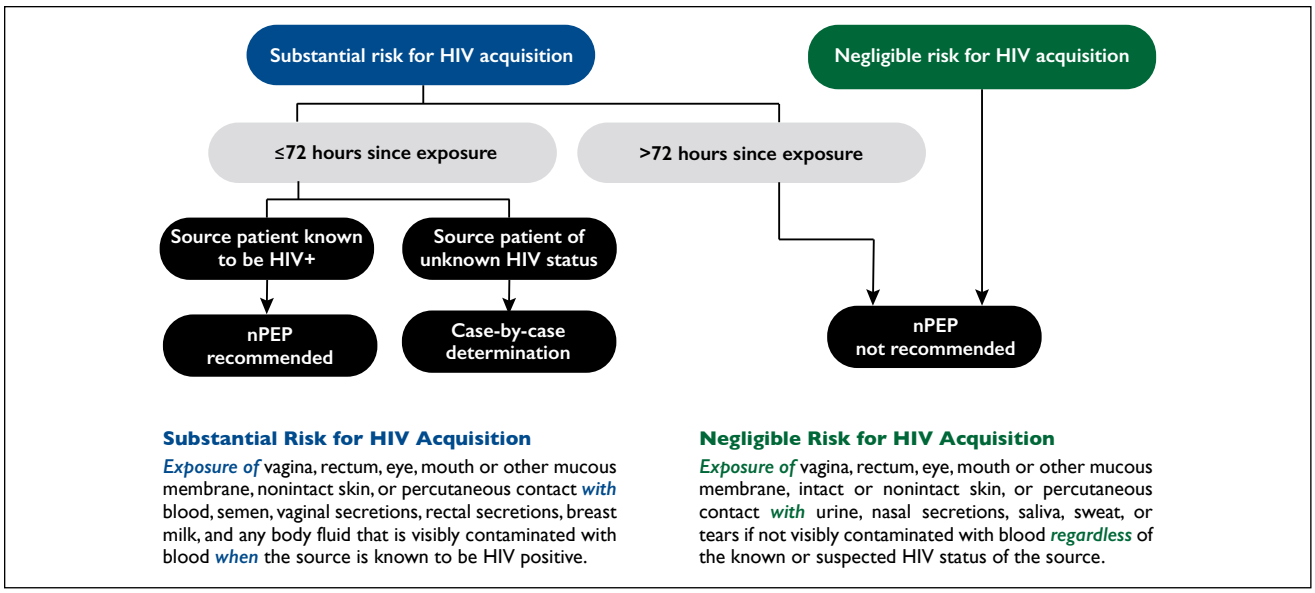

Fig. 5. Algorithm for evaluation and treatment of possible non-occupational HIV exposures. *Source: CDC.*[38]

eligible patients.[45] Preventive services with an A or B recommendation from the USPSTF are covered by most insurers without cost sharing.[46] The Affordable Care Act further ensures comprehensive PrEP coverage under most insurance plans and state Medicaid programs, making PrEP accessible at no cost to many individuals.[47]

In Pennsylvania, Medicaid covers PrEP- and nPEP-associated laboratory testing and medications.[47,48] For individuals with private insurance, medication co-pay assistance programs are available through Gilead Sciences and ViiVConnect to pay for Descovy® and Apretude®, respectively.[48] The national Ready, Set, PrEP program covers the cost of Truvada® and Descovy® for individuals without insurance.[8]

Locally, free PrEP-associated laboratory testing for individuals without insurance is available at the STI clinic at LGHP Comprehensive Care, located at 554 N. Duke Street in Lancaster, through a state-funded provider agreement. If nPEP medication access is an issue, clinicians can contact LGHP Comprehensive Care at 717-544-4943 to request a limited supply.

Table 3. CDC Testing Recommendations Prior to nPEP Consideration[38]

	Source	Exposed Persons			
	Baseline	Baseline	4-6 weeks after exposure	3 months after exposure	6 months after exposure
Test		For all persons considered for or prescribed nPEP for any exposure			
HIV Ag/Ab testing[a] (or antibody testing if Ag/Ab test unavailable)	√	√	√	√	√ [b]
Hepatitis B serology, including: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody	√	√	—	—	√ [c]
Hepatitis C antibody test	√	√	—	—	√ [d]
		For all persons considered for or prescribed nPEP for sexual exposure			
Syphilis serology[e]	√	√	√	—	√
Gonorrhea[f]	√	√	√ [g]	—	—
Chlamydia[f]	√	√	√ [g]	—	—
Pregnancy[h]	—	√	√	—	—
		For all persons prescribed tenofovir DF + emtricitabine + raltegravir *or* tenofovir DF + emtricitabine + dolutegravir			
Serum creatinine (for calculating estimated creatinine clearance[i])		√	√	—	—
Alanine transaminase, aspartate aminotranferase		√	√	—	—
		For all persons with HIV infection confirmed at any visit			
HIV viral load		√	√ [j]		
HIV genotypic resistance		√	√ [j]		

Ag/Ab = antigen/antibody combination test; HIV = human immunodeficiency virus; nPEP = non-occupational postexposure prophylaxis; tenofovir DF = tenofovir disoproxil fumarate.

[a] *Any positive or indeterminate HIV antibody test should undergo confirmatory testing of HIV infection status.*

[b] *Only if hepatitis C infection was acquired during the original exposure; delayed HIV seroconversion has been seen in persons who simultaneously acquire HIV and hepatitis C infection.*

[c] *If exposed person susceptible to hepatitis B at baseline.*

[d] *If exposed person susceptible to hepatitis C at baseline.*

[e] *If determined to be infected with syphilis and treated, should undergo serologic syphilis testing 6 months after treatment.*

[f] *Testing for chlamydia and gonorrhea should be performed using nucleic acid amplification tests. For patients diagnosed with a chlamydia or gonorrhea infection, retesting 3 months after treatment is recommended.*
- *For men reporting insertive vaginal, anal, or oral sex, a urine specimen should be tested for chlamydia and gonorrhea.*
- *For women reporting receptive vaginal sex, a vaginal (preferred) or endocervical swab or urine specimen should be tested for chlamydia and gonorrhea.*
- *For men and women reporting receptive anal sex, a rectal swab specimen should be tested for chlamydia and gonorrhea.*
- *For men and women reporting receptive oral sex, an oropharyngeal swab should be tested for gonorrhea.*

[g] *If not provided presumptive treatment at baseline, or if symptomatic at follow-up visit.*

[h] *If woman of reproductive age, not using effective contraception, and with vaginal exposure to semen.*

[i] *eCrCl = estimated creatinine clearance calculated by the Cockcroft-Gault formula: eCrClCG = [(140 - age) x ideal body weight] + (serum creatinine x 72)(x 0.85 for females).*

[j] *At first visit where determined to have HIV infection.*

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Anti-Obesity Pharmacotherapy Review

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Obesity is a complex chronic condition with a steady increase in prevalence in the United States from 30.5% to 41.9% since the year 2000.[1] Obesity is linked to many complications including cardiovascular disease, stroke, diabetes, and certain cancers, which can, in turn, increase the estimated cost and burden of disease. Treatment of obesity means understanding the chronic nature of the condition and that there is a natural tendency to regain weight.[2] This is due to hormonal changes that occur following weight loss and adaptation of metabolism while in a calorie deficit.[2] As such, the presence of excess weight and obesity and prevention of weight gain should be considered in treatment decisions and prior to medication initiation.

