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Generating New Knowledge

Corey D. Fogleman, MD, FAAFP
Editor in Chief

Listening in on a leadership Town Hall this month, I was reminded that research matters. We were encouraged to take the data we have, ask the questions it inspires, and create the knowledge of the future.

Research enriches us and makes us better clinicians. In 1999 the Accreditation Council on Graduate Medical Education (ACGME) established core competencies describing the development of medical learners, and in 2012 the Council further developed this concept by introducing Milestones. Within this context, Milestones are a set of observable behaviors that signify physician development through the arc and continuum of their education. While the competencies include Patient Care and Medical Knowledge, Professionalism, and Communication, of particular interest is that one-third of these include Practice-Based Learning and Improvement or Systems-Based Practice.

In the latter two, as in all the competency areas, we are reminded of our obligation to uphold our duty to continuously improve, role model, and strive to achieve an ever more idealized community and society. How should we do that? By continuing to participate in and report on our research, process-improvement, and quality-improvement initiatives.

We expect energy from our learners, as well as inquisitiveness and innovation. Students and residents are expected to demonstrate investigatory and analytic thinking. We want them to help us evaluate patient care practices, appraise and assimilate scientific evidence, and improve their patient care. As mentors and role models, we ought to do the same.

Further, full-fledged physicians are able and should continue to move from our knowledge of study designs and statistical methods toward appraisal of our practices. This could regard patient outcomes and access to care, or even inclusion in medical decisions and equity, especially for medically underserved communities. In this way, we discover and refine new and efficient ways to implement therapeutic effectiveness.

We must be skilled digesters of medical information — to understand the difference between evidence-based and anecdotal reasoning, the subtleties that separate correlation from cause and effect. Beyond this, however, we should feel empowered and inspired, endowed to look for new therapies, identify approved therapies that are not effective, and overall make health care more affordable and accessible. This is what is meant by participating in continuous self-education — to recognize the deficiencies in our practices and systems, to invoke polices that require more research, and then use our skills, our leadership, and the resources around us to start making these changes happen.

It is not only in the interest of a noble dedication to the art of medicine that we should dedicate ourselves to this, however. Continuing to develop and maintain our skills as innovators and scientists is clearly in the interest of our patients and our community, and more research should occur in every medical setting, be it private practice or the hallowed inpatient setting, whether here at Penn Medicine Lancaster General Hospital or far beyond.

Doing research can also serve us on a personal level. Certainly, research is challenging, as it demands patience and attention to detail. Yet — even as we're concerned that we might be too busy or risk becoming burned out — we might ask ourselves: what gives us joy in medicine? Do we derive pleasure from treating a particular disease process or seeing patients within a particular context? We might further ask how we can do more of that.

One way is by engaging the science and publishing what we discover. By doing so, we will each not only have the chance to become something of an expert in the subject, but more of our colleagues and peers will look to us to help when questions in that medical arena arise. In essence, research and process improvement efforts deliver back to us.

There are many ways to be involved. Frontline researchers need the support of advisory councils and peer reviewers, both as they begin their project and throughout the journey to publication. The Institutional Review Board (IRB) serves a vital role in protecting human subjects. Many projects necessitate further compliance committees to ensure the protection of all involved.

The current literature corroborates that patients do better in a research-intense environment; in fact, mortality rates for even those patients deemed "lower severity" tend to be lower at academic medical centers.[1] Any number of reasons might explain this correlation, not the least of which is that academic centers are nimble, their practitioners accustomed to openly discussing errors. Humility means we can learn from our mistakes, that we can adapt and improve. I am not suggesting that we should transfer all our patients to university-affiliated centers; rather, community hospitals like LGH should behave more like academic institutions, as might the outpatient practices where most of our patients are seen.

We are especially fortunate here at Penn Medicine Lancaster General Health to have access to an innovation lab to help us make these changes happen, and I'm excited to have another column in this issue describing the Innovation Accelerator Program (see page 86). We also have a resource-rich Research Institute and a remarkable set of experts within to help us make strides in this arena. Our Business Intelligence department can help us mine the capacity within Epic to develop baseline datasets, and project managers can help us negotiate the process. This is precisely the model followed by a group of residents and faculty who recently pursued questions about supplements for the treatment of COVID-19 infection.[2] (Spoiler alert: vitamin C as treatment has no utility.)

LG Health has hired a new vice president of research administration, Edmond Kabagambe, DVM, PhD, MS, MBA. I recently sat down with Dr. Kabagambe regarding what he'd like to see as the new direction of our Research Institute. In his words, he is interested in "greasing the wheels with regard to moving toward research as a regular part of practice" and sees our local providers "developing the experimental therapeutics and devices they will then put to use as treatment options." To this end, he wants to help local practices gain funding for local efforts, making it easier for Lancaster practitioners to use LG Health Foundation funding and grants and effectively engage in collaborative scholarly endeavors, even with other institutions.

One way to initiate this would be to decrease barriers to participation in research. For example, a shorter Collaborative Institutional Training Initiative (CITI) refresher course was rolled out in October 2022, and plans are underway to roll out a Penn-generated Ethics of Research course that will be worth 4.5 CME credits as an alternative to CITI training requirements. He would like to increase the number of Phase III trials across all service lines while also increasing early phase first in-human studies here at LG Health.

The Research Institute already has a few Phase I and Phase II studies that will begin enrolling patients in the next six months. These efforts will pave the way for pharmacokinetic studies and vaccine development trials here at LGH. He envisions collaboration between more tenured and less seasoned clinicians at LG Health, to help them gain exposure to the practice of research and to bring fresh minds and ideas to the process. He seeks new avenues with administrative support, software (e.g., EndNote), and funding for travel and publication submissions.

Dr. Kabagambe, recently an assistant vice president of research at Ochsner Health System, based in New Orleans, Louisiana, explained to me his plans for a living database of protocols to better track proposals submitted for funding, proposals that have received funding, and those in various phases of the publication process. He also hopes to begin better tracking research inquiries/requests to Business Intelligence and other service departments, to document the use and need for services, to potentiate resource acquisition. In the long run, he would like to see more of us working toward the goal of publication in high-impact journals. This will certainly follow a closer collaboration with Penn Medicine partners and involvement in multidisciplinary research that covers multiple service lines.

Ours is, of course, already an area in which innovation is in action, and so it is with pleasure that we also continue the Spotlight on Clinical Research column by Heather Madara and Dr. Roy Small. Their contribution this time around highlights unique and rather exciting advances being made by local physician scientists (see page 91).

I invite you to peruse all the enticing articles in this issue and wish to thank the inspiring group of writers who have touched on topics both current and timeless — from monkeypox to hookworm, from TTP to the SARS-CoV-2 vaccine. Even more, I invite you to continue *your* scholarly work, and to reach out to our research and innovation departments about help with pursuing your project. Our readers no doubt will look forward to seeing your publication soon, here in this journal or in others.

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JLGH Fall 2022 Recap

Q&A for Extended Learning

The last issue of The Journal of Lancaster General Hospital *offered a review of syphilis and updated national practice guidelines related to buprenorphine treatment for opioid use disorder, as well as an introduction to LG Health's Lead-Free Families Initiative and the Center for Health Care Innovation in Lancaster, among other topics of interest. Review the questions and answers below to see how much you remember from the Fall issue. Need a refresher? All issues of* JLGH *are available online at JLGH.org.*

Q **Up to 80% of pregnant women with untreated syphilis transmit syphilis to their fetus, making treatment of the utmost importance. What treatment is recommended for this population?**

A Intravenous penicillin G benzathine is the only therapy with confirmed efficacy for syphilis during pregnancy. Three doses of 2.4 million units should be given at one-week intervals. If not administered exactly seven days apart, the regimen must be restarted.

Q **In 2020, the American Society of Addiction Medicine released a focused update to its National Practice Guideline for the treatment of opioid use disorder. List some changes.**

A Comprehensive assessment should not preclude prompt initiation of buprenorphine. Buprenorphine dose should be sufficient to enable patients to discontinue illicit opioid use; 16 mg or more per day may be appropriate. Patients who are stable on buprenorphine/naloxone treatment may continue this regimen if they become pregnant. The addition of full agonist opioid to the regular dose of buprenorphine can be effective for severe acute pain.

Q **Penn Medicine Lancaster General Health launched the Lead-Free Families Initiative in August 2021. How can physicians make referrals to the program?**

A To remove lead hazards from Lancaster County homes, providers can type "Amb ref lead" into the Epic order search or call 717-544-LEAD (5323). Individuals may also self-refer by emailing info@leadfreefamilies.org.

Q **The Center for Health Care Innovation (CHCI) at LG Health is modeled after the Penn Medicine CHCI in Philadelphia. What is the name of the Center's signature program and what is its goal?**

A CHCI at LG Health's signature Innovation Accelerator Program is a year-and-a-half-plus-long program to support staff in their efforts to develop, test, and implement new approaches to improve health care delivery and patient outcomes.

Q **Per the European Society of Cardiology, the American College of Cardiology, and the American Heart Association, does aspirin still provide a net benefit as primary prevention of cardiovascular disease?**

A No. These groups agree that the balance of benefits and harms is equally weighted, so physicians should no longer recommend aspirin for the primary prevention of cardiovascular disease.

Have an idea for a story? We want to hear from you.

The Journal of Lancaster General Hospital is looking for human interest stories including, but not limited to, staff experiences, patient experiences, and anything else that might be educational for our readers — the medical staff of Penn Medicine Lancaster General Health. If you have an idea for a story, scan the QR code at left or visit our website at JLGH.org to share your idea.

A Clinical Primer on the 2022 Monkeypox Outbreak in the United States


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HISTORY OF MONKEYPOX

Monkeypox virus was first identified in 1958 among monkeys in a Danish laboratory, hence its name.[1] The first human case was diagnosed in 1970 in a nine-month-old boy in what is now the Democratic Republic of the Congo (DRC).[2] The virus has remained endemic in the DRC and was also found to be endemic in multiple other African nations.

The two distinct phylogenetic clades of monkeypox virus are: Clade I (previously known as the Central African/Congo Basin clade) and Clade II (previously known as the West African clade).[3] The clade names were changed to avoid stigmatization of these regions. Clade I has higher transmissibility and mortality rates compared to Clade II, which produces a more self-limited disease with lower mortality rates. Clade II is further divided into Clade IIa and Clade IIb, with the latter referring to the currently circulating international variant.[3]

Prior to the current outbreak, monkeypox cases outside of endemic regions were due to international travel or importation of infected animals. In 2003, the United States recorded the first monkeypox cases outside of the African continent. Forty-seven cases were discovered across six different states, spread from imported pets to pet prairie dogs to humans.[4] Travel-related cases have been documented in Israel, the U.K., and Singapore.[5]

For years, concerns have been raised about the possibility of more significant outbreaks given increased population growth, encroachment on animal reservoir habitats, increasing human movement, and enhanced global interconnectedness.[5] Monkeypox virus isolates from the 2022 outbreak in the United States appear to be phylogenetically different, raising concern for increasing mutation rates and transmissibility; alternatively, the virus may just have reached a population whose behaviors allow it to spread more quickly.[6]

VIROLOGY

Monkeypox virus, the causative agent of monkeypox, is a double-stranded DNA virus of the genus *Orthopoxvirus* and within the family *Poxviridae*.[7] Variola virus, the causative agent of smallpox, is also contained in the genus *Orthopoxvirus*; a common clinical mimic, molluscum contagiosum, is in the family *Poxviridae*, but as a different genus does not cause false positives for monkeypox testing. Monkeypox virus is a zoonosis capable of infecting multiple mammalian species, including rodents, non-human primates, and humans. Although the primary animal reservoir is not definitively known, rodents — not monkeys — seem to represent the largest population hosting the virus.[8]

The current monkeypox outbreak is being transmitted through human contact, specifically skin-to-skin contact, fomite transmission such as contact with clothing or bedding of infected individuals, and respiratory secretions.[9] This outbreak has disproportionally affected men who have sex with men (MSM), and risk factors of infection include young age, HIV seropositivity, a history of prior sexually transmitted infection (STI), and engaging in high-risk sexual activity such as condomless sex. In this particular outbreak, concerns have been raised as to whether there is direct sexual transmission of the monkeypox virus.[10] Studies have shown viral shedding present in seminal fluid, but currently there is insufficient evidence showing significant infectivity of this fluid.[11]

CLASSIC MONKEYPOX VS. 2022 OUTBREAK: CLINICAL DIFFERENCES

Classically, monkeypox presents with generalized prodromal symptoms such as fever, headaches, chills, malaise, and lymphadenopathy, followed by a characteristic rash.[5] Signs and symptoms generally reflect a milder form of smallpox. The rash usually starts in the

mouth and spreads to the face and extremities without sparing the palms and soles. Lesions begin as macules, then progress to umbilicated papules, vesicles, pustules, and finally scabs (see Fig. 1). Pain can be present, but not in every case. Pruritus is common during the healing process. Lesions are similar in size and present at the same stage. They number between 10-150 total and can persist for up to four weeks. The incubation period is generally thought to be around 7-14 days but could last as long as 21 days. Individuals are infectious from the onset of prodromal symptoms until a new layer of skin forms after the final scab falls off. Severe complications are rare, with exact incidences unclear, but include bacterial superinfection, encephalitis, pneumonitis, and conjunctivitis/keratitis.[12]

The disease presentation in the 2022 outbreak is somewhat different. The characteristic rash is still present, but it can be limited to genital, perigenital, and perianal areas; it often spares the face; and it may be in different stages of development. There may be mild or no systemic prodromal symptoms, and the systemic (previously prodromal) symptoms may begin after rash onset. Systemic symptoms include fever, lymphadenopathy, pharyngitis, headache, lethargy, myalgia, low mood, and proctitis.[13]

The Centers for Disease Control and Prevention (CDC) categorizes severe illness from monkeypox as developing one of the following from the infection: sepsis, encephalitis, periorbital infection, abscess formation, confluent skin lesions, and lesions located in the oropharynx and anogenital regions that can cause severe pain. Mild to moderate infections encompass all other infections; the distinction between mild and moderate is clinical and not well defined.

