# JLGH

SUMMER 2026
VOL. 21 – NO. 2

a record of
MEDICAL PROGRESS

*The Journal of Lancaster General Hospital*

Pages are perforated for easy removal. →
Fold twice in each direction before tearing.

# Table of Contents



*See page 63 for an update from the Lancaster Medical Heritage Museum.*

The Journal of Lancaster General Hospital *is printed on paper with a 10% post-consumer waste fiber content. The UV inks used are 99.5% free of volatile organic compounds (VOCs), unlike conventional inks, making them more environmentally friendly. If you do not wish to keep this print issue of the journal for future reference, the editors encourage you to recycle it. At Penn Medicine Lancaster General Health and other facilities, you may place it in any Shred-It® bin available. Shred-It® recycles 100% of the paper it collects. If you do not have access to a Shred-It® bin, please refer to your institution's or municipality's guidelines for recycling non-glossy paper.*

FROM THE EDITOR'S DESK

# Patterns in Medicine

**Corey D. Fogleman, MD, FAAFP**
*Editor in Chief*

Having an open mind about patterns can help us help our patients. We certainly know to look for patterns when trying to make diagnoses. We can also augment patient counseling regarding life patterns — or what we might call "habits" — when we describe effective ways patients might avoid ruts and instead "get in the groove." Artists and scientists who are trying to discern whether the patterns they observe are meaningful, and describe what that meaning may be, need space and forum to present their ideas. We at *JLGH* are happy to be one such opportunity.

In this issue, our Sports Medicine colleagues present the suggested workup for a syndrome whose very concept may be news to many: Relative Energy Deficiency in Sport, or REDs. This is an umbrella term that includes the female athlete triad and may expand the scope of what primary care clinicians, as well as orthopedic colleagues, think about, screen for, and educate regarding when treating young athletes, no matter the gender. REDs represents a group of symptoms that clinicians have been witnessing and patients have been experiencing for many years, and a pattern that the International Olympic Committee finally began to codify in 2014. Reports like these, by those who are looking for and have found new patterns, are just the sort of exchange in which readers of journals like *JLGH* may be interested.

> *"Having an open mind about patterns can help us help our patients."*

We are uniquely privileged this issue to present the work of two study teams. The first report is by a group of pharmacists who identified prescribing patterns in our primary care colleagues that run counter to accepted guidance. Their work has already saved money, and efforts like these may further decrease costs, save patients from drug interactions, and certainly can lead to better care.

The second is a collection of investigations by our colleagues in the Department of Trauma and Acute Care Surgery who identified how frailty assessments among patients admitted to our hospital may or may not predict ICU stays, hospital lengths-of-stay, and mortality, among other correlations. It's an attempt to determine whether there are meaningful patterns that might lead to improved care among our elderly patients.

Heather Madara from the LG Health Research Institute presents a thoughtful Clinical Research Spotlight that considers a stirring log of transgressions committed against patients and citizens, from enslaved women to institutionalized children. Her concluding comments are a call to action — to educate ourselves and each other, and to stand up in the face of injustice.

I also invite you to read the narrative essays by Dr. Kirsten Johnsen Martin and Dr. Scott Paist, along with the case presentation by Madeline Cingle, PA-C. Each writes eloquently about meaningful interactions and the lessons we can learn. Certainly, the ramifications of worsening dementia, poor communication between clinician and patient, as well as iatrogenic electrolyte disturbances, are scenarios in which we can always use a refresher.

We at *JLGH* are happy to work with our clinician authors to cultivate meaningful and thought-provoking articles and stories that can help you in the practice of medicine. I encourage you to read through this Summer issue and continue the conversation about the patterns you may find all around you.

## RESOURCES FOR CLINICIANS

*The Journal of Lancaster General Hospital* offers an extensive list of resources for clinicians online. Those to help you in your practice link to programs and guidelines related to:

- Treatment and diagnosis of diabetes.
- Weight management.
- Pediatric headaches.
- Other diseases and illnesses.