Many medication classes are associated with weight gain or metabolic risks, including certain anticonvulsants (e.g., valproic acid, carbamazepine, gabapentin, pregabalin), antipsychotics (e.g., clozapine, olanzapine, quetiapine, risperidone), antidepressants (e.g., mirtazapine, tricyclic antidepressants), antihyperglycemic agents (e.g., insulin, sulfonylureas, thiazolidinediones), hormones, antihistamines, and glucocorticoids.[3] Although full discussion of the metabolic adverse effects of medications is outside the scope of this review, it is important to consider lower-risk medications when possible. For example, consider utilizing lower metabolic risk antipsychotics such as aripiprazole, lurasidone, and ziprasidone or utilizing agents that promote weight loss in type 2 diabetes such as metformin, glucagon-like peptide-1 (GLP-1) receptor agonists, and GLP-1/glucose-dependent insulinotropic polypeptide (GIP) dual receptor agonists when appropriate.[4,5]

Lifestyle interventions, including calorie deficit and physical activity, are recommended as first-line treatment for excess weight and obesity and should be addressed at every visit. Given the physiological changes noted above, caloric intake may need to be adjusted as weight loss occurs. The ultimate goal of weight loss is to optimize patient health outcomes; total body weight loss goals differ based on comorbidities.[2] For example, 5% to 15% total body weight loss is recommended for overweight or obese persons with type 2 diabetes, hypertension, or dyslipidemia, while up to 40% is recommended for metabolic dysfunction-associated steatohepatitis (see Table 1).[2]

The 2016 American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) Clinical Practice Guidelines for Obesity and the 2022 American Gastroenterological Association (AGA) Clinical Practice Guideline on Pharmacological Interventions for Adults with Obesity recommend that pharmacotherapy be considered in combination with lifestyle interventions in patients with a body mass index (BMI) ≥27 kg/m2 with weight-related comorbidities (diabetes, hypertension, dyslipidemia, etc.) or with a BMI ≥30 kg/m2.[2,6] These guidelines provide a comprehensive summary of weight management agents, although newer agents have become available since publishing.

Currently approved agents for weight management include anorexiants (e.g., phentermine, diethylpropion), orlistat, phentermine/topiramate extended release (ER), naltrexone/bupropion ER, liraglutide, semaglutide, and tirzepatide. Initial pharmacotherapy choice should be based on patient preferences and existing comorbidities, as well as contraindications and prescribing considerations such as those listed in Table 2 on pages 115-116. Medications such as setmelanotide for obesity due to specific genetic disorders are not included in this review.

Orlistat is an oral agent that decreases the intestinal absorption of dietary fat and is available both over-the-counter (alli®) and via prescription (Xenical®). In the Xenical® in the Prevention of Diabetes in Obese Subject (XENDOS) trial, treatment with orlistat 120 mg three times daily for one year resulted in weight loss of 10.6 kg compared to 6.2 kg with placebo ($p < 0.001$).[7] A significantly greater reduction in weight with orlistat compared to placebo was sustained after four years of treatment, 5.8 kg versus 3.0 kg, respectively. Due to its

mechanism of action, it must be used in combination with a low-fat diet (≤30% of daily calories from fat) to reduce gastrointestinal adverse events, and therapy with this agent necessitates use of a multivitamin that includes fat-soluble vitamins (A, D, E, K, and beta carotene) taken at least two hours before or after orlistat.

Gastrointestinal adverse reactions including bowel urgency and frequency, oily evacuation and rectal leakage, and flatulence with discharge can be bothersome. Given the small magnitude of benefit and risk of adverse reactions, the AGA guidelines suggest against the use of orlistat for patients who have excess weight or obesity.[6]

Phentermine and topiramate ER (Qsymia®) is a combination medication approved for chronic weight management. Phentermine is a sympathomimetic agent that decreases appetite through direct central nervous system stimulation, and topiramate acts by decreasing appetite and increasing satiety.[2] In a 56-week trial, patients with a BMI of at least 27 kg/m2 and two or more comorbidities (hypertension, dyslipidemia, diabetes, etc.) had a significant mean weight loss of 9.8% with phentermine/topiramate 15/92 mg per day versus 1.2% with placebo.[8] After 108 weeks of treatment, participants had a mean weight loss of 10.5% with the combination versus 1.8% with placebo (p <0.0001).[9]

Table 1. **Guideline-Recommended Weight-Loss Goals**
(for patients with excess weight or obesity and the listed comorbidity)

Comorbidity	Recommended Weight Loss
Metabolic syndrome	10%
Prediabetes	10%
Type 2 diabetes mellitus	≥5-15%
Dyslipidemia	≥5-15%
Hypertension	≥5-15%
Metabolic dysfunction-associated steatotic liver disease	≥5%
Metabolic dysfunction-associated steatohepatitis	10-40%
Polycystic ovary syndrome	≥5-15%
Female infertility	≥10%
Male hypogonadism	≥5-10%
Obstructive sleep apnea	≥7-11%
Asthma/reactive airway disease	≥7-8%
Osteoarthritis	≥10% ≥5-10% when coupled with exercise
Urinary stress incontinence	≥5-10%
Gastroesophageal reflux disease	≥10%

Based on the 2016 American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines.[2]

Additionally, about 70% of patients treated with phentermine/topiramate 15/92 mg per day achieved at least 5% weight loss after 56 weeks.[8,10] Phentermine/topiramate is a schedule IV controlled substance with a risk of dependence and misuse. It is only available through the Qsymia® Risk Evaluation and Mitigation Strategy (REMS) program due to the risk of birth defects and congenital malformations.

Naltrexone/bupropion ER (Contrave®) is another combination agent that works on the appetite regulatory center in the brain to decrease food cravings and appetite.[2] The Contrave Obesity Research trials (COR-I and COR-II) included participants with a BMI of ≥27 kg/m2 with controlled hyperlipidemia and/or hypertension or a BMI of ≥30 kg/m2 for 56 weeks.[11,12] Participants in the COR-I trial receiving naltrexone/bupropion ER 32/360 mg per day lost 6.1% of total body weight compared to 1.3% with placebo (p <0.0001).[11] Similarly, participants in the COR-II trial receiving naltrexone/bupropion ER 32/360 mg per day lost 6.4% of total body weight compared to 1.2% with placebo (p <0.001).[12]

In the COR Intensive Behavior Modification trial, all treated patients received an intensive behavioral modification (BMOD) program in addition to naltrexone/bupropion ER or placebo. The intensive BMOD program included 28 group sessions that reviewed patients' eating and activity logs, meal planning, problem solving, stimulus control, and other weight control topics. Intensive BMOD in combination with naltrexone/bupropion ER led to a significantly greater reduction in total body weight of 9.3% versus 5.1% with placebo.[13] Naltrexone/bupropion ER should be avoided in those with bipolar disorder, seizure disorders, history of anorexia, or with uncontrolled hypertension. Due to the naltrexone component, it must be avoided in patients taking chronic opioid therapy.[2]

Liraglutide (Saxenda®) and semaglutide (Wegovy®) are both GLP-1 receptor agonists that increase satiety and decrease appetite. In the Semaglutide Treatment Effect in People with Obesity (STEP-1) trial, once-weekly semaglutide 2.4 mg resulted in a statistically significant mean weight loss of 14.9% versus 2.4% with placebo at week 68.[14] In the SCALE Obesity and Prediabetes trial, liraglutide 3 mg daily versus placebo

for 56 weeks resulted in a statistically significant mean total body weight reduction of 8.0% versus 2.6%.[15] Between these two agents, semaglutide may be the preferred option given the once-weekly dosing and increased efficacy compared to liraglutide. The STEP-8 trial[16] demonstrated that after 68 weeks, semaglutide use resulted in a mean weight loss of 15.8% compared to 6.4% with liraglutide (p <0.001).

Semaglutide may also be preferred given the recently expanded labeling for cardiovascular risk reduction, which was the result of the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial.[17] Semaglutide (Wegovy®) 2.4 mg once weekly resulted in a 20% relative risk reduction over 40 months in the composite cardiovascular end point (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in patients with established cardiovascular disease (CVD) on standard of care therapies (i.e., lipid-lowering therapy, beta blocker, antiplatelet, and/or angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker).

Both agents have also been shown to be cardioprotective and reduce cardiovascular events in type 2 diabetes trials (although doses differed), so may be preferred in patients with established CVD or at high risk for CVD.[5] Gastrointestinal side effects such as nausea, vomiting, bloating, diarrhea, or constipation are most common with these agents, especially on initiation and dose escalation. These agents should be avoided in patients with gastroparesis, personal or family history of medullary thyroid carcinoma, and personal history of multiple endocrine neoplasia syndrome type 2 (MEN2).