EPIDEMIOLOGY OF 2022 OUTBREAK

As of November 2022, there have been 77,092 cases of monkeypox worldwide in 109 countries. There have been 28,442 cases in the United States with six deaths, and 800 cases in Pennsylvania.[14] Thirteen cases have been diagnosed within the Penn Medicine Lancaster General Health system. Nationally, cases peaked in mid-August and are declining overall, presumably due to education and prevention, diagnosis and treatment, and vaccination.

The highest incidence of cases remains among MSM, with the highest burden in the 31-35 age group (see Fig. 2 on page 70).[15] Initially, the most affected racial group was white individuals, but this has transitioned to Black individuals being most affected. Behavioral data collected from gay, bisexual, and MSM through a monkeypox supplemental survey of the American Men's Internet Survey in August demonstrate active behavioral modification, with 48% of respondents reducing number of sexual partners, 50% reducing one-time sexual encounters, and 50% reducing sex with partners met on dating apps or at sex venues.[16]

Internationally, specifically in South America and Africa, case numbers continue to rise.[17] Given the novelty of the virus outside of endemic regions, likely underreporting/under-identification of cases, potential for spread to new animal reservoirs, and likely return to

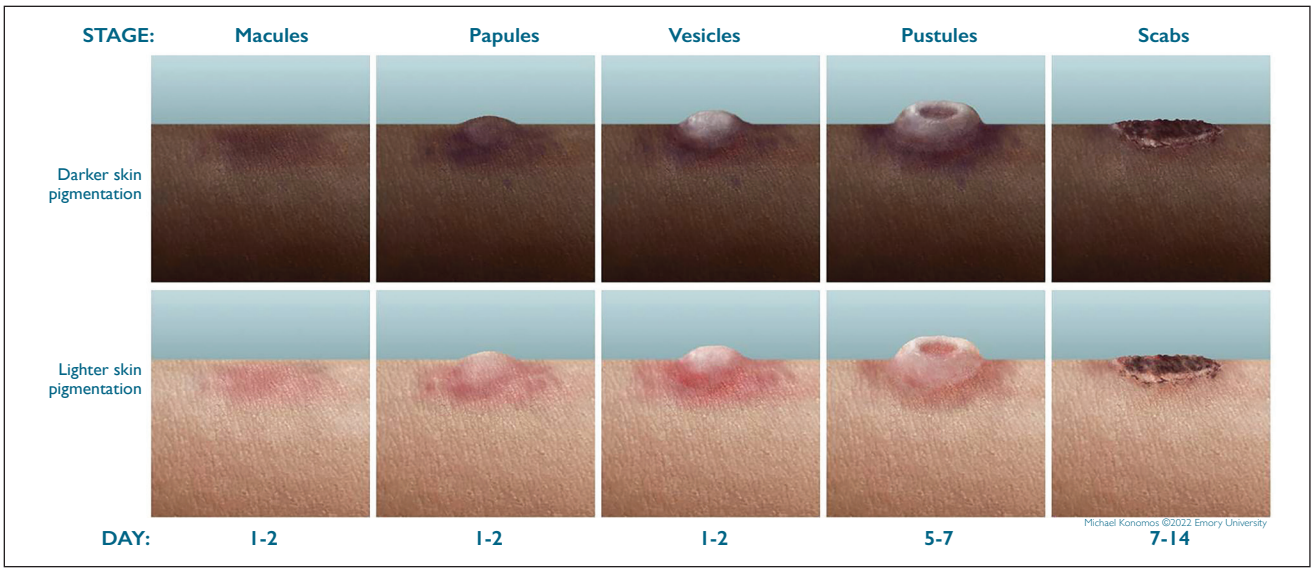


Fig. 1. Monkeypox skin lesion progression. Clinicians should be aware of how lesions may present on the spectrum of skin pigmentation.
Source: Titanji et al.[5], licensed under CC BY-NC-ND 4.0.

pre-outbreak sexual habits in high-risk populations, the direction the epidemic will take and whether the virus will become endemic in a larger number of countries remain unpredictable. Additionally, vaccines are not yet available in Africa, hampering control in endemic countries, thus long-term projections are unreliable. However, short-term epidemic case forecasts published weekly by Chowell-Puente, an infectious disease modeler out of Georgia State University, have been generally accurate to date.

PREVENTION

For the general public, the CDC recommends that people avoid close, skin-to-skin contact with anyone with a rash that could be monkeypox and avoid contact with any objects or materials that have come in contact with a person who could have monkeypox.[18] Frequent handwashing with soap and water is also recommended.

Providers should wear a gown, gloves, eye protection (goggles or face shield), and an N95 respirator while interacting with patients with suspected monkeypox infection. Patients should be evaluated and treated whenever possible in a single-person room. While special air handling is not required for initial evaluation and treatment, any aerosolization procedures, such as intubation and extubation, should be done in an airborne infection isolation room.[18]

Prior vaccination against smallpox appears to provide some protection against symptomatic and severe illness from monkeypox. In one study in the DRC, individuals who were previously vaccinated against smallpox were shown to have a fivefold lower risk of monkeypox compared to unvaccinated individuals during a monkeypox outbreak in 2010.[19] In the United States, data from the 2003 monkeypox outbreak also suggest that a history of smallpox vaccination reduced the chance of symptomatic monkeypox infection.[20] However, this immunity likely wanes with time and there is insufficient evidence to evaluate whether previous smallpox immunization confers protection in the current outbreak.

VACCINATION

Two vaccines are available to reduce risk of severe monkeypox infection. The preferred vaccine is the modified vaccinia Ankara (MVA) vaccine, which is available as JYNNEOS in the United States.[21] It is an attenuated pox virus vaccine that has been approved for the prevention of monkeypox and smallpox, and it has a strong safety profile. It can be given as a two-dose series over four weeks subcutaneously. Due to supply shortages, the CDC and Food and Drug Administration (FDA) approved intradermal administration of this vaccine under Emergency Use Authorization. The intradermal route requires one-fifth of the standard vaccine dose, and early studies show a similar immune response in comparison to subcutaneous administration.[22]

The second vaccine available is called ACAM2000. It was developed as a smallpox vaccine but has been made available for use against monkeypox under an Expanded Access Investigational New Drug protocol by the CDC. While large doses of this vaccine are available, it has both more side effects and more contraindications than the MVA vaccine.[21]

Two special populations to consider when counseling on vaccination include pregnant patients and immunocompromised patients. While there are minimal data available on monkeypox and monkeypox vaccine in pregnancy, the American College of Obstetricians and Gynecologists (ACOG) recommends pregnant patients who are eligible for vaccination receive JYNNEOS because the vaccine-associated risks in pregnancy appear

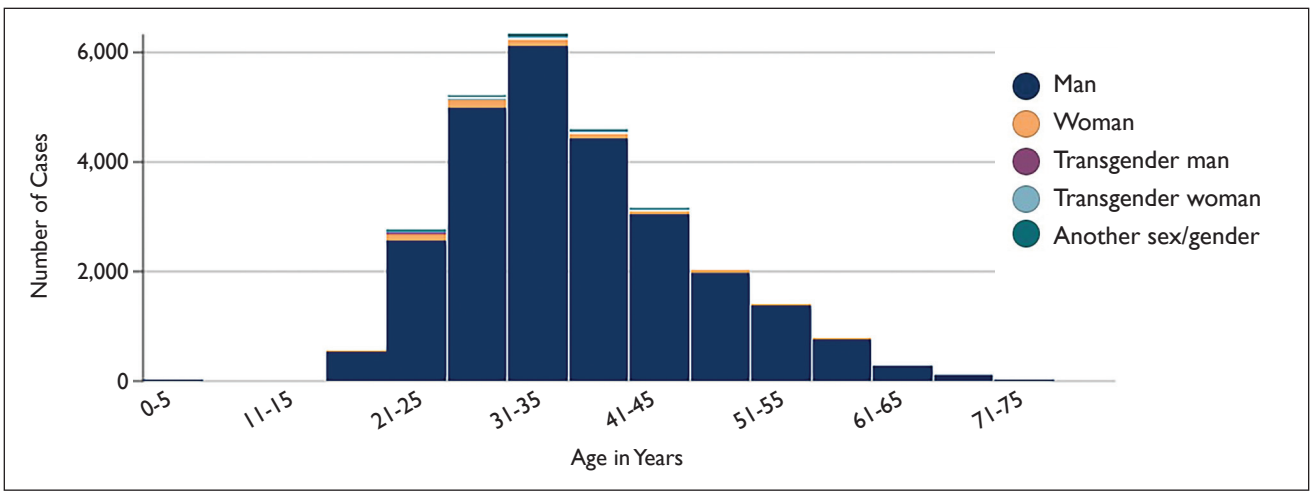
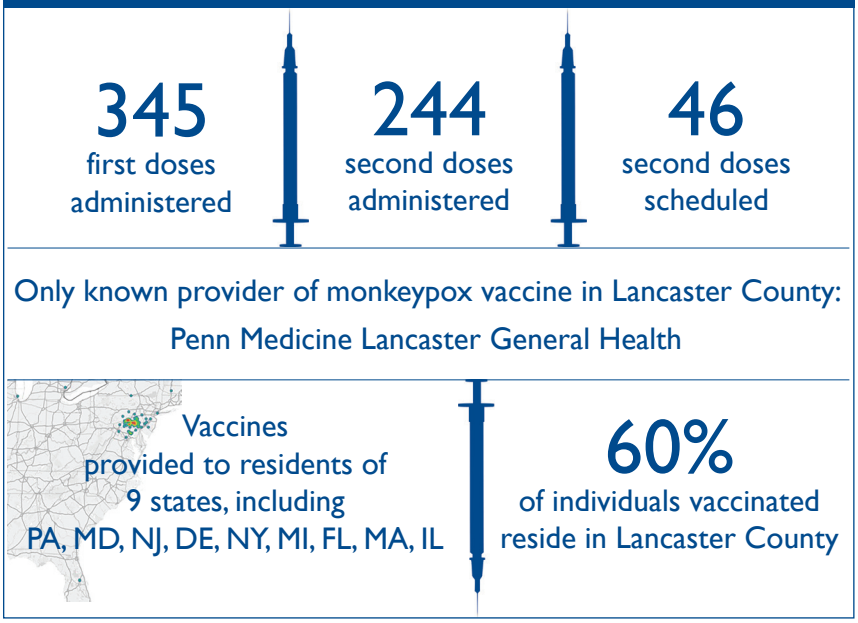


Fig. 2. U.S. cases of monkeypox reported to CDC: age and gender.[15]

to be lower compared to ACAM2000, which is contraindicated in pregnancy. It is unknown if patients who have received JYNNEOS can safely breastfeed, but because the MVA vaccine is replication deficient, it is unlikely to pose a significant risk of transmission to breastfed infants.[23] JYNNEOS is approved for use in immunocompromised individuals who are not recommended to receive other live vaccines.

Eligibility for the vaccine is governed by local and state health departments and depends on community prevalence and individual risk factors. In general, the CDC recommends prioritizing post-exposure prophylaxis (PEP), which means vaccinating individuals after known exposure. PEP vaccination should ideally be done within four days of exposure to prevent disease but may be considered up to 14 days after exposure to decrease disease morbidity.[24]

Fig. 3. Monkeypox Vaccinations at LG Health
(as of October 24, 2022)



Secondarily, public health entities are encouraged to consider expanded post-exposure prophylaxis (PEP++) when resources are available. PEP++ refers to the vaccination of individuals who may have had exposure to monkeypox, individuals who have had experiences that may increase their risk of monkeypox exposure, or individuals who live in a defined geographic area where monkeypox transmission is occurring at high rates.

Lastly, pre-exposure prophylaxis (PrEP) is vaccination before exposure to monkeypox and has been largely restricted to people in occupational risk groups, such as laboratory workers, health care workers, and public health responders directly handling viruses or treating patients with monkeypox.[24] Locally, vaccination eligibility guidelines are available at www.lghealth.org/monkeypoxvaccine. Vaccination clinics were held at LG Health from August to October (see Fig. 3) but have been stopped as the community need has largely been met. LGHP Comprehensive Care will continue to have a small number of vaccine doses available for patients to start and complete the vaccine series, as needed. The CDC offers a monkeypox vaccine locator online at mpoxvaxmap.org.

Data are emerging regarding vaccine uptake and effectiveness from across the United States. To date, 1,012,283 doses of JYNNEOS vaccine have been administered.[25] A CDC-led, monkeypox-specific follow-up study of the American Men's Internet Survey found that about one in five respondents received at least one dose of monkeypox vaccine. Uptake was highest among Hispanic or Latino men (27.1%) and lowest among non-Hispanic or African American Black men (11.5). Rates varied considerably between urban (27.8%) and rural areas (5-7%).[16]

Data suggest vaccination is an effective tool in controlling the outbreak. In one monitoring study by the CDC that included data from 32 U.S. jurisdictions among vaccine-eligible males aged 19-49, unvaccinated individuals were at 14 times the risk of acquiring monkeypox compared to their vaccinated counterparts.[25] However, these data were not controlled for age, underlying conditions, or behavior, so larger studies are needed to determine true vaccine effectiveness.[17]

DIAGNOSIS

The diagnosis of monkeypox is based on clinical evaluation (see above) and laboratory confirmation via PCR testing from monkeypox lesions.[26] Locally, this is a send-out lab that takes 3-5 days to result. Testing the appropriate patient and testing them correctly is critical because medications for treating monkeypox are distributed by the Pennsylvania Department of Health and only available for laboratory-confirmed cases. For the most part, only patients with a rash consistent with monkeypox should be tested. Providers testing patients should collect swabs from multiple lesions, two swabs per lesion. Collecting samples from lesions on different

Table 1. Potential Treatment Options for Monkeypox

Medication Name	Approved for ...	Used at LG Health for Monkeypox?
Tecovirimat	Smallpox	Yes
Cidofovir	Cytomegalovirus	No
VIGIV	Smallpox	No
Brincidofovir	Smallpox	No*

**Yet to be released from Strategic National Stockpile*

parts of the body is preferred, but it is important to keep swabs from lesions, crusts, and exudate in separate specimen containers. The lesion should be swabbed vigorously but not unroofed. If a patient does not have a rash but has systemic symptoms, a high risk of exposure, and pharyngitis or proctitis, an oropharyngeal or rectal swab, respectively, should be collected using the same supplies used for testing of lesions. The sample must be refrigerated within an hour of collection.