Additional links direct visitors to mental health, veterans care, firearm injury prevention, and other patient safety resources. Scan the QR code at left for access, or visit the Resources/Links tab on our website at JLGH.org.

## 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.
- Anything else that might be educational for our readers — the medical staff at Penn Medicine Lancaster General Health.

If you have an idea for a story, scan the QR code at right or visit our website at JLGH.org to share your idea.

# JLGH Spring 2026 Recap

## *Q&A for Extended Learning*

*The Spring issue of* The Journal of Lancaster General Hospital *offered articles on pain, immunotherapy, artificial intelligence, lower extremity edema, and other practice recommendations. Review the questions and answers below to see how much you remember from the issue. Need a refresher? All issues of* JLGH *are available online at JLGH.org.*

**Q: What is pain catastrophizing (PC), and why is screening for PC important for patients undergoing total hip arthroplasty?**
A: Pain catastrophizing is a psychological experience — a combination of exaggerated negative thought and affect — when experiencing and anticipating pain. Research has found that screening for and addressing PC can lead to better outcomes.

**Q: How should we manage new or worsening neurological symptoms in patients who are receiving an immunotherapy agent, such as pembrolizumab?**
A: These symptoms should prompt an immediate evaluation by the treatment team and consideration of consultation with the neurology service. Early intervention can potentially prevent complications, including respiratory failure and death.

**Q: Name two artificial intelligence (AI) image generators that are generally considered safe for supervised use by young children.**
A: LittleLit.ai is considered safe for children ages 5 years and up, and Craiyon/DALL-E mini is considered safe for children ages 8 years and up. Clinicians are encouraged to remind young people that AI tools cannot replace artistic passion and practice.

**Q: Name some possible causes of lower extremity edema.**
A: Lower extremity edema may be caused by chronic kidney disease, cirrhosis, deep vein thrombosis, venous insufficiency, heart failure, cellulitis, lymphedema, medication side effects, or malignancy.

**Q: What first-line antibiotic therapy can be used for acute bacterial rhinosinusitis?**
A: If antibiotic treatment is chosen, clinicians should prescribe amoxicillin, with or without clavulanate, for five to seven days.

# Relative Energy Deficiency in Sport

**Kevin Pan, DO, MEd**
*PGY-4, Sports Medicine Fellow*
*Penn Medicine Lancaster General Health*

**Minuette Laessig, MD**
*PGY-2, Family Medicine Resident*
*Penn Medicine Lancaster General Health*

**Laura DiPaolo, MD, CAQSM**
*Associate Program Director, Primary Care Sports Medicine*
*Penn Medicine Lancaster General Health*

**Geoffrey Dreher, DO, CAQSM, FAOASM**
*Program Director, Primary Care Sports Medicine*
*Penn Medicine Lancaster General Health*


Pan


Laessig


DiPaolo


Dreher

In 2014, the International Olympic Committee (IOC) coined the term "Relative Energy Deficiency in Sport" (REDs) and defined it as a disorder of low energy availability with characteristic symptoms that impact males and females.[1] They updated their statement in 2023 to further explain the impact of REDs.[2]

The underlying cause for REDs is a mismatch between energy used and energy consumed, leading to low energy availability and pathological long-term outcomes when not properly treated.[3] Clinically, REDs can present in any athlete of any gender or age, and may be characterized by declining athletic performance, sexual dysfunction including decreased libido, oligomenorrhea, amenorrhea, and stress fractures; it may be associated with disordered eating.

Additionally, athletes may have a constellation of other health issues such as frequent illness, syncope, slowed pediatric growth and development, weight loss or low BMI, hypotension and bradycardia, hypercholesterolemia, depression, anxiety, decreased bone mineral density, and body dysmorphia.[3] A core tenet of REDs is that any athlete of any gender and at any competition level can experience the above symptoms.

Clinicians play an integral role in identifying and managing athletes with REDs, not just because of their role in completing pre-participation physical examinations (PPEs). These examinations are important opportunities for early detection to identify athletes who may have concerns for REDs. The continuity of care with an athlete puts clinicians at a unique nexus of not only managing their athletes' health but being able to identify the complex, systemic health issues that REDs can cause.