Finally, tirzepatide (Zepbound®) is the newest agent approved for chronic weight management from a novel class of agents. It is a GLP-1/GIP dual receptor agonist that increases satiety and decreases appetite.[18] In the Study of Tirzepatide in Participants with Obesity or Overweight (SURMOUNT-1) trial, tirzepatide was used in patients with a BMI of ≥27 kg/m2 with controlled hyperlipidemia and/or hypertension or a BMI of ≥30 kg/m2. This agent resulted in a statistically significant weight reduction (up to 20.9% versus 3.1% with placebo) at each of the three studied doses (5 mg, 10 mg, and 15 mg).[19]

Tirzepatide 10 mg and 15 mg also resulted in a reduction in total body weight of up to 14.7% compared to 3.2% with placebo (p <0.0001 for all comparisons) in patients with a BMI of ≥27 kg/m2 and uncontrolled type 2 diabetes.[20] These findings suggest tirzepatide has more substantial weight management effect than any other currently available pharmacologic agent. The Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes (SURPASS 2) trial found that tirzepatide was superior to semaglutide with body weight reductions of up to 13.1% compared to 6.7%, respectively.[21] However, no head-to-head data are available for use in obesity without type 2 diabetes.

Additional cardiovascular outcomes trials (CVOT) to assess cardiovascular safety, such as the Study of Tirzepatide Compared with Dulaglutide on Major Cardiovascular Events in Participants with Type 2 Diabetes (SURPASS-CVOT) trial, are ongoing and anticipated to be completed around June 2025. Prescribing precautions and adverse reactions for tirzepatide are similar to those for GLP-1 receptor agonists.

Anorexiants, such as phentermine and diethylpropion, are sympathomimetic agents that suppress the appetite through direct stimulation of the central nervous system. These stimulants are considered alternative agents and are approved by the Food and Drug Administration (FDA) for short-term use (≤12 weeks) only due to significant cardiovascular and psychiatric risks and the potential for misuse and dependence.[2,6] Although these agents are labeled for short-term use only, they have been studied off-label for up to two years with sustained efficacy and safety.[22,23] Clinicians should continuously monitor patients closely for cardiovascular side effects — such as increased heart rate or blood pressure and arrhythmias, psychosis, or new mood disorders — and signs of misuse/diversion if these agents are used long term.

Insurance coverage for weight management agents varies among plans and can be a barrier to initiation of therapy. In general, patients must have a BMI >30 kg/m2 or a BMI of >27 kg/m2 with at least one weight-related complication (such as hypertension, dyslipidemia, sleep apnea, etc.). Given the high cost of brand-name medications, many plans will require prior authorization, and some plans have stricter criteria such as BMI >35 kg/m2 or BMI >40 kg/m2 or may require documentation of at least six months of diet and lifestyle modification prior to coverage. The 2024 Pennsylvania Medicaid preferred drug list includes Zepbound®, Wegovy®, and Saxenda® as preferred agents, but requires prior authorization. For oral agents, only phentermine is a "preferred" product — and still requires prior authorization — while the other oral agents are non-preferred medications.[24]

Table 2. **Prescribing Considerations of Chronic Weight Management Agents**

Generic (Brand) Dosage Forms	**Adult Dose**	**Contraindications**	**Warnings and Precautions**	**Comments**
Semaglutide (Wegovy®) Single-dose pen 0.25 mg/0.5 mL, 0.5 mg/0.5 mL, 1 mg/0.5 mL, 1.7 mg/0.5 mL, 2.4 mg/0.5 mL	Titrate to target dose of 2.4 mg subcutaneously once weekly: Weeks 1-4: 0.25 mg Weeks 5-8: 0.5 mg Weeks 9-12: 1 mg Weeks 13-16: 1.7 mg Weeks 17+: 2.4 mg If not tolerated, may use an alternative maintenance dose of 1.7 mg.	• Personal or family history of medullary thyroid carcinoma (MTC) • Multiple endocrine neoplasia type 2 (MEN 2)	• Not studied in history of pancreatitis or gastroparesis • Caution use in history of gallbladder disease • Psychiatric effects	• Approved for ≥12 years of age • Single-use pens; needles included • Ozempic® indicated for type 2 diabetes
Liraglutide (Saxenda®) 18 mg/3 mL multi-dose pen 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, 3 mg	Initiate at 0.6 mg subcutaneously once daily for 1 week and titrate up by 0.6 mg weekly to target dose of 3 mg. Patients may continue maximum tolerated dose if goal weight loss is achieved on that dose (even if <3 mg).	• Personal or family history of MTC • MEN 2 • Pregnancy		• Approved for ≥12 years of age • Separate prescription for pen needles required • Victoza® indicated for type 2 diabetes
Tirzepatide (Zepbound®) Single-dose pen 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL	Initiate at 2.5 mg subcutaneously once weekly and titrate to 5 mg after 4 weeks; may titrate by 2.5 mg every 4 weeks if needed to a max of 15 mg once weekly.	• Personal or family history of MTC • MEN 2	• Not studied in history of pancreatitis or gastroparesis • Caution use in history of gallbladder disease • Psychiatric effects	• Approved for ≥18 years of age • Single-use pens; needles included • Mounjaro® indicated for type 2 diabetes
Phentermine/Topiramate (Qsymia®) Extended-release capsule 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, 15 mg/92 mg	Initiate at 3.75 mg/23 mg once daily for 14 days, then increase to 7.5 mg/ 46 mg once daily for 12 weeks, then evaluate weight loss and escalate dose to 11.25 mg/69 mg for 14 days, then increase to maximum dose 15 mg/92 mg once daily or taper to discontinue if ≥5% of weight loss has not occurred.	• Glaucoma • Hyperthyroidism • Use of monoamine oxidase inhibitor (MAOI) within 14 days • Pregnancy	• Cardiovascular effects • Cognitive dysfunction • Psychiatric disturbances • Hyperthermia • Hyperkalemia • Hypotension • Metabolic acidosis • Acute myopia and glaucoma • Kidney stones • Suicidal ideation	• Approved for ≥12 years of age • May precipitate seizures if abruptly stopped; taper to discontinue • Schedule IV substance with risk of dependence and misuse • Only available under the Qsymia Risk Evaluation and Mitigation Strategy program • Requires renal and hepatic dose adjustment
Naltrexone/Bupropion (Contrave®) Extended-release tablet 8 mg/90 mg	Initiate at 1 tablet (8 mg/90 mg) once daily for 1 week, then increase to 1 tablet twice daily for 1 week, then increase to 2 tablets in the morning and 1 tablet in the evening for 1 week, then increase to target dose of 2 tablets twice daily.	• Pregnancy • Chronic opioid, opioid agonist, or partial opioid agonist use • Uncontrolled hypertension • Seizure disorder • Anorexia nervosa or bulimia • Acute opioid, alcohol, benzodiazepine, barbiturate, or antiseizure withdrawal • Use of MAOI within 14 days	• Boxed warning for neuropsychiatric reactions and suicidal ideation • Cardiovascular effects • Hepatotoxicity • Narrow-angle glaucoma • Seizures	• Approved for ≥18 years of age • Should not be used in combination with other bupropion-containing agents • Requires renal and hepatic dose adjustments

continued on page 116

Table 2. **Prescribing Considerations of Chronic Weight Management Agents** (cont.)

Generic (Brand) Dosage Forms	Adult Dose	Contraindications	Warnings and Precautions	Comments
Orlistat (Xenical®, alli®) Xenical®: 120 mg capsule (Rx only) alli®: 60 mg capsule (OTC)	Xenical®: 120 mg three times daily with up to 1 hour after meals (may decrease to 60 mg if poorly tolerated) alli®: 60 mg three times daily with meals	• Pregnancy • Cholestasis • Chronic malabsorption syndrome	• Cholelithiasis • Hepatotoxicity • Increased urinary oxalate	• Approved for ≥12 years of age • Caution when using with warfarin, levothyroxine, cyclosporine, and anticonvulsants; levels should be closely monitored
Phentermine (Adipex-P®, Lomaira™) Capsule, tablet 15 mg, 30 mg, 37.5 mg	Adipex-P®: 15 mg to 18.75 mg once daily or 30 mg to 37.5 mg in 1 or 2 divided doses Lomaira™: 8 mg 3 times daily 30 minutes before meals	• Pregnancy or breastfeeding • History of cardiovascular disease (arrhythmias, heart failure cardiovascular disease, stroke) • Uncontrolled hypertension • Hyperthyroidism • Glaucoma • History of substance use disorder • Use of MAOI within 14 days	• Cardiovascular disease • Seizure disorders • Tourette syndrome	• Approved for ≥17 years of age • Schedule IV substance with risk of dependence and misuse • Renal dose adjustment required
Diethylpropion 25 mg immediate-release (IR) tablet, 75 mg extended-release (ER) tablet	IR: 25 mg 3 times daily 1 hour before meals ER: 75 mg once daily in the midmorning	• Advanced arteriosclerosis • Severe hypertension • Pulmonary hypertension • Hyperthyroidism • Glaucoma • History of substance use disorder • Use of MAOI within 14 days	• Heart failure • Central nervous system effects • Primary pulmonary hypertension • Valvular heart disease	• Approved for ≥17 years of age • Schedule IV substance with risk of dependence and misuse

Sources: Package insert and Lexicomp® for all medications.