Culture-based testing is not recommended for clinical practice or diagnosis.[27] Locally, testing supplies can be requested through the LG Health core laboratory courier. The swabs are polyester tipped and sent in viral transport media; these are the same swabs used for herpes simplex virus testing.

MANAGEMENT

Isolation

Patients diagnosed with monkeypox, and those awaiting test results, should remain isolated for the duration of the illness, which lasts until scabs fall off and a new layer of skin is present for all prior lesions. This typically takes two to four weeks.[28] If a patient is unable to remain fully isolated, they should:

- Avoid crowds.
- Avoid any physical or sexual contact.
- Avoid contact with pets and animals.
- Wear a mask at all times when around other people.
- Cover up all rashes or lesions.
- Avoid sharing utensils or cups.
- Avoid sharing clothing or bedding.
- Wash hands with soap and water frequently.

Contact Tracing

Whenever possible, patients should create a list of close contacts, including anyone with whom they have had close physical contact in the three weeks prior to infection, and notify them of their possible exposure to monkeypox so that those close contacts can be evaluated for vaccination (see PEP and PEP++ above). The state health department will also assist in contact tracing and confidential exposure notification, as needed.

Mild to Moderate Illness: Supportive Care

For many immunocompetent individuals, monkeypox illness is mild and only requires supportive care. Early pain management of skin lesions is key to effective supportive care. Acetaminophen and NSAIDs are recommended as first-line therapies for pain control. Topical steroids and anesthetics, such as hydrocortisone and lidocaine cream, can be effective adjunct agents but must be used carefully in patients with open wounds.

For patients who develop proctitis, stool softeners, Sitz baths, sucralfate enemas (need compounded), or calmol suppositories can be added to the aforementioned pain regimens. Itching can be treated with oral antihistamines or topical antipruritics, such as diphenhydramine cream, calamine lotion, or mild topical steroids. Lesions should be closely monitored for signs of superimposed bacterial infection, abscess formation, or spread to sensitive areas — such as anogenital, ocular, and oropharyngeal lesions — which require more aggressive treatment and closer monitoring.

Severe Illness and Vulnerable Populations: Antiviral and VIVIG Therapies

While there is no specific treatment yet approved for monkeypox, antiviral and immunoglobulin therapies developed for other conditions have been made available to treat monkeypox with the hope that they may help slow the progression of symptoms and curtail the duration of illness, especially in cases of severe illness or in vulnerable patient populations.

Severe illness includes sepsis, encephalitis, periorbital infection, abscess formation, confluent skin lesions, and lesions located in the oropharynx and anogenital regions that can cause severe pain.[29] Patient populations that are susceptible to rapid disease pro-

gression and severe illness who should be considered for these therapies include those living with uncontrolled HIV/AIDS cancer or other immunocompromising conditions, as well as those receiving radiation therapy, immune modulating therapies (TNF inhibitors, high-dose corticosteroids), and transplant recipients.[29] In addition, children younger than 8 years old, pregnant and breastfeeding patients, and patients with skin disease (e.g., psoriasis, eczema, severe acne) should also be considered for these antiviral therapeutics.

In the outpatient setting, patients who meet these criteria can be referred to the LGHP Comprehensive Care practice for treatment. Patients who are admitted to Lancaster General Hospital with suspected severe monkeypox require a consult to LGHP Infectious Diseases to determine their management.

See Table 1 for potential treatment options for monkeypox. The three medications currently available include: tecovirimat (TPOXX), cidofovir (Vistide), and intravenous vaccinia immune globulin (VIGIV).

Tecovirimat is an FDA-approved treatment for smallpox available in pill and IV formulation. It has been made available for use in monkeypox cases through the CDC's New Investigational Drug protocol, which allows for expanded use during a poxvirus outbreak.[30] The NIH is studying the efficacy of tecovirimat against monkeypox in a new clinical trial,[31] but there is no definitive data on effectiveness at this time. It is the medication most widely available and has been used to treat patients in Lancaster.

Cidofovir is an antiviral medication developed to treat cytomegalovirus retinitis in patients with AIDS; it has shown some effectiveness against orthopoxviruses in cellular and animal studies.[32] As a result, it has been made available for treatment of monkeypox infections, though no human data are available to confirm its efficacy. VIGIV was developed to treat complications of smallpox vaccination. It is unknown whether it is effective against monkeypox, but researchers hypothesized that it may be helpful in patients with severe immunodeficiency in T-cell function who cannot receive vaccination against monkeypox. Brincidofovir is another antiviral medication developed to treat smallpox which may be available in the future to treat monkeypox; however, it has not been released from the Strategic National Stockpile for use during the current outbreak due to questionable effectiveness and known increased risk of toxicity compared to tecovirimat.[29]

STIGMA

While countries with endemic monkeypox transmission are in Africa and the highest incidence of monkeypox in the United States is among MSM, this is neither an African disease, nor a disease of MSM. To prevent stigma, providers must provide clear, evidence-based, and non-discriminatory messages. Anyone, regardless of sexual partners, can acquire monkeypox. As described above, the modes of infection are the same for all individuals: skin-to-skin contact (which can occur during sex), contact with fomites, or respiratory secretions.

The CDC has outlined specific communication recommendations to prevent stigma, which include using inclusive language such as "us" and "we"; avoiding sensational language and images; using language that resonates with the audience; using positive and diverse images; and emphasizing preventive strategies, symptom recognition, and the treatable nature of the disease to allay public fear and promote self-action.[33,34]

For individuals in high-risk groups, it is beneficial to work with already-established community-specific avenues of communication, such as specific websites, dating apps, and community partners. In these settings, relatable, personal stories can be helpful. Educational materials available from the CDC meet these guidelines.[34] Utilization of these methods will decrease silent spread in the community and the worsening of an individual's symptoms that can result when fear of experiencing stigma delays presentation for care.[35]

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A Woman Cured of Refractory Atypical HUS-TTP after Bilateral Nephrectomy

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INTRODUCTION

This case report describes a patient who was diagnosed with atypical hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) who required continuous plasma exchange for a period of eight months. She developed seizures when attempts were made to wean her off plasma exchange, and her case was not responsive to immunosuppression and treatment with rituximab (Rituxan). Ultimately, however, her microangiopathy resolved after she underwent a bilateral nephrectomy.

CASE REPORT

A 24-year-old female was in her usual state of wellness until she presented in April 2008 to Lancaster General Hospital (LGH) with profound fatigue. Her exam was normal, including no evidence of rash; vitals were also normal, including a normal blood pressure. Lab evaluation revealed *de novo* acute renal failure (Cr = 13 mg/dL, ref. 0.5-1.0 mg/dL), with microangiopathic hemolytic anemia — hemoglobin = 6.7 g/dl (ref. 12-16 g/dl) — and thrombocytopenia — platelet count = 96,000 platelets/µL (ref. 150,000-450,000 platelets/µL). Her lactic acid dehydrogenase (LDH) was elevated to 284 U/L (ref. 48-115 U/L) on presentation. Her urinalysis was consistent with acute tubular nephritis. As reference, labs were drawn two years earlier revealing a creatinine of 0.8 mg/dL and a hemoglobin of 11.1 g/dL.

Follow-up labs conducted at that time revealed that her ANA (antinuclear antibodies) was negative and a haptoglobin was <5.8 mg/dL (ref. 41-165 mg/dL). A stool study for *E. coli* 0157:H7 was also negative, and a blood smear revealed only a scant amount of schistocytes. However, an ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) test was normal.[1] The conclusion by her care team at LGH was that she had an atypical HUS-TTP.

After several days of dialysis and blood product resuscitation, she underwent a percutaneous renal biopsy. This revealed 13 to 16 glomeruli, found to be globally sclerotic. Three glomeruli revealed significant evidence of thrombotic microangiopathy, and she was positive for perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA). The biopsy demonstrated a cellular crescent, presumed to be consistent with an anti-myeloperoxidase (MPO) vasculitis (see Figs. 1a and 1b on page 76). Thus, atypical HUS-TTP remained the working diagnosis.

At the time of her admission, the patient was treated with daily plasma exchange, as well as hemodialysis three times a week. Her platelets and hemoglobin stabilized, then rose at the time of hospital discharge (see Fig. 2 on page 76). In the setting of a positive ANCA and MPO, she was placed on daily prednisone and mycophenolate mofetil (CellCept). She was discharged from LGH on May 6, 2008. She continued hemodialysis three times per week for end-stage renal disease; daily plasma exchange was continued after her discharge home.

When her LDH levels fell, she was weaned off plasma exchange. However, her LDH began to rise again, and she developed a new-onset headache on May 16, 2008, thus she was readmitted to LGH, had a witnessed seizure, and was subsequently started on levetiracetam (Keppra).

She reinitiated daily plasma exchange and required twice-daily plasma exchange treatments. During this admission, her LDH peaked at over 400 U/L. Her platelets nadired to a low of 85,000/µL. She appeared to clinically respond to prednisone, CellCept, and plasma exchange. However, despite this initial treatment, she continued to have headaches and nausea, and her platelets began to decline again. After a discussion with the patient and her mother, a decision was made to transfer her to a tertiary care academic center for additional evaluation and management. She was transferred to Johns Hopkins University Hospital on June 6, 2008.

On the morning of June 9, 2008, the patient demonstrated an altered mental status. She would not speak in

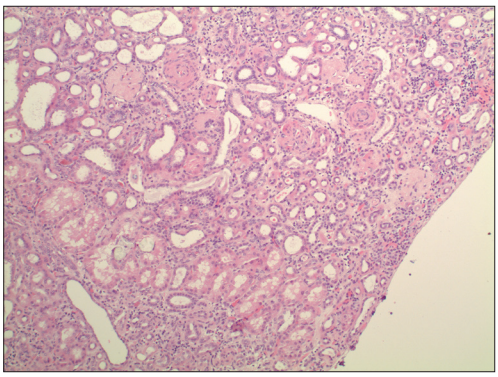
response to questions and would only follow simple commands. There was a concern for stroke, metabolic derangement, or seizure. A head CT was negative, and an EEG showed no focal seizure activity but did demonstrate severe diffuse cerebral disturbance consistent with metabolic derangement. This was attributed to uremia, and a consult was placed to the neurology service. The hematology service and rheumatology service were also involved in the workup.

The patient's platelets at this time ranged between 80,000-120,000/μL, and her LDH was in the 300s. Plasmapheresis was initially started but then held by discharge. She required a transfusion of two units of packed red blood cells when her hemoglobin dropped to 6.3 g/dl. ADAMTS-13 was again negative, and consulting providers thus concluded that TTP was unlikely.[1] Additionally, ANCA was negative, and ANCA-associated vasculitis did not adequately explain the clinical picture.

Systemic lupus erythematosus, immunoglobulin A nephrology, microscopic polyangiitis, and antiphospholipid syndrome were felt to be possible, but unlikely, as their findings were inconsistent with the full clinical picture. Her providers also believed that she did not have a rheumatologic process. The hematology department considered as their final diagnosis that renal disease plus HUS could be explained by Factor H or Factor I deficiency.

A lack of adequate red cell production as evidenced by anemia and persistently low reticulocyte count led to bone marrow biopsy, however this was negative for any conclusive pathologic hematological process. There was no indication for immunosuppression, and consulting physicians agreed there was no evidence of vasculitis after repeat studies. It was not possible to identify any precipitant (e.g., quinine) for her disease. She was discharged home from Johns Hopkins on June 17, 2008.

The patient was weaned off her seizure medications at the time of discharge. As the medical team believed that TTP was unlikely, the patient was also weaned off treatment with plasma exchange as she was discharged from Johns Hopkins. Unfortunately, she suffered another seizure while at home in Lancaster and was readmitted to



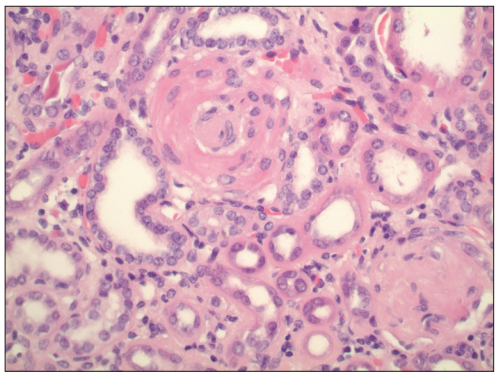


Fig. 1a (left). 20x magnification, showing thyroidization of the kidney tissue, including dilation of tubules in the upper left-hand corner, chronic change features usually seen in end-stage renal disease.

Fig. 1b (right). 40x magnification, demonstrating an atherosclerotic small blood vessel in the upper center and a sclerotic glomerulus in the lower right-hand corner. These features are also consistent with chronic kidney disease, most often seen in those much older than this patient.