### REDs SYMPTOMS

*Adapted from Boston Children's Hospital*[4]

- ☑ Fatigue
- ☑ Rapid weight loss
- ☑ Missed periods or delayed puberty
- ☑ Low libido
- ☑ Frequent illness
- ☑ Hair loss
- ☑ Trouble focusing
- ☑ Trouble staying warm
- ☑ Irritability and depression

## UNDERSTANDING THE POPULATION

### REDs and Athletes

Estimates suggest that 15% to 70% of male athletes and 23% to 79.5% of female athletes may have REDs, highlighting the need to better recognize the disorder in the athlete population.[2] For example, in one survey of high school nurses, only 19% could identify the components of the female athlete triad.[5] Athletes with REDs most commonly participate in endurance, aesthetic, or weight-class sports (see Table 1 on page 36).[6] Prolonged low energy availability compromises multiple physiological systems, leading to decreased endurance, reduced muscle and bone strength, impaired concentration and coordination, and potential fertility issues.

REDs also increases the risk of injury, delays healing, and contributes to impaired judgment and depression.[7] In the female athlete, one of the most severe

consequences is menstrual dysfunction, including loss of regular menstruation and ultimately amenorrhea, which is a part of the female athlete triad.[8] Adolescent athletes are also particularly vulnerable to long-term consequences because REDs can disrupt the critical period of bone mass accumulation.[9]

**Table 1. Examples of Sports Emphasizing Aesthetics, Endurance, or Weight**

| |
|---|
| Wrestling (and other weight class combat sports) |
| Gymnastics |
| Dance |
| Figure skating |
| Cheerleading |
| Rowing |
| Jockeying |
| Long- and middle-distance running |
| Pole vaulting |

*Adapted from the American Academy of Pediatrics*[11]

**Table 2. Potential Indicators of REDs Clinical Assessment Tool (CAT) in Athletes**[2]

| |
|---|
| **Severe Indicators** |
| • Primary amenorrhea |
| • Prolonged secondary amenorrhea |
| • Clinically low free or total testosterone |
| **Primary Indicators** |
| • Secondary amenorrhea because of functional hypothalamic amenorrhea |
| • Sub-clinically low free or total testosterone |
| • Low total or free T3 |
| • Greater than one high-risk (femoral neck, total hip, sacrum, pelvis) or greater than two low-risk fractures in the past two years |
| • Decreased bone mineral density (Z-score <–1) or decrease from last testing |
| • Altered growth curves |
| • Positive eating disorder screening |
| **Secondary Indicators** |
| • Oligomenorrhea caused by functional hypothalamic amenorrhea |
| • Low-risk stress fracture in the past two years (i.e., those involving posterior tibia, 2nd to 4th metatarsals, femur, inferior and superior pubic rami, sacrum and fibula) |
| • Elevated total or LDL cholesterol |
| • Depressed mood or increased anxiety |

### REDs in the Male Athlete

Research on the impact of REDs in the male athlete has increased since the International Olympic Committee's 2014 statement, with hundreds of articles highlighting the impact of REDs on male athletes.[2] Factors contributing to REDs in males vary and are often unique to the sport itself, such as making weight in wrestling.[10] Indications that a male athlete has REDs include decreased libido and decreased morning erections.[2]

Male athletes are similarly at risk of fatigue, impaired bone health, and decreased performance, along with many of the concerns that impact female athletes. Clinicians, coaches, and athletic trainers can help by recognizing symptoms of REDs in male athletes.