Whether weight management is treated with lifestyle interventions only or in combination with pharmacotherapy, frequent follow-up and monitoring are essential to ensure the efficacy and safety of interventions. Most available agents require frequent titrations during initial therapy to ensure tolerability. The initial target for weight loss is at least 5% of body weight, with progressive reduction as treatment continues.[2,6]

Weight should be monitored at every appointment to ensure efficacy, and if 4% to 5% weight loss has not been achieved following 12-16 weeks of therapy, the patient is considered a non-responder and the medication should be discontinued. Alternative therapies may be considered, however there are no data to suggest who is going to be a non-responder or whether those individuals will respond to other medications.

It is important to note that patients tend to regain weight that was lost when antiobesity medications are discontinued. For example, patients who were treated with tirzepatide or semaglutide regained about two-thirds of lost weight within one year after medication withdrawal.[25,26] For this reason, these agents should be treated as chronic medications, and clinicians should discuss this risk with patients prior to initiating, as well as discontinuing, these agents.

Results from a recent study on a tapering strategy of these injectable agents presented at the European Congress on Obesity showed that patients continued to lose weight during the taper and that weight loss was sustained for at least six months after the taper was completed.[27] Tapering, as opposed to abrupt discontinuation, may be a reasonable strategy to consider in patients desiring to discontinue these agents.

Table 3. **Review of Total Body Weight Loss of FDA-Approved Weight Management Agents**

Trial	Treatment Duration	Intervention	Total Body Weight Change	
XENDOS[7]	4 years	Orlistat 120 mg 3 times daily versus placebo	Orlistat: -5.8 kg Placebo -3.0 kg	p <0.001
CONQUER[8]	56 weeks	Phentermine 7.5 mg/topiramate 46 mg once daily or phentermine 15 mg/ topiramate 92 mg once daily versus placebo	7.5 mg/46 mg: -7.8% 15 mg/92 mg: -9.8% Placebo: -1.2%	p <0.0001 for all comparisons with placebo
SEQUEL[9]	108 weeks		7.5 mg/46 mg: -9.3% 15 mg/92 mg: -10.5% Placebo: -1.8%	p <0.0001 for all comparisons with placebo
EQUIP[10]	56 weeks	Phentermine 3.75 mg/topiramate 23 mg once daily or phentermine 15 mg/topiramate 92 mg once daily versus placebo	3.75 mg/23mg: -5.1% 15 mg/92 mg: -10.9% Placebo: -1.6%	p <0.0001 for all comparisons with placebo
COR-I[11]	56 weeks	Naltrexone 16 mg/bupropion 360 mg/day or naltrexone 32 mg/bupropion 360 mg/day versus placebo	16 mg/360 mg: -5.0% 32 mg/360 mg: -6.1% Placebo: -1.3%	p <0.0001 for all comparisons with placebo
COR-II[12]	56 weeks	Naltrexone 32 mg/bupropion 360 mg/day versus placebo	32 mg/360 mg: -6.4% Placebo: -1.2%	p <0.001
COR-BMOD[13]	56 weeks	Naltrexone 32 mg/bupropion 360 mg/day versus placebo plus intensive behavior health modifications	32 mg/360 mg: -9.3% Placebo: -5.1%	p <0.001
STEP 1[14]	68 weeks	Semaglutide 2.4 mg once weekly versus placebo	2.4 mg: -14.9% Placebo: -2.4%	p <0.001
SCALE Obesity and Prediabetes[15]	56 weeks	Liraglutide 3 mg once daily versus placebo	3 mg: -8.0% Placebo: -2.6%	p <0.001
STEP 8[16]	68 weeks	Semaglutide 2.4 mg once weekly versus liraglutide 3 mg once daily versus placebo	Sema. 2.4 mg: -15.8% Lira. 3 mg: -6.4% Placebo: -1.9%	p <0.001 for all comparisons
SURMOUNT 1[19]	72 weeks	Tirzepatide 5 mg, 10 mg, or 15 mg once weekly versus placebo	5 mg: -15.0% 10 mg: -19.5% 15 mg: -20.9% Placebo: -3.1%	p <0.001 for all comparisons with placebo
SURMOUNT 11[20]	72 weeks	Tirzepatide 10 mg or 15 mg once weekly versus placebo	10 mg: -12.8% 15 mg: -14.7% Placebo: -3.2%	p <0.0001 for all comparisons with placebo

In summary, the management options for patients who are overweight and obese has drastically changed over the past few decades.

Obesity is recognized as a chronic condition and should be treated as such. Tirzepatide and semaglutide are the injectable agents that may be preferred given their increased efficacy and once-weekly dosing, with liraglutide being another efficacious injectable agent.

Phentermine/topiramate and naltrexone/bupropion may be alternative agents if oral medications are preferred, but contraindications should be carefully considered.

Orlistat may be the most accessible option for patients as it is available over-the-counter, but strict adherence to a low-fat diet is necessary to reduce side effects. Lastly, phentermine and other stimulant agents are alternatives typically recommended for short-term use if accessibility limits preferred agents, and they must be carefully monitored for misuse and cardiac or psychiatric side effects.

Comorbidities, concomitant medications, cultural beliefs, and social determinants of health should all be considered in ongoing weight management. Incorporating patient needs and desires into decision-making, and understanding how to navigate the insurance barriers and health care system, will increase the chance for weight loss and health maintenance for each patient.

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NARRATIVE MEDICINE

Fertility Treatments: Increasingly Successful, Difficult to Access

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Healers have been treating infertility as a medical problem for millennia. Texts from traditional Chinese medicine, Ayurvedic practitioners,[1] and ancient Greek and Egyptian physicians document therapeutic approaches,[2] while archeologists have found ancient statues among the remnants of early civilizations. Many of these statues are postulated to represent fertility goddesses, including that of the Venus of Willendorf (see Fig. 1).

Our understanding of the biology of human conception has only come to fruition within the last 100 years. While Naegele's rule to estimate the date of anticipated birth — using the last menstrual period — was first published in the 1700s,[3] ovulation and its timing within the menstrual cycle was not described until the 1920s.[4] The fertile window was further described and defined in the 1990s.[5]

Like patients who must negotiate other specialized fields of health care, patients who have infertility face practical concerns that stretch beyond biology and physiology. Over the past 100 years, advances in the field of reproductive medicine have been concurrent with the development of birth control methods and overall delayed childbearing, as well as a patchwork availability of insurance and access to needed health care.

And while we have an improved understanding of reproductive biology, the inability to conceive has continued to carry the stigma of being "a woman's problem." Couples who know better may still feel ashamed that the ability to conceive reflects the strength of their relationship or sex life.