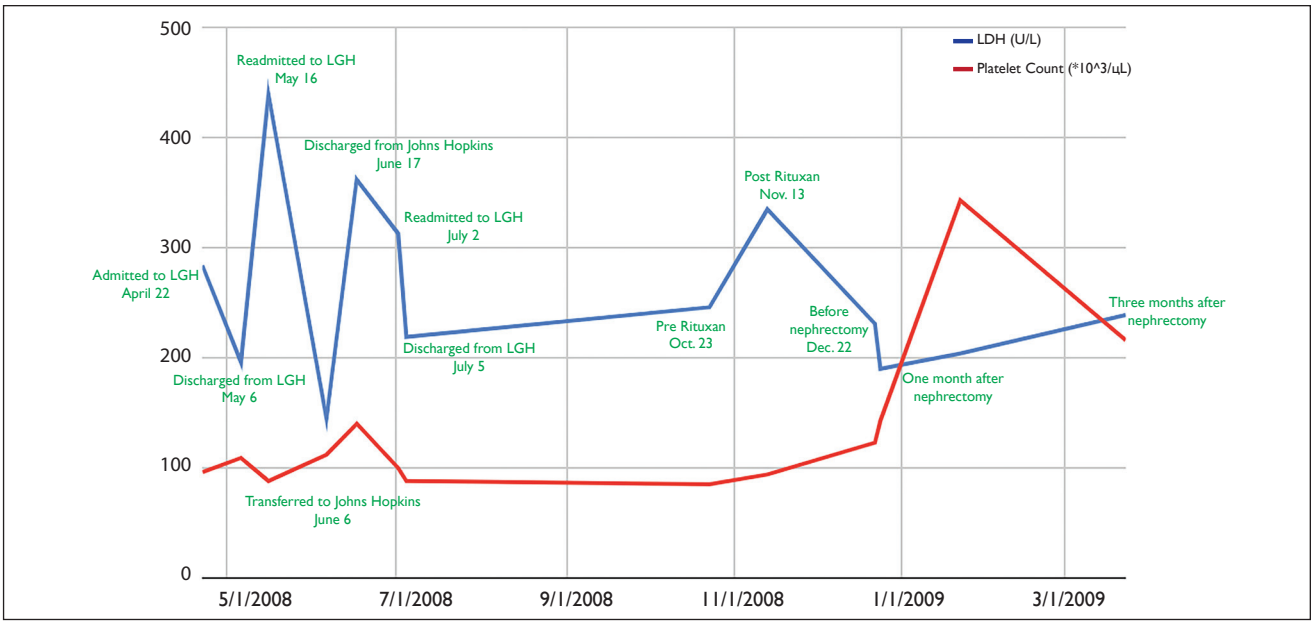


Fig. 2. Patient's LDH and platelet count from first admission through postop. Normal range for LDH = 49-206 U/L and for platelet count = 150-450 *10^3/μL.

LGH in July 2008. At that time, her LGH care team resumed her anti-seizure medications and plasma exchange treatments in accordance with the original working diagnosis of atypical HUS-TTP.

She then stabilized clinically with twice-weekly plasma exchange treatments. When attempts were made to decrease her plasma exchange treatments to once weekly, her platelet count declined from 155 to 94 to 85 platelets/uL; concurrently, her LDH rose from 186 U/L to 221 U/L to 246 U/L. Therefore, she was maintained on plasma exchange twice a week.[2]

The patient began treatment with peritoneal dialysis and was placed on the kidney transplant list. In October 2008, treatment with Rituxan 375 mg/m2[3] weekly along with twice-weekly plasma exchange[2] did not result in any meaningful improvement in her platelet count.

As it was impossible to wean her off plasma exchange after five months of twice-weekly plasma exchange treatments, an outside consultation was obtained from James George, MD, professor of medicine at the University of Oklahoma, former president of the American Society of Hematology, and a nationally known expert in platelet disorders. He reasoned that the kidneys were the source of her atypical HUS-TTP and thus recommended a bilateral nephrectomy as the curative treatment for her ongoing hemolysis.[4,5]

The patient ultimately underwent this operative procedure on December 23, 2008. Pathology of the bilateral nephrectomy was consistent with Morcellated kidneys showing end-stage changes. Renal artery margins showed moderate intimal thickening with no evidence of vasculitis of either the renal artery or renal vein.

Within a week of her nephrectomy, the patient's LDH normalized, her platelet count rebounded to normal levels, and her hemolysis completely resolved. In a short time, she no longer needed plasma exchange treatments. She remained on dialysis for several years after this cure and did well without any further requirements for plasma exchange. She was awaiting a kidney transplant when she died suddenly in the setting of substance abuse, complicated by concurrent dialysis treatment nonadherence.

DISCUSSION

In this case, despite eight months of therapy with plasma exchange, immunosuppression, and Rituxan treatments, the patient was unable to be weaned off plasma exchange. The nidus of her microangiopathic hemolytic anemia appears to have been her renal disease. When the kidneys were removed, her hemolysis resolved.

The efficacy of plasma exchange as a cure in atypical HUS-TTP remains around 75%.[6] The use of plasma exchange is considered successful when the platelet count remains >150K over a minimum period of two days.[7] There remain resistant and/or refractory cases in which the use of Rituxan, steroids, or the more recently approved Caplacizumab may also be utilized to cure the disease.[8] However, some cases may remain refractory to all of the above, such as was true this patient.[4,5]

Very limited data indicate that bilateral nephrectomy may serve as a rescue therapy in plasma-exchange resistant disease due to the assumption that the kidney microvasculature is the site of platelet consumption and the ongoing nidus of disease persistence.[1,2] In patients with atypical HUS-TTP who present with end-stage renal disease refractory to plasma exchange and other accepted therapies, bilateral nephrectomy may be considered as a potential curative option.[1,2]

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Shots in Arms
Lessons Learned from a COVID-19 Mass Vaccination Site

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When it became clear in late 2020 that a COVID-19 vaccine would be ready for distribution, the federal government and local institutions across the country began planning for mass vaccination centers. Galvanized by the charge to get "shots in arms" in Lancaster County and the surrounding area, a public-private partnership formed to create the Vaccinate Lancaster Community Vaccine Center.

The partnership, sponsored by a federal grant via the county commissioners, brought together a team of health care, entertainment, safety, and logistics experts. Together, this team delivered more than 238,000 doses over the course of 104 days. This article outlines the critical components that helped to achieve these results.

THE TEAM AND ITS WORK

Health systems from across the area came together, with one — Penn Medicine Lancaster General Health — assuming leadership, along with Rock Lititz, a local company with expertise in the live event industry, and TriStarr, a local staffing agency. The diversity in backgrounds across the leadership team, along with the desire to help mitigate and potentially end the impact of the global pandemic in their respective industries, proved to be highly effective in creating an aligned and agile operating team.

This team worked quickly to create the infrastructure necessary to launch a community vaccination center. The local mall's property management group, Brookfield Properties, donated a 10,000-square-foot vacant department store to serve as the base of the operation.

Prior to the center's opening, operational leaders met to establish and record workflows by developing a mockup of the site. To maximize flow and capacity, they created a unique vaccine delivery model where patients remained in their chair for the entire experience, including the required 15-minute observation period.

Patient chairs were grouped into units of five, called "cells." Each vaccinator was assigned a cell. In a 10-hour day, one vaccinator could administer 150 shots, spending up to four minutes with each patient. Cells were then grouped to create a pod, supported by a greeter and an additional staff member to ensure patients were ready for vaccination. In total, the center could support 12 pods or up to 6,600 patients each day.

Vaccine preparation, which included reconstitution and drawing up individual doses, was completed onsite using an hourly batching process. Initially, the medical team administered vaccines by appointment only, allowing them to hone production using data analytics to predict vaccine volume and minimize waste. They also implemented and improved upon a complex end-of-day reconciliation process in an effort to use all drawn doses by day's end. To ensure minimal waste, patients with future appointments were called and asked to be on a daily standby list. As all associated processes improved, walk-ins were accepted to further improve access.

Other initiatives to improve access included the availability of a community website and call center, an on-demand interpreter service on a mobile cart, and staff to provide wheelchairs and serve as guides for those with mobility needs. Privacy areas were available for those with medical, religious, or cultural concerns that precluded them from being vaccinated in a public setting. Over time, Vaccinate Lancaster offered car vaccinations for those unable to safely enter the facility and designated a private space to vaccinate in a supine position those at risk of syncopal episodes.

The center further supported pop-up clinics in the community by offering staffing and supplies. When vaccine eligibility was expanded to include children 12 years of age and older, center staff modified a pod to allow parents and legal guardians to accompany the minors. Staff also modified pods into a family area to support groups of three or more, while offering activities to serve as distractions.

Visual management proved to be critical to ensuring safety and efficiency, particularly with multiple vaccine manufacturers (i.e., Johnson & Johnson's Janssen, Pfizer-BioNTech, and Moderna) and dose series onsite. Upon entering, individuals were registered and provided

a color-coded sticker and documentation. Color-coding ensured that individuals followed the correct path, landed in the correct queue, and ultimately settled into the correct chair to receive the appropriate vaccine. Minors were identified with badges to ensure consent was obtained and proper techniques followed.

Production and delivery of vaccines were color-coded and kept geographically separate to minimize any risk associated with movement of vaccine. Staff aiding in emergency situations, such as vaccination adverse events, wore high-visibility vests to make them easily identifiable. The presence of local constables throughout the center provided a visual cue to both staff and community members that safety was a top priority.

IMPROVING OPERATIONS

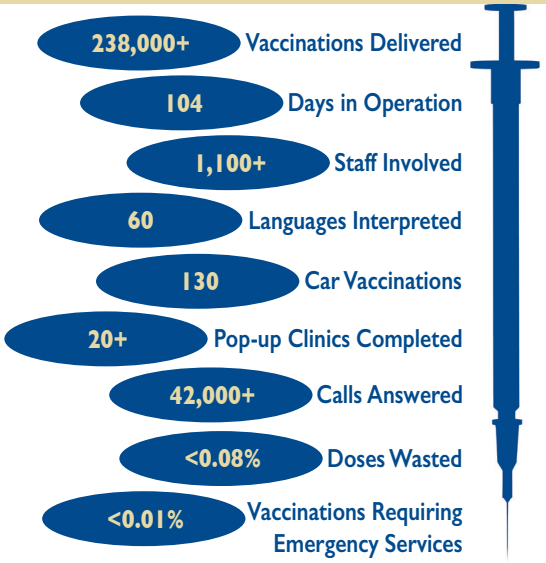
Communication in such a fast-paced operation was of utmost importance. Key leaders and personnel carried radios to allow real-time communication. Staff huddles were held twice daily for each functional team (logistics, registration, clinical, supply, pharmacy), followed by leader huddles to ensure the flow of information. Lean management principles were applied to bring ideas or concerns forward, solidify standard processes, share key metrics, and encourage performance improvement in the form of rapid cycle experiments. Care was taken to limit experiments to two per day to avoid overwhelming the staff and operation.

When appointment volume ramped up, staffing was a critical component in the ability to turn cells and pods "on" or "off." Given the hours of operation (10 hours, 7 days/week), initial staffing projections proved to be inadequate, particularly for vaccinators. Leaders brought in additional staffing resources, such as the National Guard and a nursing agency, in an expedited fashion. Leaders also developed a streamlined orientation process to ensure staff were properly and quickly trained. An easy-to-use online staffing software tool was used to schedule and communicate with staff.

As demand began to wane, efforts shifted to creating warm hand-offs for both patients and staff. The call center followed up with patients who had outstanding second dose appointments to encourage patients to complete their series prior to closing. Additionally, a process was created and staffed to schedule second dose appointments at partner health systems. For staff seeking employment opportunities, those in good standing were invited to a job fair where all partnership entities were present.

While the center proved highly effective at delivering a high volume of vaccinations efficiently (see Fig. 1), leaders recognized opportunities for improvement along the way. Patients reported having an excellent experience once they were present at the center, however the process to register for an appointment was challenging.

Fig. 1. Key Results



In the initial phases of vaccination, demand far exceeded the guaranteed supply delivery to the center. During this time, patients could register online, but were not guaranteed an appointment unless randomly selected via a digital lottery. As a result, individuals who were technically savvy created multiple registrations, giving them an unfair advantage.

CONCLUSION

Ultimately, the collaboration and work by many helped to save countless lives. Creating a unique and precise operational model — and evolving that model to meet the needs of various community constituents — proved to be successful in meeting the center's objectives in a short amount of time. The center had the potential to provide far greater than the number of vaccines administered, leading to further need to study engagement opportunities across a diverse community.

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Holding Out Hope or Permitting Suffering?

A Case of Medical Ethics

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"If you can, help others, if you cannot do that, at least do not harm them."
— Dalai Lama XIV

THE CASE OF E.C.*

E.C. was a 26-year-old Black female with a past medical history of lupus. She previously required a 13-month hospital stay for infection with parechovirus necessitating a tracheostomy and PEG tube placement. Having recovered from that set of circumstances, she presented to Lancaster General Hospital in January 2022, 15 days after testing positive for SARS-CoV-2. Her COVID-19 symptoms were worsening upon presentation and included fever, cough, and respiratory distress. Her condition quickly deteriorated, and she soon required ventilator support and venovenous extracorporeal membrane oxygenation (VV ECMO).

The patient did not have advanced care planning documents, and according to PA Act 169,[1] the patient's father was her health care representative; thus, consent for each of these measures was obtained from her father. What followed was a protracted hospitalization, lasting 97 days (see Fig. 1). During her stay, numerous health care professionals were involved in E.C's care.

Although her care team soon realized that her condition was not survivable, E.C.'s father continued to choose for the health care team to pursue all life-preserving measures. During this time, her father appeared emotionally unable to hear any negative news regarding her prognosis. He did not visit her in person. As a result, several ethical dilemmas became evident in her care, and the Penn Medicine Lancaster General Health Ethics Committee was consulted to help provide assistance to all involved.

ETHICAL QUESTIONS AND CONSIDERATIONS

The following are some of the ethical considerations surrounding E.C.'s care. The Ethics Committee members, in their consultation, weighed these factors, among many, as they formulated their recommendations regarding E.C.'s case.

Who is the appropriate decision-maker? E.C. did not have an advanced directive and did not have capacity to make decisions after she had been sedated, intubated, and started on ECMO. According to PA Act 169,[1] her father would be her health care representative. A health care representative has the responsibility to use substituted judgment to act as the patient would if they had decision-making capacity. When a patient is unconscious or in an end-stage condition, a health care representative may make decisions involving withdrawal of life-sustaining care.