## PRE-PARTICIPATION EXAM

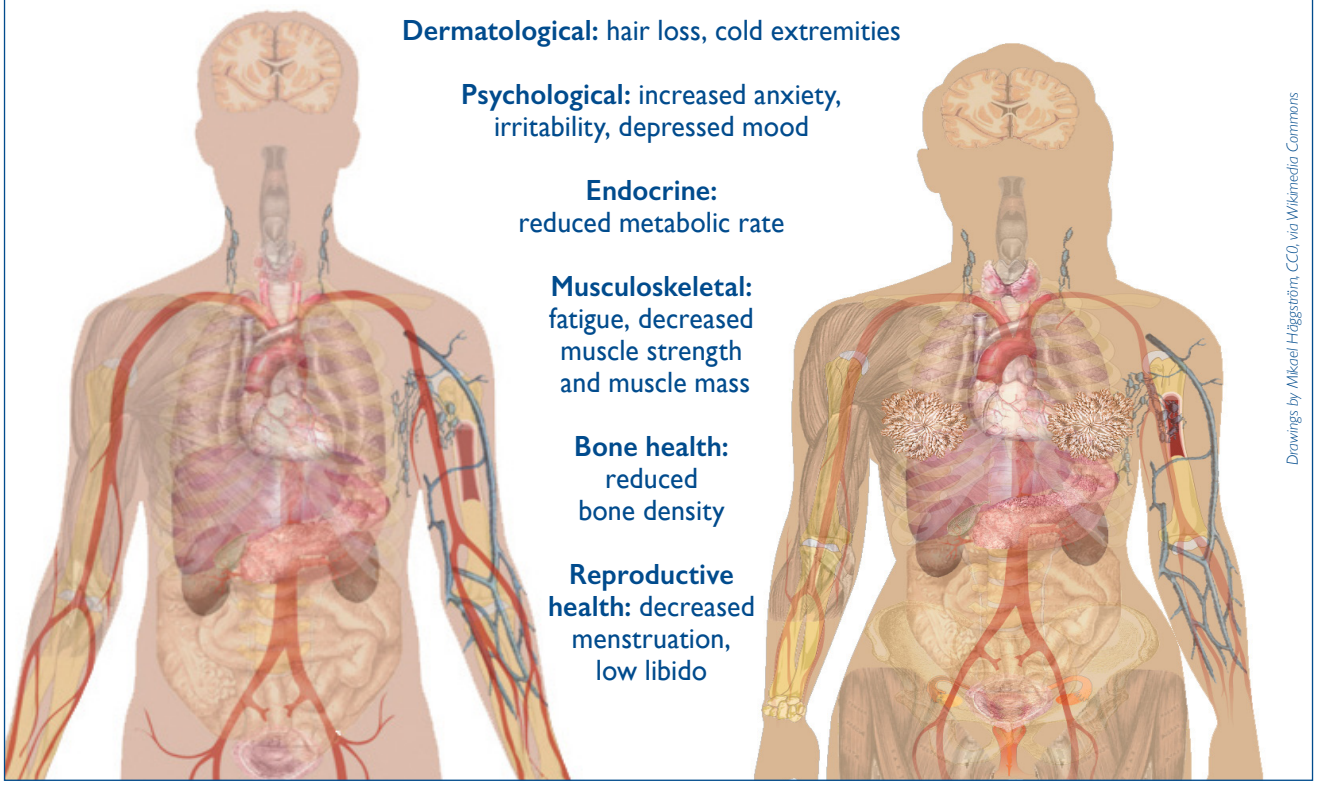
Clinicians managing an athlete's health care have a unique opportunity because they can see the entire picture of a patient's health and understand the complexities of each body system. Many athletes will appear at their primary care office for an annual sports physical or annual physical examination.

The annual sports physical is an opportunity to address the risk for REDs. Important questions to ask athletes include[11,12]:

- Have you ever had a menstrual period?
- How old were you when you had your first menstrual period?
- When was your most recent menstrual period?
- How many periods have you had in the past 12 months?
- Are you presently taking any female hormones (estrogen, progesterone, birth control pills)?
- Do you worry about your weight?
- Are you trying to or has anyone recommended that you gain or lose weight?
- Are you on a special diet or do you avoid certain types of foods or food groups?
- Have you ever had an eating disorder?
- Have you ever had a stress fracture?
- Have you ever been told you have low bone density?