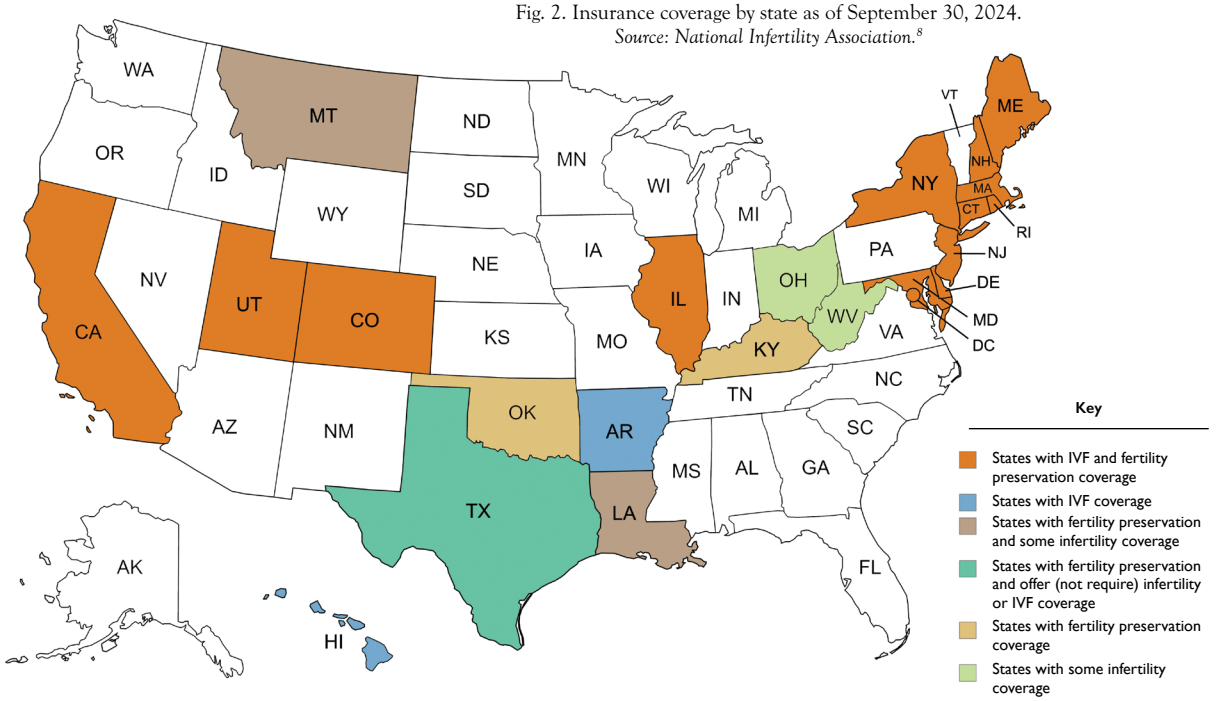
These stigmas may be compounded by a broad lack of recognition by authority figures as well as the lay public. The World Health Organization did not recognize infertility as "a disease of the reproductive system" until 2009. The American Medical Association only formally recognized infertility as a disease at its 2017 annual meeting, nearly 40 years after the first birth using in vitro fertilization (IVF) and 50 years after the Food and Drug Administration (FDA) approved the use of clomiphene citrate. Although our ability to help patients has dramatically increased, this ability has come with economic costs, bringing into focus questions about how patients can access treatment and who decides which treatments are covered by insurance.

Worldwide, different systems of payment for health care include nationalized medicine with primarily government-funded insurance, private-insurance models, and fee-for-service care. In the United States, health insurance has evolved as a quilt of these options and for many includes employer-based benefits initially designed to recruit and retain a Great Depression-era workforce.[6] However, because insurance coverage has developed in this manner in the United States, wide geographic and social discrepancies exist regarding which treatments are covered and who has access to that care.

Some U.S. state legislatures have prioritized access. Although injectable fertility medications — made with purified urinary gonadotropins from post-menopausal women — became available in the 1960s,[7] the real game-changer for infertility was IVF. The first IVF baby, Louise Brown, was born July 25, 1978, in England, and three-and-a-half years later, Elizabeth Carr was the first IVF baby in the United States. Shortly after these success stories, nine U.S. states — Arkansas, California, Hawaii, Massachusetts,

Fig. 1. Statue of the Venus of Willendorf, estimated to have been carved more than 29,000 years ago.
Artwork from MatthiasKabel, CC BY-SA 3.0, via Wikimedia Commons.

Fig. 2. Insurance coverage by state as of September 30, 2024.
Source: National Infertility Association.[8]



Maryland, Montana, Rhode Island, Texas, and West Virginia — developed mandates that insurance make infertility treatments available.[8] However, the amount of coverage and types of treatments covered were and remain markedly variable among U.S. states.

When IVF techniques were first being employed, the success rates were low and the treatments were far more invasive than they are today. Oocytes were originally retrieved laparoscopically, and the monitoring of the developing follicles containing the oocytes was rudimentary without transvaginal ultrasound, which was not developed until the late 1980s. Low rates of success and a limited ability to cryopreserve additional embryos necessitated that practitioners often transfer more than one embryo for patients who accepted the risk of multiple gestation.

As IVF became more successful, the rate of higher order multiple births — triplets, quadruplets, etc. — increased, climbing from a baseline of less than 45 per 100,000 births in 1980 to a rate of 193 per 100,000 births in 1998.[9] As a result, in 1998, the Society for Assisted Reproductive Technology (SART) and the American Society of Reproductive Medicine (ASRM) published guidelines to address the rising rates of multiple gestation pregnancies; the rate has dropped consistently since 2003.[9] The most recent iteration of these guidelines strongly recommends transfer of a single embryo for all favorable patients, including patients with chromosomally normal embryos across all age groups.[10]

Improvements in laboratory techniques within the field of embryology and the overall efficiency of IVF cycles have contributed to increased success rates. Nationally reported data for 2021 — the most recent year with complete statistics — show that more than 82% of patients up to age 37 years who proceed with an egg retrieval will have extra embryos available for cryopreservation.[11] Using current protocols for embryo cryopreservation, greater than 95% of embryos will survive the freezing and warming process. For most patients, this translates to having more than one chance at achieving pregnancy from a single egg retrieval.

The cumulative success rates with single embryo transfer, particularly for patients with a favorable prognosis, are excellent. Nationally, the 2021 SART report indicates that a new patient presenting to an IVF clinic has a 65% of livebirth for women under 35 years old and remains as high as 41% for women ages 38-40 years.[11]

Lack of insurance coverage and overall costs associated with treatment remain a barrier. Although the process leading up to an egg retrieval is the most costly and arduous aspect of an IVF cycle, patients who want to approach treatment "one embryo at a time" will accrue even greater costs with each transfer than patients who would potentially choose to transfer multiple embryos from a single egg retrieval procedure. Without

insurance coverage for fertility treatments, patients are financially incentivized to transfer more than one embryo; insurance coverage for IVF has been shown to result in a higher rate of single embryo transfer and a lower rate of multiple gestation.[12,13]

Infertility now affects one in six couples, in part due to increasing age at first pregnancy and changes in sperm viability. In 2022, for the first time, the U.S. Census Bureau reported the median age of first birth to be 30 years,[14] a significant increase from the average age of first-time mothers of 21.4 years that the Centers for Disease Control and Prevention reported in 1970.[15] Worldwide, there has been a decline in reported semen parameters over the past 50 years,[16] with urologic experts calling for increased research into male fertility to understand the causes and implications.

As the rate of infertility increases and the U.S. birth rate decreases, providing access to safe and effective fertility care, including IVF, will become even more important.[17] Insurance coverage and access vary from state to state (see Fig. 2). Advocacy may as yet yield coverage for patients who are currently excluded, including cancer patients who need fertility preservation.[18]

Our needs and desires change, and for couples there can be years of desperate hope not to become pregnant, followed by an equally fervent desire to conceive. While some may find that controlling fertility is a polarizing prospect, empowering patients along the road toward desired parenthood may ultimately be seen as dignifying and noble.

I am grateful that the Penn Medicine employees I see as patients have insurance coverage for fertility treatment. I look forward to the day when Pennsylvania will join its neighboring states in mandating access to fertility care.

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PHOTO QUIZ FROM URGENT CARE

Thyroglossal Duct Cysts

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CASE HISTORY

An otherwise well-appearing 5-year-old presents to Urgent Care complaining of a skin problem. The child's father, the main source of history, points out a lump on the child's neck. The father states that he noticed the lump two or three days ago; he denies any fever or other cold symptoms. The patient reports no pain at this time and denies drainage, sore throat, or neck pain; neither patient nor father reports knowledge of an insect bite.

Upon exam, the provider notes a raised area in the center of the neck that is slightly red but not tender (see Fig. 1). The patient denies difficulty breathing or swallowing.

QUESTIONS

1. What is the differential diagnosis?
2. What diagnostic studies should be ordered?
3. What are concerning symptoms that would warrant emergent treatment?
4. What steps should be taken to confirm a diagnosis?
5. What is the definitive treatment for the diagnosis?