When does care become potentially inappropriate? "Potentially inappropriate treatment [or] non-beneficial treatment [references a] medical effort to provide a benefit to a patient when reason and experience suggest it is highly likely to fail and whose rare exceptions cannot be systemically produced."[2] ECMO, for example, is designed as a bridge to recovery or transplant. When both outcomes became exceedingly unlikely, one could argue that continuing ECMO became inappropriate.

The term "futile" has fallen out of favor. "Futile" does not take into account that all decisions regarding medical interventions are made based on weighing the probabilities of particular outcomes.

What principles of biomedical ethics are involved? In this case, all four principles are involved, namely autonomy, beneficence, non-maleficence, and justice. These principles must be weighed and balanced against one another.

- *Autonomy:* Patients have the right to make their own informed decisions about their care, provided they have the cognitive ability to weigh the risks and benefits of treatment decisions. Autonomy as an ethical principle holds enormous weight in

**Names changed out of respect for privacy rights of individuals involved.*

Western biomedical ethics. This right extends to the health care agent/representative acting on a patient's behalf.

In this case, however, the patient's representative was not present with the patient in the hospital for extended periods of time and repeatedly declined to receive bad news surrounding her prognosis. Thus, the Ethics team had concerns about the representative's informed, cognitive ability to make decisions. Nevertheless, the team tried to provide a complete picture of the situation while attempting to reduce undue psychological stress on E.C.'s father.

- *Beneficence:* Health care providers must act in the best interests of their patients. ECMO is a life-sustaining treatment, and withdrawal of ECMO in this case would lead to death. In previous hospitalizations, E.C's father had seen her make miraculous recoveries despite her care team delivering poor prognoses. As such, he was wary of prognostication. On the flip side, in the absence of potential meaningful recovery, ECMO could lead to unnecessary prolongation of patient suffering.
- *Non-maleficence:* Harms to patients must be minimized when providing care. E.C., especially toward the end of her hospital course, was showing signs of suffering and possible iatrogenic harm. For example, it was documented thoroughly in the record that she was experiencing body decompensation with pressure ulcers and critical limb ischemia. Her body started to go through the process of auto-mummification. She would frequently cry with repositioning. The care team witnessing this experienced significant distress. There was increasing mention in the medical record over time of the patient's tears, and concern that the level of care being provided was prolonging E.C.'s suffering.
- *Justice:* In recognition of limited resources, care must be provided equitably. This includes ECMO, ICU rooms, ventilators, staff, and blood products, all of which were utilized in the care of E.C. In addition, E.C. continued to test positive for SARS-CoV-2 during her hospitalization. Thus, there was additional concern for the safety of the staff involved in her care.

POTENTIAL BIASES AND PRECEDENT

We also note potential biases in this case. Racism permeates the structural underpinnings of American health care and has direct negative implications for

Fig. 1. Hospitalization Overview

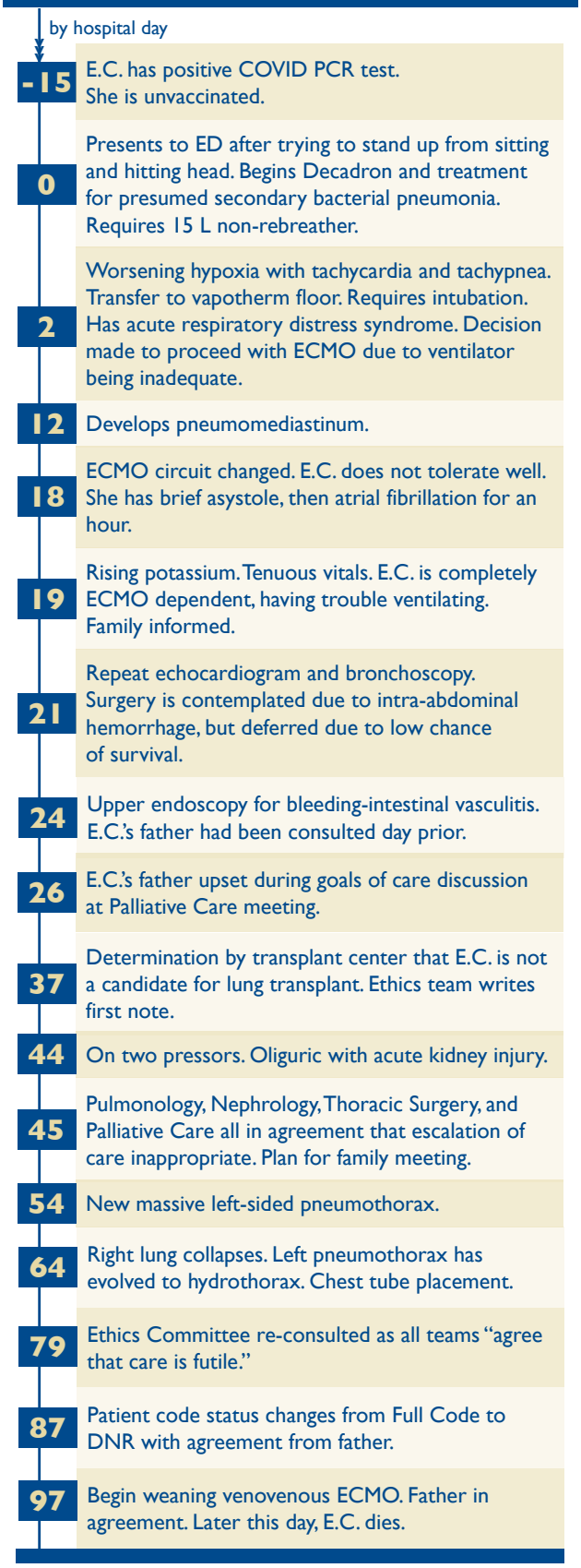

Fig. 2. Resources Available to Support Care Teams

- LG Health Critical Response Team
- Free counseling services through EAP and Penn Cobalt
- Nurse Leadership: nurse managers, nursing professional development practitioners, clinical nurse specialists
- Palliative Care Team
- Chaplain Department

Additionally, the LG Health Ethics Committee can be consulted by any member of a patient's care team for any patient in the LG Health system as these questions arise. Please reach out if you feel that a patient, family, or the care team could benefit from an Ethics Committee consult. The committee thanks you for your care of patients and your care of one another.

clinical outcomes for Black patients. Mistrust of the health care system may have stemmed in part from this reality. Further, bias related to age may have impacted her care. Had E.C. been elderly, the family and care team may have perceived the appropriateness of her care differently.

The above considerations are contextualized by policy and precedent. Navigating cases where the care team and family cannot come to an agreement regarding the appropriateness of care can be challenging. The LG Health policy on medically inappropriate care focuses on the care team clearly explaining prognosis and discussing the patient's goals of care. If there is disagreement between the care team and the patient and family, the care team may call upon other entities. These include the Biomedical Ethics Committee consult team, hospital chaplain, hospice workers, social workers, patient care representatives, nurses, legal staff, community clergy, and physicians offering a second opinion. Further, the Biomedical Ethics Committee members may meet to facilitate discussions and come to a common understanding with the patient/family.

If an understanding is still not reached, little precedent or guidance is available for how to proceed.[3] AMA policy on Medically Ineffective Interventions follows a similar theme of first attempting all routes to get family and the care team in agreement. This policy addresses limiting inappropriate interventions but does not address withdrawing care already in place.[4]

Pennsylvania state law is equally ambiguous regarding this situation. Physicians, it states, are not subject to criminal or civil liability for "refusing to comply with a direction or decision of an individual based on a good faith belief that compliance with the direction or decision would be unethical or, to a reasonable degree of medical certainty, would result in medical care having no medical basis in addressing any medical need or condition of the individual."[5]

However, this act does not provide a definition of "unethical" or what is meant by "having no medical basis" in patient care. Importantly, regarding this case, it also does not address the withdrawal of treatment. Overall, if the patient, their family, and the care team cannot come to an agreement concerning appropriate treatment, there is very little to guide the next steps.

LESSONS LEARNED

Providers can learn many lessons from this difficult case, along with considerations for future cases like this one. The first is the importance of advanced directives. E.C. was a medically complex patient with a history of a prolonged hospital stay. Having advanced care planning documents would have been helpful to the care team. This case serves as an important reminder about the importance of advanced care planning with patients who have a high likelihood of hospital admission, regardless of age.

Another important lesson to consider is the responsibility of health care representatives to act in the best interest of the patient, rather than acting on what *they* want for the patient. One could argue that, in purposefully avoiding "bad news" about E.C. and shielding himself from the reality of her prognosis, her father did not have the information to act in her best interest.

When looking at this case from a legal perspective, it becomes clear that there is very little precedent to guide providers who believe that continuing care is inappropriate without patient/family agreement. In some cases, seeking guardianship would be another avenue to explore, but this would require evidence that the family was not acting in the best interest of the

patient.[6] This is difficult to prove legally and is further complicated by the emotional distress that was contributing to E.C.'s father's decision-making. Hospital policy, the AMA, and Pennsylvania state law all stress the importance of coming to an agreement or transferring the patient if an agreement cannot be reached.

But what happens when neither is possible? With the growing complexity of health care decision-making, there is a need for more guidance in cases such as these.

In the meantime, considering timed trials-of-interventions (e.g., an early discussion of a two-week ECMO trial) could help providers set expectations with families and help them better understand the limits of these interventions before they reach the point of being inappropriate. Conversations should begin early and be revisited often regarding the potential risks and benefits of each treatment avenue. All appropriate treatment paths should be given a reasonable chance. It is the health care team's responsibility, *prior* to the initiation of complex intervention, to define what is considered an appropriate trial-of-intervention duration.

The final important lesson from this case is the need for care team support. Nurses, patient care assistants, providers, social workers, and many others were involved in this distressing case and were ethically conflicted about the care they were providing to E.C. Cases such as these contribute to burnout and bring to light the need for resources to support members of the care team as they process their own response to them (see Fig. 2). The care team's effort in communicating with family, caring for E.C., and advocating for her best interest is commendable, but the personal toll of providing such care must also be acknowledged.

CONCLUSION

This case eventually reached its conclusion following multiple meetings and conversations between the care team and E.C.'s family. As a result of consistent and open communication between the family and the care team, E.C.'s father agreed to the withdrawal of life-sustaining measures and a palliative approach to her care. E.C. passed away shortly thereafter surrounded by her family.

We offer special thanks to everyone who participated in the care of E.C. While her name was changed to protect patient privacy, we know that many will recognize her story. E.C. was far more than her illness. A note from the palliative care team detailed how E.C. was very close to her sister and that her nephews were her world. She was learning to cook, and despite all her medical challenges, remained hopeful. She was always looking for a way to help others.

Health care providers desire to help others, too, and cases like that of E.C. can be particularly distressing as teams struggle to ask themselves, "Are we doing the right thing?"

ACKNOWLEDGEMENTS

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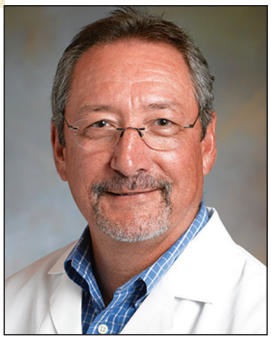


Time for Health Care Reform: A Call for Moral Clarity, Ingenuity, and a Willingness to Try

Edward T. Chory, MD

As I retired in January 2020 after a 40-year surgical career, the American College of Physicians (ACP) published a supplement to the *Annals of Internal Medicine* endorsing health care reform and suggesting a single-payer model. In it, the case was described clearly and with some urgency:

> The U.S. health care system is gravely ill, and the symptoms are many: Costs are too high, many people lack affordable coverage, incentives for hospitals and physicians are misaligned with patients' interests, primary care and public health are undervalued, too much is spent on administration at the expense of patient care, and vulnerable individuals face daunting barriers to care. Health care expenses are the leading cause of private citizen bankruptcies in the United States.[1]

Further, this supplement describes a system that "fosters barriers to care for and discrimination against vulnerable individuals." The supplement concludes by stating:

> The ACP rejects the view that the status quo is acceptable, or that it is too politically difficult to achieve needed change. Dr. Atul Gawande wrote, "Better is possible. It does not take genius. It takes diligence. It takes moral clarity. It takes ingenuity. And above all, it takes a willingness to try." ... We urge others to join us.[1]

The buildup to the 2020 election was getting started, with Bernie Sanders beating the drum of Medicare for All. I attended a University of Pennsylvania Leonard Davis Institute of Health Economics conference in February to hear keynote speaker Paul Starr, MD, who won the Pulitzer Prize in 1984 for his magnum opus, *The Social Transformation of American Medicine: The Rise of a Sovereign Profession and the Making of a Vast Industry.* What I heard him say was that Medicare for All was not politically feasible. I was crushed. If ever the time was right, it was 2020.

The graphic representation in Fig. 1, comparing both health care expenditures and longevity before the COVID pandemic, makes the need for reform obvious.

Almost all would agree change is needed. Yet we're hampered by disagreement about whether incremental change versus wholesale overhaul is warranted. Margo Sanger-Katz did a fine job simplifying the case with her analogy of health care as an old house in a 2019 *New York Times* article. Her premise: is our health care system a fixer upper, or should we tear it down and rebuild?[2]

In many ways, our health care system saps the competitiveness and efficiency of our economy, not to mention of our patients, many of whom need us most. Now we are nearly three years into a pandemic that has left more than one million Americans dead. This infectious disease crisis has exposed many shortcomings with our American health care "system." In fact, one can make the argument that our situation is now even worse than that described by reformers who in 2020 suggested dramatic change.

The longer we wait, the higher the price we may have to pay. It is no secret that costs are rising, and even those within a more robust system, such as in Canada and the United Kingdom, are making hard decisions, including rationing. Yet we in medicine can do things now, including changing how we practice, reforming our addiction to high-tech intervention, and valuing low-tech prevention. Serious work can be undertaken to engage our communities to alter the social determinates of disease. I hope every clinician takes a long look into the mirror and tries to remember why they practice medicine and how best to serve their patients. Our system may be wasteful and unjust, but surely we have not forgotten our priorities.