These are all risk factors that can be assessed in the PPE or annual physical examination with the athlete. There is also a portion of the Pennsylvania Interscholastic Athletic Association (PIAA) PPE that includes

**Body Systems That May Be Affected by REDs**




similar screening questions. Identifying athletes at risk of REDs early on is crucial to help prevent the deleterious impact on an athlete's health. Diagnosis can be in conjunction with a multidisciplinary team including a physician or other clinician, dietitian, and mental health professional.[12]

## SCREENING

Screening tools can be utilized to determine if an athlete is at risk for REDs. Commonly used screening tools include LEAF-Q screening for female athletes over 18 years old, LEAM-Q for male athletes over 18 years old, and REDs specific screening tool (RST) for athletes 11-18 years old.[13-15] LEAF-Q includes questions about injuries, gastrointestinal function, menstrual function, and use of contraceptives. LEAM-Q includes questions about dizziness, gastrointestinal function, body temperature regulation, illness, injury, energy, and libido.

Research suggests that decreased libido was one of the most effective self-reported symptoms to help identify male athletes who require further clinical assessment for low energy availability.[14] RST prompts the clinician to ask similar questions, including screening for eating disorders, depression, anemia, and time spent doing sport in a child-friendly manner with screening tools for male and female athletes.

After completing screening, if the athlete demonstrates that they are at risk of having REDs, the clinician can proceed to risk assessment as below. Positive screening depends on the tool used.

## RISK ASSESSMENT

The first risk assessment introduced was the REDs Clinical Assessment Tool (CAT) in 2014, which was replaced by REDs CAT2 in 2023. In the original risk assessment, the athlete was categorized into green, yellow, and red risk categories based on clinical criteria; the new update includes all the previously mentioned criteria in addition to orange, which is an intermediate category.[2]

Table 2 lists potential indicators of the REDs CAT in athletes. Risk category green is very low risk with no primary indicators and at most one secondary indicator. Risk category yellow is mild risk with up to two primary indicators or greater than two secondary indicators. Risk category orange is moderate to high with three primary indicators or two primary

and greater than two secondary indicators. Risk category red is an extreme risk with greater than four primary indicators or three primary and greater than two secondary indicators.[2]

## WORKUP

Labs and imaging can assist in diagnosis and risk stratification of REDs, as well as evaluation for secondary causes of symptoms in athletes that are suspected or diagnosed with REDs.

Athletes suspected of having REDs can include those with menstrual dysfunction, stress fractures, disordered eating, unexplained performance decline, significant fatigue, and difficulty recovering from training.

### REDs DIAGNOSTIC CODES

*The diagnosis of REDs can be coded using the symptoms that make up the syndrome. Examples might include:*

| | |
|---|---|
| ☑ Other fatigue | R 53.83 |
| ☑ Amenorrhea | N 91.0 or N 91.9 |
| ☑ Oligomenorrhea | N 91.5 |
| ☑ Decrease libido | R 68.82 |
| ☑ Osteopenia | M 85.80 |
| ☑ Depressed mood | F 32.9 |

For all athletes suspected of having REDs, basic bloodwork including CBC, CMP, TSH, T3, and total cholesterol is recommended.[2]

Athletes who are experiencing menstrual dysfunction — including primary amenorrhea, secondary amenorrhea, and oligomenorrhea — should have the initial workup described above for all athletes, as well as β-hcg, prolactin, FSH, LH, estradiol, and pelvic ultrasound (see Fig. 1).[16]

Athletes who have been diagnosed with eating disorders may need lab work including CBC, CMP, magnesium, phosphorus, amylase, TSH, and a lipid panel.[17]

When helping male athletes, in addition to the basic bloodwork for all athletes described in Fig. 1, consider a testosterone level, especially in male athletes with decreased morning erections or decreased libido.[11]