ANSWERS

1. The differential diagnoses include abscess, thyroglossal duct cyst, insect sting, cellulitis, and brachial cleft cyst.
2. Ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI) can be utilized to help identify potential cysts versus an infectious process.
3. While erythema, warmth, and tenderness might suggest acute infection, and "b symptoms" such as night sweats and weight loss suggest malignancy, concerning symptoms that warrant emergent treatment include an inability to handle secre-

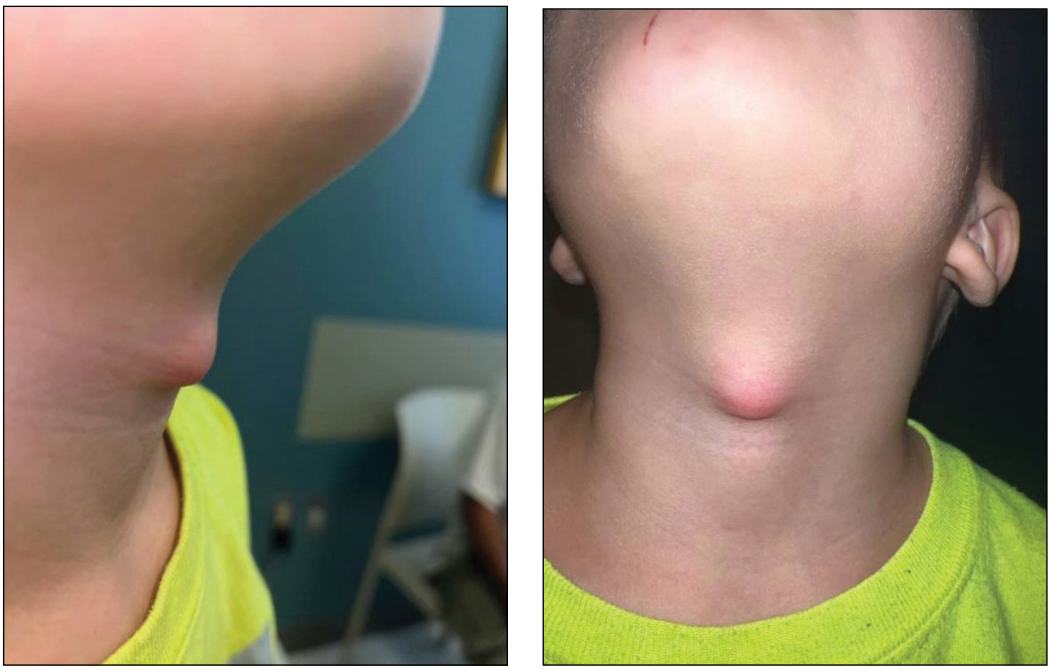

Fig. 1. Photos of patient's neck taken in urgent care setting showing lump and redness from two different angles.
Photos by Briana A. Mack, PA-C.

tions, poor phonation, trismus, or any respiratory compromise.

4. The patient in this case was sent to the Emergency Department for further diagnostic imaging (see Table 1 for study details and results). Study results suggested a thyroglossal duct cyst, possibly infected.
5. The Sistrunk procedure is the standard surgical approach for a thyroglossal duct cyst. The procedure involves the removal of the cyst, along with a portion of the thyroglossal duct and the midline segment of the hyoid bone.

DISCUSSION

Thyroglossal duct cysts (TGDCs) are the most common congenital neck cysts, arising from the remnants of the thyroglossal duct, a developmental structure involved in the descent of the thyroid gland from the base of the tongue to its final position in the neck. TGDCs can present as midline neck masses, often becoming apparent in childhood or early adulthood.

The thyroglossal duct is an embryologic structure that is typically obscured as the thyroid gland moves to its position in the neck. If this duct does not completely shrink, a cyst can form. TGDCs are usually located in the midline of the neck, but can occasionally be found off-midline, reflecting variations in the duct's developmental course.[1]

Patients with TGDCs typically present with a midline neck swelling that moves with swallowing or tongue protrusion, a characteristic feature due to the cyst's attachment to the hyoid bone.[2] The cyst may become infected, causing pain, erythema, and increased swelling. Chronic infections can result in sinus tract formation or abscess development, complicating diagnosis and treatment.[3]

Diagnosis is primarily clinical, based on the location and mobility of the cystic mass. Imaging studies such as ultrasound, CT scan, or MRI can assist in defining the cyst's extent and ruling out other conditions.[4] Ultrasound is particularly useful due to its ability to distinguish TGDCs from other cystic or solid neck masses.

The definitive treatment for TGDCs is surgical excision. The Sistrunk procedure is the standard surgical approach, which involves the removal of the cyst along with a portion of the thyroglossal duct and the midline segment of the hyoid bone. This technique aims to minimize recurrence by addressing the cyst and any potential remnants of the duct.[5]

Table 1. Diagnostic Study and Result of Patient Complaint

Procedure	US SOFT TISSUE HEAD/NECK
Comparison	None
Reason for Study	Erythematous nontender lump anterior neck x 3 days
Findings	Complex fluid collection with peripheral flow measuring 1.7 x 1.3 x 0.6 cm
Abnormal Lymph Node	None
Neck Mass	None
Impression	There is a mildly complex fluid collection/cyst at the midline anterior neck at the level of the hyoid bone. The findings are suspicious for a thyroglossal duct cyst, which is possibly infected. Correlate clinically; options for further imaging evaluation include an MRI or CT of the neck.

Recent studies emphasize the importance of complete excision in preventing recurrence, with reported recurrence rates ranging from 0% to 5% when the Sistrunk procedure is correctly performed.[1,6] Infected cysts may require preoperative antibiotic therapy to manage infection before surgical intervention.

This patient was seen in the Emergency Department, treated with amoxicillin/clavulanic acid, and referred to the Ear, Nose, and Throat service for further treatment.

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SPOTLIGHT ON CLINICAL RESEARCH

Investigator-Initiated Research at LG Health

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Editor's note: This is the 21st in a series of articles from the Penn Medicine Lancaster General Health Research Institute that describes ongoing research studies. Members of the LG Health staff who are conducting research and wish to have their studies described here are encouraged to contact the offices of JLGH *at 717-544-8004.*

Health care providers are in a prime position to answer the questions faced in day-to-day practice and improve how health care is offered. One way to do this is through clinical research.

Penn Medicine Lancaster General Health (LG Health) is among the most active community-based health systems in the nation for clinical research. Because research ideas often arise while caring for patients, our investigator-initiated studies, often referred to as IIS, are a unique resource for LG Health clinicians. These research questions, and subsequent research studies, have the potential to offer new treatments that can save lives and improve quality of life for the patients of LG Health. It also provides professional development opportunities for providers and staff.

Acting on an idea or solution for one of these research questions may seem like a daunting task. At LG Health, dedicated research professionals provide investigators with the guidance, resources, and infrastructure needed to conduct clinical research aimed at improving and advancing medical care. The Research Institute also ensures that all research remains safe for patients and other study participants.

The Research Institute offers support throughout the entire lifecycle of an investigator-initiated study. The study lifecycle follows six steps (see Fig. 1):

1. Proposal Development
2. Funding
3. Study Startup (Protocol Development)
4. Study Activation
5. Participant Enrollment
6. Data Analysis and Dissemination (Close-out)

During proposal development, the design and methods for the study are established. The design of a research study is the overall plan or blueprint that guides the process of conducting research and will encompass the methods that will be used to collect and analyze data. The research design will include the research objectives and hypothesis, which define the goals of the research study and answer the question regarding what the research is trying to demonstrate.

Collected data will be qualitative, quantitative, or a mix of both (mixed methods research). The research design (e.g., experimental, observational, survey, case study, longitudinal, etc.) will help determine the methods used for data collection and subject sampling.

The research team offers special attention to feasibility, budget, timeline creation, and staffing needs. They can then help apply for and secure internal (e.g., Louise von Hess Research Grant) or external funding for the research project. If support is needed for billing at any point during the study, the research team can provide guidance regarding that as well.

Once funding has been obtained, the research team will work with investigators to develop a research protocol. They will support the investigator through developing study-related materials (e.g., informed consent form, data-collection tools, promotional materials, etc.) and submitting to the University of Pennsylvania Institutional Review Board (IRB) for approval.

After IRB approval, the study activation process can be initiated. This step focuses on implementing the protocol and training those conducting the project. This may include pharmacy staff, unit staff, research coordinators, or anyone else needed per the protocol.

After all team members are trained, study activities can begin. These activities focus on enrolling participants and may include recruitment, obtaining consent, and collecting data. Each research project is unique, and not all projects have the same activities or procedures. For example, retrospective data-

collection studies do not typically involve patient consenting due to the study design and data confidentiality measures in place. It is important to be aware of the research requirements that apply to your project.