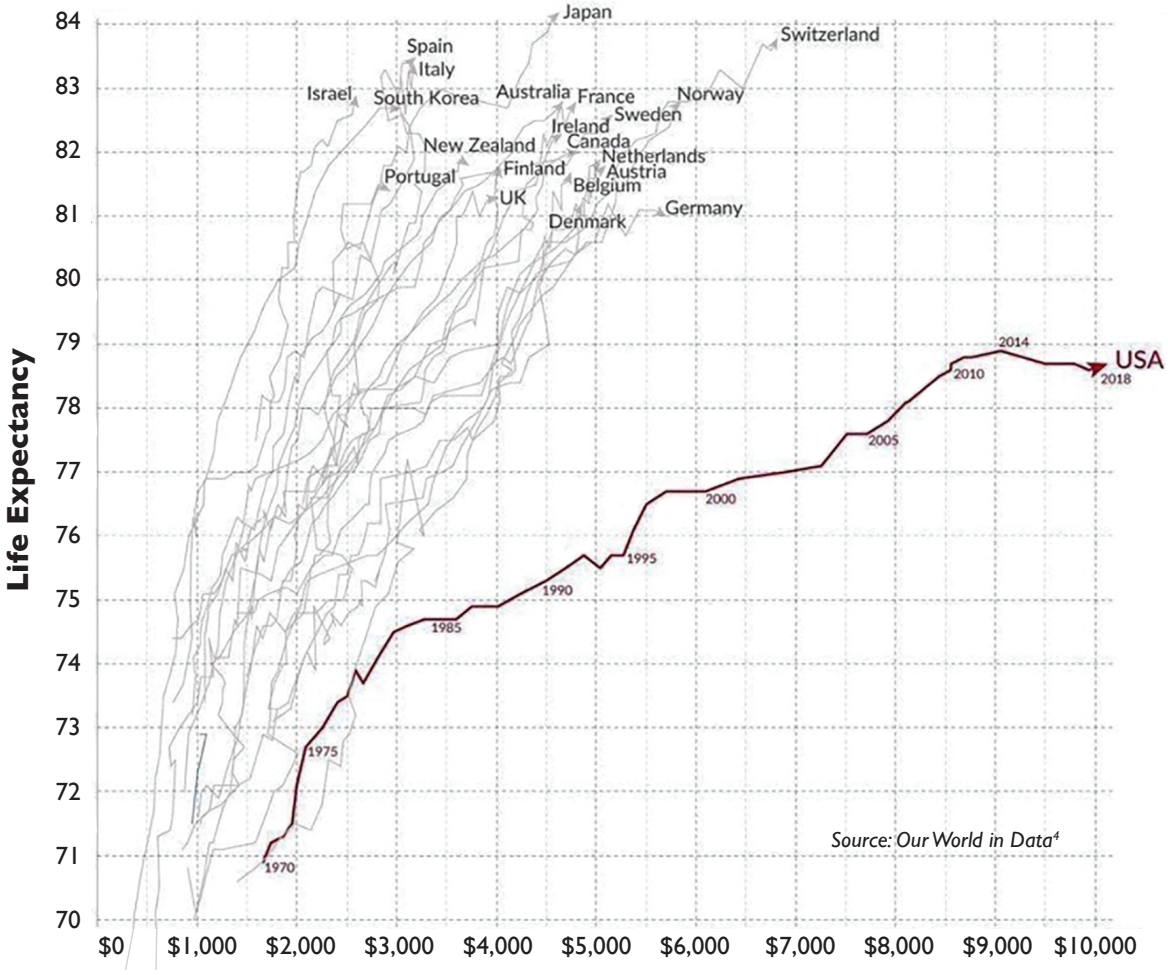
Further, we must engage and urge Congress that it is long past the time to take meaningful legislative action. The irony of calling for government-run health care is not lost on me; certainly, there is a risk that inefficient bureaucracy would invite criticism, but the administrative bloat and waste in our current way of providing care is worse. The Congressional Budget Office's most recent analysis reveals that Medicare for All would result in savings.[3] In turn, that savings could be directed to areas we would deem important, such as in our communities to benefit quality of life and augment those social determinants of disease.

Missing from the debate as we make efforts to im-

prove our current health care structure is consideration of options other than expanding Obamacare or Medicare for All. Switzerland, Germany, and Taiwan provide universal coverage and high-quality care with hybrid systems that involve highly regulated private insurance. We need to expand the discussion to understand and consider these types of solutions — but first we must face the fact that our current system of providing health care is too expensive, inequitable, and not providing the care we all need and deserve.

We can do so much better. We need to join the ACP in following Dr. Gawande's direction: "It takes moral clarity. It takes ingenuity. And above all, it takes a willingness to try."

Fig. 1. **Life Expectancy vs. Health Expenditure, 1970-2018**



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Edward T. Chory, MD, is a retired general surgeon who spent 29 years caring for the citizens of Lancaster County.

Understanding the IAP Application Process

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The signature Innovation Accelerator Program (IAP) at the Center for Health Care Innovation (CHCI) at Penn Medicine Lancaster General Health offers consultative and facilitative services to those working on the frontlines of care who are trying to improve outcomes and patient experience. This invitation to participate in new advances in all areas of LG Health helps stir the culture and mindset of innovation across the system.

Working closely with innovation advisors, teams selected to participate in the program move through three phases of work — introduced to *JLGH* readers in the Fall 2022 issue — to validate solutions and bring successful innovations to scale. This article explains the IAP application process, as well as Phase 1.

IAP APPLICATION PROCESS AND SELECTION CRITERIA

Every IAP project is selected through a process over several months that includes submitting a completed application and attending interviews with the team at CHCI at LG Health.

The Center encourages applicants to submit projects under any theme; for the third round of IAP projects, the team was particularly interested in applicants who believe their ideas can make meaningful and measurable change by one of three avenues:

- Advancing value-based care models.
- Creating consumer-focused health care experiences to reduce friction and drive higher levels of engagement.
- Making LG Health the preferred place for employees by leveraging data and eliminating the burden of health care administration.

A major evaluation criterion by which applicants are judged is whether they have a clear and compelling problem. The IAP is designed to let the problem discovery process guide the team — a key part of the methodology at the core of how the Center's team works. Applicants must explain why the problem is important, as well as why existing solutions have not succeeded.

Further, projects are selected in consideration of other important criteria, such as:

- Whether the applicant can be a committed Champion with capacity to push the work forward.
- The team's willingness to rapidly explore multiple opportunities.
- The project's potential impact once a solution is proven effective and deployed at LG Health.
- The potential to replicate and/or scale the solution in other settings.

All projects also must have an Executive Sponsor — usually an employee with the standing and ability to open doors/remove barriers, ensure capacity, and set the environment for the Champion's success in the project.

Teams selected to participate in Phase 1 of the program receive mentorship and dedicated time from advisors at CHCI at LG Health, along with up to $10,000 in out-of-pocket expenses to test and develop their concepts. At the end of Phase 1, teams present their work to health system leadership for the opportunity to receive additional investment for a Phase 2 of the project.

PHASE 1 APPROACH AND TOOLS

Over a six-month period, teams explore the problem and its potential solutions during which small-scale implementation may prove the solution's viability.

Phase 1 starts with a workshop to orient IAP winners regarding CHCI at LG Health's human-centered-design approaches and innovation framework. This framework, the Double Diamond (see Fig. 1 on page 88), takes an iterative and agile approach in which ideas, assumptions, and concepts are continually refined and improved. The Double Diamond's four stages — Discover, Define, Ideate, and Validate — transition between *divergent* thinking or actions and *convergent* thinking or actions.

Teams then embark on activities to help understand the problem space and how they'll rapidly test solutions and gather evidence to move the needle.

The objective of the first diamond is to define the problem, specifically the problem that will bring about the desired outcome. To achieve this, teams must understand possible drivers. In this "Discover" stage, they will use a variety of tools and approaches of contextual inquiry to understand the users' experiences and uncover unmet or hidden needs. An example of a contextual inquiry method is "A Day in the Life," during which project teams experience a problem area as a user might.

Alternatively, teams may act as a "concierge," accompanying users as they navigate barriers. Project teams may also simply observe users to see how they use a product or service. During this period of contextual inquiry, teams also review existing research to better understand the problem context.

In the next part of the problem definition stage, teams define the problem and what might be causing it by synthesizing the data and insights gathered in the previous stage. This "sense-making" process helps manage complexity and discern patterns and themes. The tools used in "Define" include creating a journey map to visualize a user's experience or creating an assumptions matrix to determine how to de-risk a potential solution. Innovation is inherently risky; embarking on low-cost, quick experiments helps mitigate risk. Another tool, the problem octopus, organizes interconnected root causes and serves to gain consensus on the origins of the problem.

The first diamond culminates in a specific, defined problem. During work on BP Pal, an IAP project currently in Phase 2, the team found there was no efficient way for patients and providers to communicate blood pressure readings between office visits. Without insight into the patient's health between office visits, the patient and provider may not understand the patient's condition, risking a lack of patient participation and investment in their disease management.

Before teams can define solutions, they need to identify the needle, or measurable outcome, they want to move with that solution. In an example of an IAP project, Screen on Time, the measurable outcome was an increase in patient engagement in a way that allows them to respond to outreach around colorectal cancer screening.

Once teams have a defined needle, they move into "Ideation" to look for solutions to move the needle. This is when they experiment with different solutions in the opportunity areas to understand what is needed to target the problem drivers and ultimately change the problem space. Using tools such as "nudging" to steer users to a certain action, they may even look beyond the health care universe and think about how non-medical minds might try solving this problem.

When teams move forward with an idea, they must validate it to determine how it might impact the problem space. This is the stage during which they build proof for additional resources needed to embark into Phase 2. Fake back ends, for example, facilitate the path to run a "mini-pilot." This opportunity allowed testing of a BP Pal intervention with just seven patients, during which the IAP team could quickly gather feedback and metrics.

The types of innovation tools that exist are vast and continually evolving. Which ones to use, and which combination of them to use, is determined by

Selection Criteria for IAP Applications

- Is there a clear and compelling problem?
- Does the idea align with the Center's mission and goals?
- Will the applicant be a committed Champion with capacity to push the work forward?
- Is the team willing to rapidly explore multiple opportunities?
- What is the project's potential impact once a solution is proven effective and deployed at LG Health?
- Does the project have the potential to replicate and/or scale the solution in other settings?
- Does the project have an Executive Sponsor?

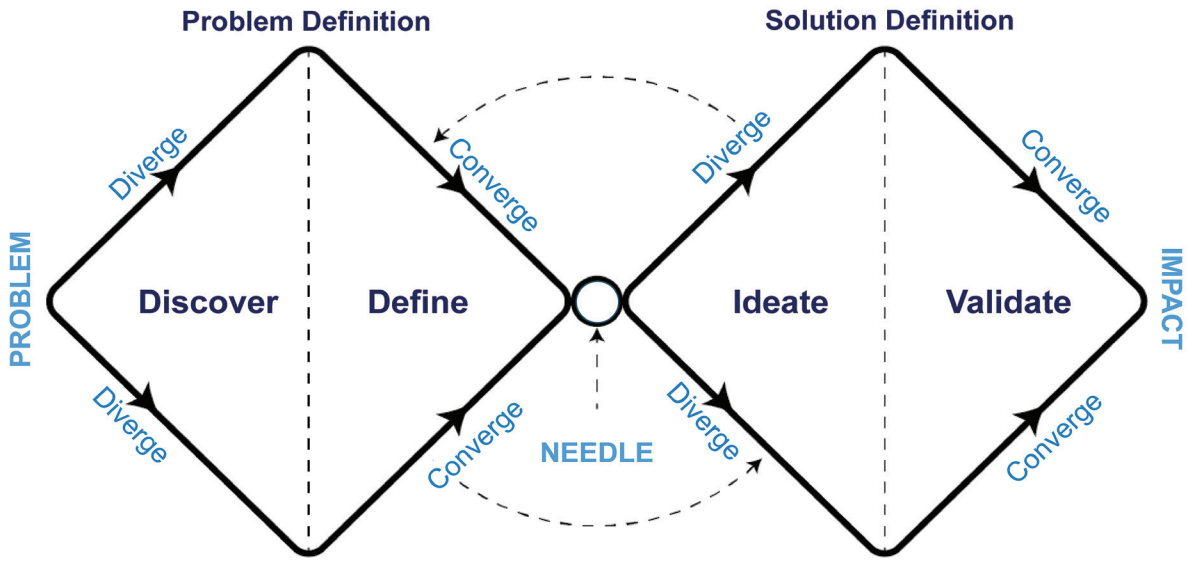

Fig. 1. The Double Diamond framework.

several factors, among them the problem space context and team time and resources available.

PHASE 1 SUCCESS CRITERIA

At the end of Phase 1, IAP teams participate in a "Pitch Day" in front of a live audience of invited key stakeholders. This event takes place approximately six months after a team begins the program and marks their graduation from Phase 1. It is an opportunity for the team members to persuade stakeholders that a proposed solution might work and is worth the investment to move to Phase 2, where they will go from conducting small experiments to testing on a larger scale and attempting to show sustained impact to help move their solution toward eventual implementation.

The success criteria for graduation includes the team's ability to complete several milestones, as outlined above. The third round of IAP kicks off in January 2023, with winning teams selected from applications submitted during 2022.

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PHOTO QUIZ FROM FAMILY MEDICINE

Helminthiasis in Lancaster County

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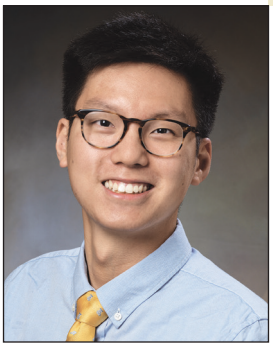

CASE HISTORY

An otherwise healthy 33-year-old patient presents to the primary care office after passing a worm in the stool. Alarmed, they had collected the worm in a medicine bottle and presented it to the physicians.