Additionally, dual-energy X-ray absorptiometry (DXA) scans are recommended if an athlete has an eating disorder, BMI under 18.5 or BMI under the 5th percentile, greater than 10% recent weight loss, menstrual dysfunction, low energy availability for greater than six months, or a history of stress/insufficiency fracture.[9] Though fracture risk cannot be determined by DXA scans in pre-menopausal athletes, any Z-score less than –1 should be investigated as low bone density since athletes generally have 10% to 15% higher bone densities than comparable populations.[18,19]

It should be noted that in pre-menopausal athletes, a Z-score of less than 2 is insufficient to diagnose osteoporosis; additional risk factors such as nutritional deficiencies, hypoestrogenism, or stress fracture must also be present.[19] In pediatric populations, bone mineral density will likely "catch up" after treatment, yet prolonged REDs and LEA can cause longstanding decreased bone mineral density.[9]

If low bone density is identified, additional bloodwork is recommended, including vitamin D, calcium, CBC, TSH, PTH, bone alkaline phosphatase, and 24-hour urine calcium. Clinicians can also consider cortisol, osteocalcin, and urine N-telopeptide. Finally, workup may need to include FSH, LH, estradiol for natal females, and testosterone for natal males.[9]

## MANAGEMENT AND RETURN TO PLAY

As with any syndrome, management should begin with primary prevention. Clinicians can provide nutritional education to athletes, parents, and coaches, especially those involved in high-risk sports for REDs as described above (see Table 1 on page 36).[2]

Management of REDs is focused on achieving the balance between caloric intake and energy expenditure.[6] The primary management should be non-pharmacological with changes to diet and exercise.[2] Depending on the patient's risk, consulting a dietician or psychologist may be necessary.

Clinicians may consider a referral to a specialist in the areas of sports psychology, sports nutrition, endocrinology, OB-GYN, or primary care sports medicine for additional management. Sports psychology and sports nutrition services can assist in identifying and managing the psychological drivers that impact nutritional intake. Specialists in endocrinology can help manage hormonal dysfunctions, and OB-GYN can help manage menstrual dysfunctions.

It is important to differentiate between menstrual dysfunction caused by REDs in the female athlete versus menstrual dysfunction of organic origin. Menstrual dysfunction due to nutritional deficiencies may improve with appropriate intake of food and calories. Importantly, oral contraceptive pills are not recommended as primary treatment because helping patients resume menstruation without addressing the nutritional deficiencies can mask one of the markers