After all study activities are completed and data collection ends, data analysis and results dissemination can begin. This step often includes final analysis, closing the project with the IRB, manuscript writing, and document storage. Statisticians who work in collaboration with the research team can provide the tools and expertise needed to analyze and draw conclusions about the study's findings. Some funding sources, like the Louise von Hess Research Grant, have a publication requirement that must be met, so it is crucial to be aware of all required steps.

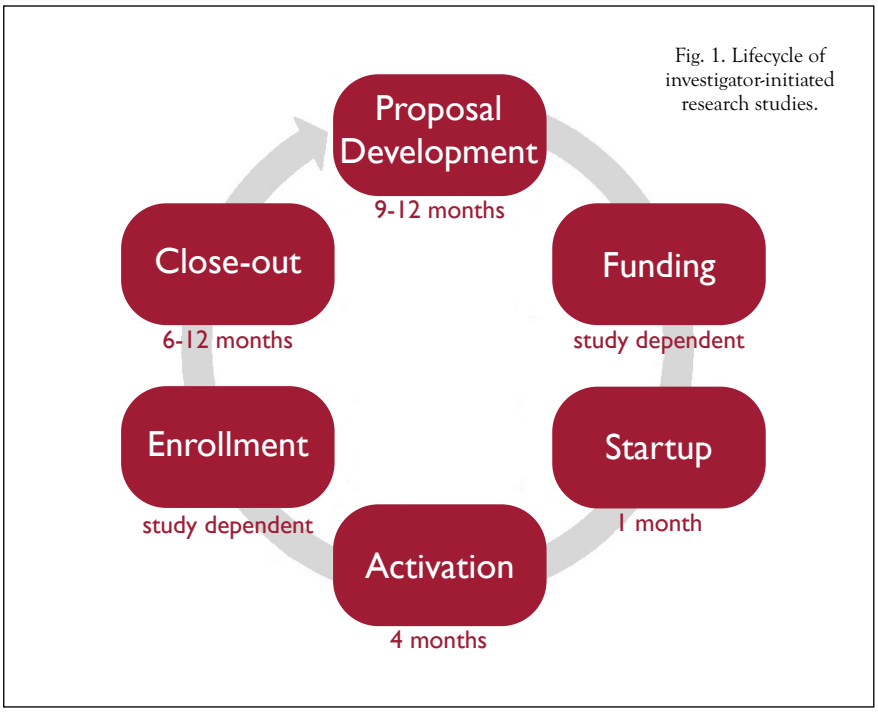

Fig. 1. Lifecycle of investigator-initiated research studies.

The research team is available to provide information, guidance, and logistical support to help researchers be effective and remain compliant at every stage of a project. For general research inquiries, you can explore the Research Institute web page accessible via Star*Net* or email the team at LGHResearch@pennmedicine.upenn.edu. For additional information about investigator-initiated studies, please reach out to Halle Becker, research project manager at the LG Health Research Institute.

To learn more about research at LG Health, health care professionals are invited to join the newly launched monthly Research Grand Rounds, where investigators and other research professionals present on the latest research topics in various therapeutic areas. Our next Research Grand Rounds will be presented by Alexis Ogdie, MD, on Thursday, January 9, 2025.

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Primary Aldosteronism, Vitamin D Testing, Sodium Intake, Blood Pressure Medications

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DIAGNOSING PRIMARY ALDOSTERONISM[1]

In approximately 6% of cases of hypertension, primary aldosteronism is the underlying cause, yet only 2% of these patients are formally diagnosed. Case detection means testing patients with a first-degree relative with primary aldosteronism, resistant hypertension, hypokalemia, an adrenal nodule, atrial fibrillation, obstructive sleep apnea, or a family history of early cerebrovascular accident.

Testing involves using the aldosterone-renin ratio; ratios of >30 indicate independent aldosterone secretion (i.e., aldosteronism). Confirmatory testing should then be performed using either the captopril challenge, oral or intravenous salt loading, or fludrocortisone suppression; persistently high aldosterone levels yield the diagnosis.

Following these, adrenal computed tomography and adrenal vein sampling help differentiate unilateral from bilateral adrenal aldosterone production. Treatment of unilateral primary aldosteronism includes adrenalectomy; bilateral disease may be treated with mineralocorticoid receptor antagonists, such as spironolactone or eplerenone.

ENDOCRINE SOCIETY ADVISES AGAINST VITAMIN D TESTING

New Endocrine Society guidelines call for limiting vitamin D supplementation beyond the daily recommended intake to specific risk groups and advises against routine 25-hydroxyvitamin D [25(OH)D] testing in healthy individuals.

The guidelines are based on evidence presented in June at the Endocrine Society annual meeting and simultaneously published in the *Journal of Clinical Endocrinology and Metabolism.*[2] The evidence suggests that the following may benefit from vitamin D supplementation:

1. Children ages 1-18 years, to prevent rickets and potentially lower the risk for respiratory tract infections.
2. Pregnant people, to lower the risk for maternal and fetal or neonatal complications.
3. Adults older than 75 years, to lower the risk for mortality.
4. Adults with prediabetes, to lower the risk for type 2 diabetes.

In those groups, the recommendation is for daily, rather than intermittent, empiric vitamin D supplementation of more than what was recommended in 2011 by the National Academy of Medicine, then called the Institute of Medicine: 600 IU/d for those ages 1-70 years and 800 IU/d for those older than 70 years.

The Endocrine Society acknowledges that the optimal dose for these populations isn't known. The guidelines recommend against testing for blood vitamin D levels in the general population, including those with obesity or darker complexions.

Those with established osteoporosis or osteopenia are not covered by this guideline, nor are patients with several diseases, such as chronic kidney disease or inflammatory bowel disease. There remain more questions than answers about who to test, who to supplement, and to what long-term benefit.

MOST ADULTS WITH HEART DISEASE CONSUME TOO MUCH SODIUM

Individuals with heart disease, on average, consume more than twice the recommended daily sodium intake, according to a study presented at the Annual Scientific Session of the American College of Cardiology (ACC) in April.

Current U.S. Department of Agriculture guidelines recommend that most adults limit their sodium intake to less than 2,300 mg/day; for individuals with cardiovascular disease, the limit is even lower at 1,500 mg/day, according to guideline recommendations from the ACC and the American Heart Association.

The study found that among a sample of more than 3,100 people with heart disease, 89% consumed

more than the recommended daily maximum of 1,500 mg of sodium and, on average, study participants consumed more than twice this amount.

Researchers estimated sodium intake based on questionnaires in which participants were asked to report everything they had consumed in 24 hours, and study participants with cardiovascular disease consumed an average of 3,096 mg of sodium per day, compared to the national average of 3,400 mg/day reported by the Centers for Disease Control and Prevention. Socioeconomics, gender, race, nor age seemed to play a role in these outcomes.

Patients can lower their sodium intake by preparing more meals at home and reading food labels, keeping in mind that a serving of any food should have less than or equal to 140 mg of sodium.

Researchers further suggest continued and better education about the benefits of limiting sodium.

COMMON BLOOD PRESSURE DRUG MAY INCREASE RISK OF BLEEDING

People with an irregular heart rhythm taking diltiazem may be at a greater risk of serious bleeding, according to a recent study in *JAMA*.[3]

Choosing Wisely

Originally published in the Winter 2012 issue of JLGH *in conjunction with the American Board of Internal Medicine's now-complete Choosing Wisely campaign, this edited reprint is offered to remind physicians of the importance of talking with patients about what tests, treatments, and procedures are needed — and which ones are not.*

RECOMMENDATIONS FROM THE AMERICAN ACADEMY OF ALLERGY, ASTHMA & IMMUNOLOGY

❶ **In the evaluation of patients with allergies, don't perform unproven diagnostic tests, such as immunoglobulin G (IgG) testing or an indiscriminate battery of immunoglobulin E (IgE) tests.** Appropriate diagnosis and treatment of allergies requires specific IgE testing (either skin or blood tests) based on the patient's clinical history. The use of other tests or methods to diagnose allergies is unproven and can lead to inappropriate diagnosis and treatment. Appropriate diagnosis and treatment is both cost effective and essential for optimal patient care.