In recent months, the patient has noticed the stool to be more loose, unusually foul smelling, and having an oily appearance, but it has not been bloody. There was no associated perianal itching. The patient recalls having had bloating and vague abdominal pain intermittently over the past year. There was also a report of a recent upper respiratory infection from which recovery was uncomplicated.

The patient enjoys gardening barefoot and reportedly goes on barefoot walks in Lancaster County Park but has not noticed any rash or foot lesions. They have never traveled outside the country, and there has been no travel outside of Lancaster County in a few years. They only drink filtered water. On review of systems, there is no recent report of fever, chills, headache, nausea, vomiting, joint or back pains, unintentional weight changes, or shortness of breath.

On physical examination, the patient is afebrile with normal vital signs. There is no cervical lymphadenopathy, and the abdomen is soft and non-distended with mild, generalized tenderness. Lung sounds are normal, and a thorough skin exam reveals no rash. The worm, approximately 1 cm in length, is grossly examined in the medicine bottle (see Fig. 1) and found to be still moving. The worm is then examined on a wet prep on 10x magnification (see Fig. 2).

QUESTION

Based on the patient's history and examination of the organism, what is the most likely diagnosis?

1. Enterobiasis (infection with pinworm)
2. Ascariasis (infection with large roundworm)
3. Necatoriasis (infection with hookworm)
4. Trichuriasis (infection with whipworm)
5. Strongyloidiasis (infection with threadworm)

ANSWER

The correct answer is 3. Necatoriasis, more commonly known as hookworm.

CASE DISCUSSION

After providing a stool sample and labs, the patient was treated with a single dose of albendazole. Interestingly, labs did not show anemia or eosinophilia, and stool studies including trichrome staining and ova and parasites were normal. At a two-week follow-up, the symptoms had completely resolved.

The five answer choices are the most common examples of soil-transmitted intestinal nematode infections,

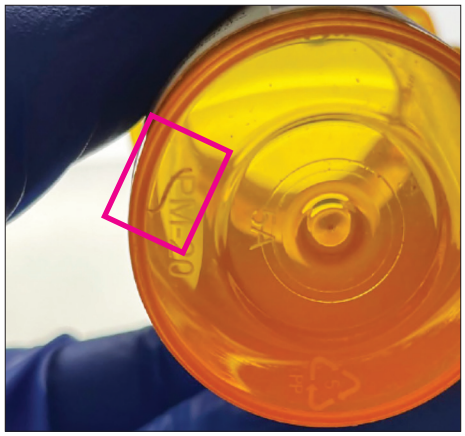

Fig. 1. Gross image of medicine bottle, containing worm.

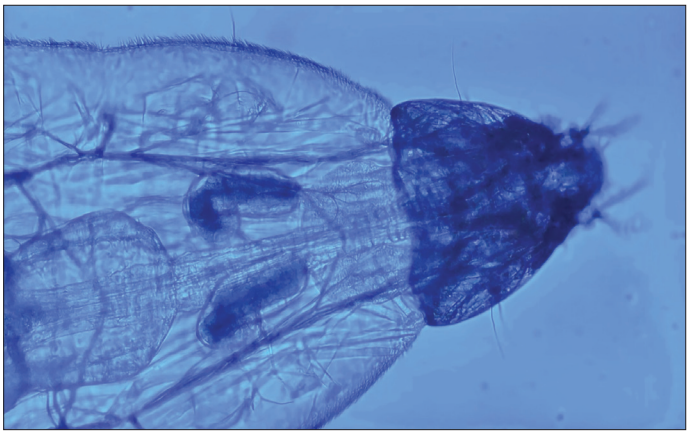

Fig. 2. Microscopic image of worm at 10x magnification.

a large subgroup of helminthiases. Intestinal nematode infections represent a high global burden of disease predominantly affecting the most resource-challenged communities; nearly two billion people worldwide, a quarter of Earth's population, have one of these infections. They are most common in tropical and subtropical areas, especially sub-Saharan Africa, the Americas, China, and East Asia. Once highly endemic in the southeastern United States over a century ago, developments in sanitation have made these much less common here, although high-quality data regarding the prevalence of these infections in the 21st century are lacking.[1]

ADDITIONAL EXPLANATION

1. The most common symptom of enterobiasis, or pinworm infection, is perianal itching; it is most prevalent in school-aged children. Adult *Enterobius vermicularis* organisms measure 8-13 mm long. Enterobiasis is treated with two doses of albendazole 400 mg two weeks apart for the entire household, and transmission is further prevented by washing bedding and clothes.[2]
2. *Ascaris lumbricoides*, the causative pathogen of ascariasis, is the most prevalent intestinal nematode worldwide. Adult organisms are among the largest of the intestinal nematodes and can be up to 35 cm long and 6 mm in diameter. Treatment is with one dose of albendazole 400 mg.[3]
3. The two primary hookworm species worldwide are *Necator americanus* and *Ancylostoma duodenale*, with the former predominating in the Americas. An estimated 576-740 million people are affected by hookworm worldwide. Hookworm is transmitted by direct skin penetration of infective larvae living in soil, typically on bare feet. Larvae migrate to blood vessels and settle in pulmonary vasculature. Eight to 21 days following infection, larvae penetrate the pulmonary alveoli and ascend the bronchial tree to the oropharynx, where they are swallowed into the gastrointestinal tract and mature into adult worms. Adults attach themselves to the intestinal wall, often resulting in occult blood loss and iron deficiency anemia. Eosinophilia is a common laboratory manifestation. Chronic nutritional impairment due to hookworm disease is a significant public health concern in underprivileged endemic regions. Diagnosis can be made with microscopy of ova or parasites in stool or PCR assays, but adult helminths can also be identified on gross examination. Adults grow up to 1 cm in length and have characteristic hook-like jaws on microscopy. The preferred treatment for hookworm infection is one dose of albendazole 400 mg.[4,5]
4. *Trichuris trichiura* is the cause of trichuriasis, or whipworm infection; adults measure up to 4 cm. Treatment is with albendazole 400 mg daily for three days. Single-dose albendazole has insufficient efficacy.[6]
5. Strongyloidiasis (or threadworm infection) is caused by *Strongyloidiasis stercoralis* and is transmitted in a similar manner to hookworm; however, autoinfection is a notable alternative pathway in the lifecycle of *S. stercoralis.* Patients with subclinical strongyloidiasis are at risk of hyperinfection with disseminated disease if cell-mediated immunity is diminished, for example, by corticosteroid administration or infection with human immunodeficiency virus (HIV). Uncomplicated disease is treated with ivermectin (200 mcg/kg daily for one or two days), which has higher efficacy than treatment with albendazole.[7]

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Collaborative Studies with the Clinic for Special Children

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Editor's note: This is the 13th in a series of articles from the Penn Medicine Lancaster General Health Research Institute that describes ongoing research studies. Other active studies have been described in previous issues of this journal.

Located in the heart of Lancaster County, the Clinic for Special Children (CSC) is a nonprofit medical clinic for children and adults with genetic disorders and other complex medical needs, serving primarily the Amish and Mennonite (Plain) communities. CSC dedicates its clinical research efforts to the genetic diseases that impact these communities; often it is the case that these disorders occur at a much higher rate among the Plain than they do in the general population due to isolation and shared genetic heritage.

While many in these communities are less likely to seek medical treatment from outside the community, the relationship CSC has built with them over the years has allowed the clinic to make a tangible impact in the health of patients and their families.

CSC started in 1989 in a single building built by the Plain communities it still serves today. Since then, an expansion and updates have allowed for the growth of the team and for medical advancements. The building includes a CLIA-certified clinical laboratory, patient exam rooms, staff offices, and community spaces.

These resources enable the CSC's four physicians and one nurse practitioner to provide services that community members would otherwise need to travel much greater distances and incur much higher costs to receive. As a result of their proximity to the patients and their indefatigable efforts, CSC has been able to "pioneer innovative treatments and gain insights that are broadly applicable to genomic medical practice as a whole."

Kevin Strauss, MD, performs the roles of both medical director for CSC and practicing pediatric physician. Under his direction, the clinic has developed many collaborations across Lancaster County and beyond, Lancaster General Hospital among them. His research accomplishments include coauthoring more than 80 peer-reviewed journal articles and serving as the principal investigator for more than 15 studies.

LGH partnered with CSC in the past for studies investigating community health and understanding the specific conditions affecting the communities it serves. These studies have examined familial hypercholesterolemia due to Apolipoprotein B-100 mutations in the Amish, novel gene-modifying therapies for spinal muscular atrophy in Mennonites, and community attitudes toward certain medical procedures such as medical photography.

Dr. Strauss notes that, "given the fruitful nature of this important collaboration between two community-centered medical facilities in Lancaster County, we anticipate and hope for future innovative research opportunities that will improve the lives of the patients we both serve."

The LG Health Research Institute is excited to announce the approval of two new studies through collaborative efforts by LGH, the University of Pennsylvania, and CSC. Anyone interested in these studies (outlined below) or the crucial work being done by CSC can reach out to the Research Institute at 717-544-1777 for more information.

Safety and Efficacy of HMI-103, a Gene Editing Development Candidate in Adults with Classical PKU Due to PAH Deficiency

Sponsor: Homology Medicines, Inc.
Principal Investigator: Kevin Strauss, MD

This Phase 1 trial is evaluating the safety and efficacy of a single intravenous administration of HMI-103, a gene editing development candidate, in participants aged 18 to 55 years with classical Phenylketonuria (PKU) due to Phenylalanine hydroxylase (PAH) deficiency. These patients must have been following a low phenylalanine diet and yet still exhibit uncontrolled disease.

The study will implement sequential ascending dose-escalation, investigating up to three dose levels of HMI-103 in the cohort. A long-term extension study lasting 13 years is planned as well.

The three dosing cohorts could include up to three participants each. LGH and CSC plan to enroll up to three participants in total.

A Randomized, Sham-controlled, Double-blind Study to Evaluate the Efficacy and Safety of Intrathecal OAV101 in Type 2 Spinal Muscular Atrophy (SMA) Patients Who Are ≥2 to <18 Years of Age, Treatment Naive, Sitting, and Never Ambulatory

Sponsor: Novartis
Principal Investigator: Kevin Strauss, MD

This Phase 3 trial will enroll treatment naive Type 2 SMA participants ages 2 through 17. The study team will screen potential participants during a rigorous screening period (lasting 45-60 days) that involves data collection and clinical assessments.

If patients meet the eligibility criteria, they enter Treatment Period 1. This period involves randomization to either study drug (intrathecal OAV101) or sham (placebo) treatment during inpatient hospitalization and monitoring for up to three days. The next phase, Follow-Up Period 1, involves a 52-week outpatient follow-up schedule with regular safety and efficacy assessments.

A final period, Treatment Period 2, will be offered to eligible participants after completing the follow-up period in which they cross over the treatment randomization from Treatment Period 1. (Those who receive OAV101 will receive placebo, and those who received placebo will receive OAV101.) They will then enter the long-term extension study, which is being planned now.

The sponsor plans to enroll 125 participants. LGH plans to enroll up to three participants.

A complete list of active clinical studies at Lancaster General Health is available online. To access the most current list, scan the QR code at left, or find the link on the JLGH.org Resources/Links page. To make a referral to any study on the list, call the LG Health Research Institute at 717-544-1777.

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Update from the Lancaster Medical Heritage Museum

Meagan Schulman, a recent Millersville University graduate and winner of the 2022 Penn Medicine Lancaster General Health Summer Internship, spent her summer researching the Lancaster County Vaccine Farm, also known as the Marietta Vaccine Farm. She discussed the project during the Lancaster Medical Heritage Museum's September "Lunch and Learn." (Scan the QR code below to view Schulman's full lecture, which will be published as a paper in the future.)

To briefly overview: In 1882 Dr. H.M. Alexander founded the Lancaster County Vaccine Farm, where he produced and supplied the entire country with smallpox vaccine. The Vaccine Farm drastically shaped not only Pennsylvania's ability to eradicate smallpox, but also that of the nation. It was beyond its years in biological products regulation and vaccine standards. What started out as one man and a calf had lasting effects on millions of people across the globe.

Smallpox was considered a "dread" disease: even if a person was spared from death, they could be scarred for the rest of their lives. Until the rise of inoculation and eventually vaccination, there was no means possible for the prevention of such a fate. Even after Dr. Edward Jenner's vaccine discoveries, it took doctors nearly another century to discover the most safe and effective way to mass produce a regulated, sanitary vaccine.

Dr. Alexander and the Lancaster County Vaccine Farm may have been lost to history, but society is still discovering the strides made in Marietta which have become a cornerstone in learning about mass vaccine production and regulation.

Recommendations from the Endocrine Society

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This is my 39th article on Choosing Wisely from the American Board of Internal Medicine (ABIM) Foundation. As noted in previous issues of *JLGH*, each specialty group is developing "Five or More Things That Physicians and Patients Should Question."

All items are developed to encourage discussion between physicians and their patients about which tests and procedures are best in each case. Additional resources are available online at ChoosingWisely.org.

RECOMMENDATIONS FROM THE ENDOCRINE SOCIETY

1. Adults with stable Type 2 diabetes on agents that do not cause hypoglycemia should avoid routine multiple daily self-glucose monitoring. Once target control is achieved and the results of self-monitoring become predictable, there is little gain in most individuals from repeated confirming. There are many exceptions, such as for acute illness, when new medications are added, when weight fluctuates significantly, when A1C targets drift off course, and in individuals who need monitoring to maintain targets.