❷ **For patients with uncomplicated rhinosinusitis, don't order sinus CTs or indiscriminately prescribe antibiotics.**

❸ **In patients with chronic urticaria, don't routinely do diagnostic testing.** In the overwhelming majority of such patients, a definite etiology is not identified. While limited laboratory testing may be warranted to exclude underlying causes, and targeted laboratory testing based on clinical suspicion is appropriate, routine extensive testing is neither cost effective nor associated with improved clinical outcomes. Skin or serum-specific IgE testing for inhalants or foods is not indicated unless there is a clear history implicating an allergen as a provoking or perpetuating factor for urticaria.[4]

❹ **In patients with recurrent infections, don't recommend replacement immunoglobulin therapy unless impaired antibody responses to vaccines are demonstrated.** Immunoglobulin (gammaglobulin) replacement is expensive and does not improve outcomes unless there is impairment of antigen-specific IgG antibody responses to vaccines, immunizations, or natural infections. Low levels of immunoglobulins (isotypes or subclasses), without impaired antigen-specific IgG antibody responses, do not indicate a need for immunoglobulin replacement therapy.

Exceptions include IgG levels <150 mg/dl and genetically defined/suspected disorders. Measurement of IgG subclasses is not routinely useful in determining the need for immunoglobulin therapy. Selective IgA deficiency is not an indication for administration of immunoglobulin.

❺ **The diagnosis and management of patients with asthma should not be done without spirometry.** Clinicians often rely solely upon symptoms to diagnose and manage asthma, but these symptoms may be misleading or from alternate causes, so spirometry is essential to confirm the diagnosis in patients who can perform this procedure.

Guidelines highlight spirometry's value in stratifying the severity of the disease and monitoring its control. The history and physical exam alone may over- or underestimate asthma control. Beyond the increased cost of care, the repercussions of misdiagnosing asthma include a delay of correct diagnosis and treatment.

Atrial fibrillation, the most common type of irregular heart rhythm, can lead to blood clots or stroke if left untreated. To prevent complications, people with atrial fibrillation are often prescribed anti-clotting medications and medications to control heart rate.

The study reviewed health records from 2012 and 2020, looking at Medicare beneficiaries ages 65 years or older with atrial fibrillation who started taking apixaban or rivaroxaban in addition to their diltiazem or metoprolol. Patients receiving diltiazem were 20% more likely to experience bleeding-related hospitalization and death. Risks seemed to be increased in those taking higher doses of medications. There were no significant differences in rates of stroke, systemic embolism, or hemorrhaging.

These results are significant because they show that while there are some benefits to using diltiazem over metoprolol, and vice versa, differences in metabolism may introduce some increased risks of bleeding in those taking diltiazem.

The research group will continue to investigate what causes different reactions to the same medications and identify ways to potentially monitor drug levels. "Genetic differences can impact how different people metabolize medications," said Eli Zimmerman, MD, a neurology professor at Northwestern Medicine and a co-author of the study.

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JLGH Fall 2024 Recap

Q&A for Extended Learning

The Fall issue of The Journal of Lancaster General Hospital *offered articles on gender-affirming hormone therapy and pediatric behavioral health, as well as a photo quiz on mastoiditis and other practice recommendations. Review the questions and answers below to see how much you remember from the issue. Need a refresher? All issues of* JLGH *are available at JLGH.org.*

Q **What are the World Professional Association for Transgender Health (WPATH) Standards of Care guidelines to begin gender-affirming hormone therapy in adults (≥18 yo)?**

A Patients should have marked and sustained gender incongruence, the ability to consent to starting therapy and understanding of reproductive impact, and appropriate co-management of their mental and physical health conditions, especially ones that could negatively affect or be negatively affected by hormone therapy.

Q **How can we differentiate ADHD from comorbid conditions in pediatric patients?**

A Rule out language barriers and developmental delay; use more than one screening tool to tease out, for example, symptoms of anxiety or autism; inquire about social and family issues; and try parent management training before prescribing medications, focusing on the symptoms that cause the most impairment.

Q **What are potential complications of improperly treated mastoiditis?**

A Potential complications include permanent hearing loss, nerve palsy, osteomyelitis, petrositis, Gradenigo's syndrome, labyrinthitis, and intracranial extension — including meningitis and subdural empyema, sigmoid sinus thrombosis, and abscess formation.

Q **Although breast cancer screening recommendations differ, what are the U.S. Preventative Services Task Force recommendations regarding breast cancer screening?**

A The Task Force recommends that all women get screened for breast cancer every other year, starting at age 40 and continuing through age 74. This is a "B" recommendation.

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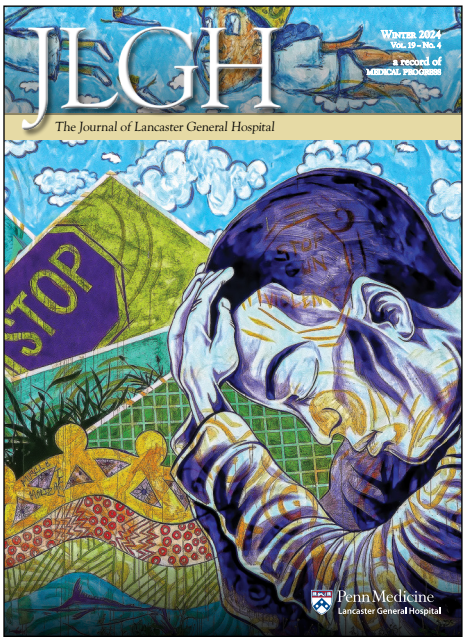

The cover photo, "Stop Gun Violence" by Terence Faircloth, is licensed under CC BY-NC-ND 2.0.

Taken in 2019, the photo details a section of a mural by Kyle Holbrook and local youth that is located at NW 1st Avenue at NW 17th Street in Miami, Florida.

See page 99 of this issue to learn more about LG Health's new firearm safety initiative in Lancaster County.

INTERESTED IN WRITING FOR *JLGH*?

The following is a summary of the general guidelines for submitting an article to *The Journal of Lancaster General Hospital*. Details are located online at JLGH.org.

- Scientific manuscripts are typically between 2,500-4,500 words. Perspective articles are usually shorter, and photo quizzes average about 725 words plus illustrations.
- Medical articles should report research, introduce new diagnostic or therapeutic modalities, describe innovations in health care delivery, or review complex or controversial clinical issues in patient care.
- Reports of research involving human subjects must include a statement that the subjects gave informed consent to participate in the study and that the study has been approved by the Institutional Review Board (IRB).
- Patient confidentiality must be protected according to the U.S. Health Insurance Portability and Accountability Act (HIPAA).
- The Journal of Lancaster General Hospital *does not allow chatbot tools such as ChatGPT to be listed as authors.* JLGH *editors warn authors that the use of these tools poses a risk for plagiarism with inappropriate use of citations, and we require that use of such tools be disclosed.*

Please contact the managing editor, Maria M. Boyer (717-544-8004), Maria.Boyer@pennmedicine.upenn.edu, to discuss submitting an article or for further information.

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EARN CME CREDIT

American Medical Association Category 2 activities consist of self-directed learning or courses that have not been through a formal approval process. According to the Pennsylvania State Board of Medicine, this includes "learning experiences that have improved the care [physicians] provide their patients." Reading authoritative medical literature — like medical journals — is one such activity.

For Pennsylvania physicians, more information and the Pennsylvania Board of Medicine CME Reporting Form are available at LGHealth.org/CME. *For advanced practice providers,* more information is available from credentialing organizations.

Physicians can also log credit and advanced practice providers can access transcripts through their eeds accounts online.

← Scan to access your eeds account.

← Scan for additional information and links to individual reporting instructions and forms.

Upcoming CME Offerings at LG Health

Pediatric Grand Rounds
January 14, February 11, March 11
7:00-8:00 a.m.

Research Grand Rounds
January 9, February 6, March 6
12:00 noon-1:00 p.m.

Department of Medicine Grand Rounds
February 5
12:00 noon-1:00 p.m.

CME On Demand

The Continuing Medical Education Department at Lancaster General Health offers a number of programs on demand at LGHealth.org, including Department of Medicine Grand Rounds; Diversity, Equity & Inclusion Lecture Series; and more.

Connect with the Continuing Medical Education Department on Instagram

Follow the CME Department on Instagram @LGHCME for regular updates on upcoming Lancaster General Health CME events, including information on regularly scheduled series and links to register for symposia.

For the most up-to-date offerings and information from the LG Health Continuing Education Department, visit LGHealth.org/CME.