2. Unless the patient has hypercalcemia or decreased kidney function, don't routinely measure 1,25-dihydroxyvitamin D. Serum levels of 1,25-dihydroxyvitamin D have little or no relationship to vitamin stores but rather are regulated primarily by parathyroid hormone levels, which in turn are regulated by calcium and/or vitamin D. In vitamin D deficiency, 1,25-dihydroxyvitamin D levels go up, not down. Serum 25-hydroxyvitamin D levels may be overused, but when trying to assess vitamin D stores or diagnose vitamin deficiency (or toxicity), 25-hydroxyvitamin D is the correct test.[1]

3. If there is no palpable abnormality of the thyroid gland, don't routinely order a thyroid ultrasound in patients with abnormal thyroid function tests. However, thyroid vascularity assessed by color flow Doppler in patients with overt hyperthyroidism (elevated free T4 and T3 and suppressed thyroid-stimulating hormone) may help distinguish Graves' hyperthyroidism and toxic nodular goiter from a destructive thyroiditis (painless, painful, or drug induced). Thyroid ultrasound is used to identify and characterize thyroid nodules. Thyroid-toxic patients with nodules may benefit from imaging. With these patients, a thyroid scan is used to assess the possibility of focal autonomy in a thyroid nodule and correlate it with the ultrasound findings. Some centers assess thyroid artery blood flow by Doppler, and that may be used to help distinguish Graves' disease from a destructive thyroiditis.

4. When assessing levothyroxine (T4) dose in hypothyroid patients, don't order a total or free T3 level. T4 is converted into T3 at the cellular level and in virtually all organs. T3 levels in blood are not reliable indicators of intracellular T3 concentration. Compared to patients with intact thyroid glands, patients taking T4 may have higher blood T4 and lower T3 levels. In most patients a normal TSH indicates a correct dose of T4.[2]

5. Unless there is biochemical evidence of testosterone deficiency, don't prescribe testosterone therapy. Many symptoms attributed to male hypogonadism are commonly seen in normal male aging or the presence of comorbid conditions. Testosterone therapy has the potential for serious side effects and represents a significant expense. Current guidelines recommend the use of a total testosterone level obtained in the morning. A low level should be confirmed on a different day, again measuring the total testosterone.

NEW HYPERGLYCEMIA CLINICAL PRACTICE GUIDELINES

In addition to the Choosing Wisely items above, the Endocrine Society in June 2022 published new recommendations concerning glycemic management in hospitalized, noncritically ill patients who have diabetes or newly recognized hyperglycemia. These include:

- In adult patients with diabetes who are undergoing elective surgical procedures, a preoperative hemoglobin A1C of less than 8% (63.9 mmol/mol) should be targeted, along with a blood glucose concentration of 100-180 mg/dL (5.6-1.0 mmol/L).
- Scheduled insulin therapy rather than noninsulin glycemic management therapies should be used in most hospitalized, noncritically ill adult patients

with hyperglycemia (with or without known type 2 diabetes).

- In maintaining glucose targets of 100-180 mg/dL (5.5-10 mmol/L), initial therapy with correctional insulin should be employed over scheduled insulin therapy (i.e., basal, or basal/bolus insulin) in hospitalized, noncritically ill adults with no prior history of diabetes who, during hospitalization, experience hyperglycemia.
- Scheduled insulin therapy should be added in patients with persistent hyperglycemia — that is, in those who have received correctional insulin alone and have two or more point-of-care glucose measurements of 180 mg/dL or greater in a 24-hour period.[3]

Top Tips

FLU SHOT RECOMMENDATIONS FOR ADULTS 65+

Many health experts believe the current flu season may be considerably worse than that of the past two years, due to relaxed COVID masking policies and lowered immunities as a result of social distancing policies. In an effort to better protect adults 65 and older, the CDC's Advisory Committee on Immunization Practices (ACIP) recommends the use of specific flu vaccines for this population, including higher-dose and adjuvanted flu vaccines. The preference applies to Fluzone High-Dose Quadrivalent, Flublok Quadrivalent, and Fluad Quadrivalent flu vaccines.

Prior to this year, the CDC has not recommended any one flu vaccine over another for any age group, and there is still no preferential recommendation for people younger than 65. People 65 and older should be given one of the three preferentially recommended vaccines; however, if one of these vaccines is not available at the time of administration, people in this age group should receive a standard-dose flu vaccine instead.

Why were these updates made to flu vaccine recommendations? While flu seasons vary in severity, during most seasons people 65 years or older bear the greatest burden of severe flu disease, accounting for the majority of flu-related hospitalizations and deaths. In recent years, it's estimated that between 70% and 85% of seasonal flu-related deaths have occurred in people 65 years or older, and between 50% and 70% of seasonal flu-related hospitalizations have occurred among people in this age group. Additionally, changes in the immune system with age mean that older adults often do not have as strong an immune response to vaccination as younger, healthy people. Given the higher risk for severe flu illness and lower protective immune response after vaccination among older adults, substantial research and development have led to the production of flu vaccines intended to provide better immunity for people in this age group.

What evidence is there to back up this preferential recommendation? The CDC's preferential recommendation is based on a review of available studies which suggests that, for this age group, higher-dose and adjuvanted flu vaccines are potentially more effective than standard-dose, unadjuvanted flu vaccines.

How do the side effects from higher-dose and adjuvanted flu vaccines compare with those of standard-dose flu vaccines? The common types of side effects from higher-dose or adjuvanted flu vaccines are similar to those from other flu vaccines and include soreness, redness, and swelling where the shot was given; fever; muscle aches; and nausea. Some of these side effects might be more common with high-dose and adjuvanted vaccines, but in studies of these vaccines, when these side effects occurred, they were usually mild. Recombinant influenza vaccine side effects were like those from other injectable flu vaccines.

BIVALENT COVID-19 BOOSTERS UPDATE[4]

The Food and Drug Administration (FDA) has authorized emergency use of bivalent COVID-19 booster vaccines produced by Moderna and Pfizer-BioNTech. Previous monovalent vaccines contained mRNA for the original Wuhan strain spike protein; the new bivalent vaccines contain the spike protein mRNA for both the original *and* omicron strains.

The booster recommendations are, in a way, simplifying things. Rather than having different numbers of boosters for different risk groups, the underlying recommendation is to ensure a primary series, followed by an "updated booster." The primary series is still defined as the original series of vaccines, depending on patient age and immune status.

Updated booster language reveals the direction that these recommendations are taking. Depending on the course of the pandemic, the medical community can expect updates to the boosters, along with recommendations to use them once available, and can stop counting *numbers* of boosters.

The Moderna and Pfizer boosters were studied in the same way that updated influenza vaccines are studied each year — with immunogenicity studies, but not clinical studies. In the immunogenicity studies, examining adults >18 years for Moderna and >55 years for Pfizer,

the boosters raised the geometric mean titers of neutralizing antibody as much or better than the original strain vaccines (for both original strain antibody and omicron antibody), regardless of prior infection status. No serious adverse events related to the vaccines occurred at 29 days follow-up, and most adverse events were "reactogenicity" events — fever, fatigue, myalgias, arm soreness, and lymphadenopathy (with Pfizer vaccine). Overall, the adverse event rates were similar to the primary series doses and original boosters.

Concerns about myocarditis from booster vaccines were reviewed. Data from the monovalent boosters indicate that it is less common with booster doses and generally has a very good prognosis, whereas the risk of cardiovascular complications from COVID-19 disease are more frequent (1.8-5.6 times) in young men than vaccine-related myocarditis. There are no data about the bivalent vaccines and myocarditis incidence.

Specific recommendations from the CDC's Advisory Committee on Immunization Practices include:

- The CDC in mid-October released new COVID-19 booster recommendations for people ages 5 and older to receive one bivalent mRNA booster after completion of a monovalent primary series or previously received monovalent booster dose(s). These recommendations, which replace all prior booster recommendations for this age group, are for use of a bivalent Moderna booster dose in people ages 6-17 or for use of a bivalent Pfizer-BioNTech booster dose in people ages 5-11. They can receive this covalent booster at least two months after their last COVID vaccine.[5]
- The Pfizer bivalent booster is approved for ages 5 and older; the Moderna bivalent booster is approved for ages 6 and older.
- Under the terms of the Emergency Use Authorization, providers *may NOT give the original vaccine boosters* to anyone due for an updated (bivalent) booster.
- It is acceptable to give a different brand of booster than the primary series if the age requirement is met.

Current guidance for the administration of COVID-19 vaccines further indicates that these vaccines can be administered at the same time as influenza vaccines. Updates are occurring to COVID-19 immunizations frequently. It's best to check the CDC website for the latest recommendations.

EFFECT OF NASAL IRRIGATION ON COVID-RELATED ILLNESS, DEATH[6,7]

Starting twice-daily flushing of the mucus-lined nasal cavity with a mild saline solution soon after testing positive for SARS-CoV-2 can significantly reduce hospitalization and death, according to a recent study published in *Ear, Nose & Throat Journal.*

Investigators report that the technique — which can be used at home by mixing a half teaspoon each of salt and baking soda in a cup of boiled or distilled water, then putting it into a sinus rinse bottle — is a safe, effective, and inexpensive way to reduce the risk of severe illness and death from coronavirus infection. Key findings include an 8.5-fold reduction in hospitalizations and no fatalities compared to controls, both "pretty significant endpoints," according to the authors.

The study appears to be the largest, prospective clinical trial of its kind. The older, high-risk population studied — many of whom had preexisting conditions like obesity and hypertension — may benefit most from the easy, inexpensive practice, the researchers say.

They found that less than 1.3% of the 79 study subjects ages 55 and older who enrolled within 24 hours of testing positive for SARS-CoV-2 over a two-month period in late 2020 experienced hospitalization, and no one died. By comparison, 9.5% of patients were hospitalized and 1.5% died in a group with similar demographics reported by the CDC during the same timeframe.

"The reduction from 11% to 1.3% as of November 2021 would have corresponded in absolute terms to over one million fewer older Americans requiring admission," the authors write. "If confirmed in other studies, the potential reduction in morbidity and mortality worldwide could be profound." The researchers also found that nasal irrigation can be effective in reducing symptom severity in both corona and influenza viruses.

CLINICALLY MEANINGFUL IMPROVEMENT FOR CHRONIC NEUROPATHIC PAIN

Anticonvulsants and serotonin-norepinephrine reuptake inhibitors (SNRIs) are among the best initial choices to improve chronic neuropathic pain, according to recent trials reported in *American Family Physician.* These include the anticonvulsants gabapentin (Neurontin) and pregabalin (Lyrica), along with the SNRIs duloxetine (Cymbalta) and venlafaxine.[8]

Moderate-quality evidence exists for both types of drugs, which were similarly effective and well tolerated. Rubefacients (usually salicylates) appear to be effective but are not as well studied and have low-quality evidence. Acupuncture, opioids, and tricyclic antidepressants cannot be recommended for chronic neuropathic pain based on current evidence.[9]

EVALUATION AND MANAGEMENT AFTER ACUTE LEFT-SIDED COLONIC DIVERTICULITIS[10]

Management of uncomplicated diverticulitis is usually conservative and includes bowel rest and fluids. Uncertainty remains, however, about the role of hospitalization and antibiotics. A review of 51 studies presented to the American College of Physicians (ACP) earlier this year included the following:

- It was unclear if patients with recent acute diverticulitis are at increased risk for colorectal cancer, although those with complicated diverticulitis do appear at a higher risk of the disease.
- Treatment with mesalamine was shown to be ineffective in preventing recurrence, and other nonsurgical treatments lacked adequate evidence.
- Elective surgical procedures reduce recurrence in patients with prior complicated, smoldering, or frequently recurrent diverticulitis, but it is unclear which of these patients may benefit most.

As a result, the ACP recommends initial management of uncomplicated diverticulitis without antibiotics, but acknowledges other questions still need to be addressed, such as inpatient versus outpatient management and elective surgery after an acute episode.

MAXIMIZING TREATMENT OF HYPERTENSION IN OLDER ADULTS[11]

Roughly one in three adults with hypertension has inadequate blood pressure control, and clinicians have two options for intensifying treatment: the dose of the current drug regimen can be maximized, or a new drug can be added. Data from randomized controlled trials suggest treatment with lower doses of combination therapy may be more effective with fewer side effects — although the best strategy in older patients remains unclear.

Researchers conducted a large-scale, population-based, retrospective cohort study, and observational data were used to emulate a target trial with two groups: new medication and maximizing dose. The cohort included people ages 65 years or older with hypertension and was limited to those with a systolic blood pressure of 130 mm Hg or higher. Two intensification approaches were used: (1) adding a new medication, defined as a total dose increase with a new medication; and (2) maximizing dose, defined as a total dose increase without new medication.

Both approaches produced systolic blood pressure reduction, with a slight advantage in the "add a new medication" group. That group reduced their systolic blood pressure by over 4.5 points as compared to 3.8 points in the maximized (dose) group.

At 12 months the results were similar, but only 50% of patients in the new medication group were able to sustain that strategy compared with two-thirds of patients who had their dose increased. This suggests that in older adults, adding a new antihypertensive medication versus maximizing dosing of existing regimen is only minimally effective, and less suitable. Maximizing dose of antihypertensive medication is a reasonable approach and may be easier to sustain.

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The photo is a colorized scanning electron micrograph of monkeypox virus (orange) on the surface of infected VERO E6 cells (green). The image was captured at the NIAID Integrated Research Facility in Fort Detrick, Maryland.

See page 68 of this issue for a clinical primer on the 2022 outbreak of monkeypox in the United States.

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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).

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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Upcoming CME Offerings at LG Health

Department of Medicine Grand Rounds
January 4, February 1, March 1, 12:00 noon-1:00 p.m.

Family Medicine Grand Rounds
January 17, February 21, March 21, 7:00-8:00 a.m.

Hospital Interprofessional Case-Based (HICB) Conference
January 18, February 15, March 15, 12:30-1:00 p.m.

Pediatric Grand Rounds
January 19, February 16, March 16, 7:00-8:00 a.m.

Special Events & Symposia — Registration Required

Chronic Pain Symposium, January 25, 6:30-8:00 p.m.
Laurence E. Carroll, MD, Legacy Event, March 13, 5:45-7:30 p.m.
A Primary Care Focus on Dementia, Date and Time TBD

CME On Demand

The Continuing Medical Education Department at Lancaster General Health offers a number of programs on demand at LGHealth.org, plus regularly updates and makes available recordings of all Medicine, Family Medicine, HICB, and Pediatric Grand Rounds sessions.

For details & additional programming, visit the LG Health Continuing Medical Education page at LGHealth.org.