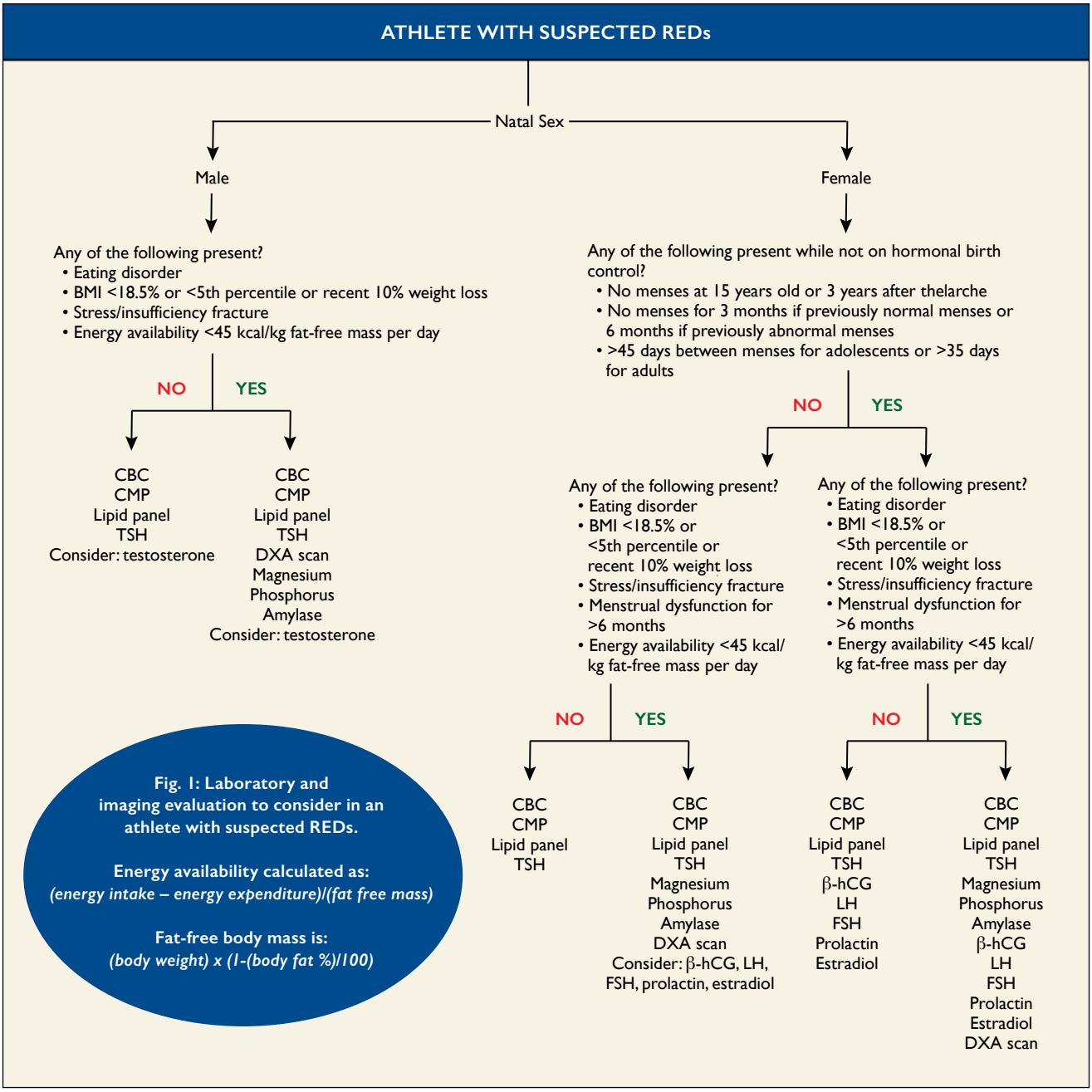



**Fig. 1: Laboratory and imaging evaluation to consider in an athlete with suspected REDs.**

**Energy availability calculated as:**
***(energy intake – energy expenditure)/(fat free mass)***

**Fat-free body mass is:**
***(body weight) x (1-(body fat %)/100)***

of REDs. Reassessment is recommended at one- to three-month intervals.[7]

Based on the REDs CAT2 model, risk is stratified into green, yellow, orange, and red as previously discussed. For athletes in the green category, no intervention is recommended with no restrictions. Athletes in the yellow risk category can train and compete without restrictions; however, they may require regular treatment and monitoring.

Athletes in the orange risk category may need activity modification as well as monthly monitoring and treatment.

Athletes in the red category are generally removed from training and competition. Treatment for these athletes at highest risk for significant injury from REDs should be immediate, and hospitalization should be considered depending on clinical situation. They will need ongoing monitoring, at daily to monthly intervals, as they progress toward recovery.

## CONCLUSION

REDs can be challenging to diagnose and manage and can affect patients in many ways. Clinicians should be comfortable with the initial screening

and management of athletes for whom they care. They should recognize that symptoms can be present in any athlete and thus all athletes should be screened for REDs.

Utilizing a multidisciplinary team can increase the success of the patient being able to return to activity/sport safely. Managing REDs requires restoring the balance between caloric intake and energy expenditure, ideally through non-pharmacological means.

## KEY TAKEAWAYS

- *Relative energy deficiency in sport (REDs) is a more encompassing term built on the foundation of female athlete triad that includes male athletes and expands our understanding to include other affected organ systems.*
- *Clinicians should understand the basic symptoms of REDs and how the disorder can impact an athlete.*
- *Clinicians should be comfortable screening for REDs at an athlete's pre-participation physical or annual physical examination.*
- *Utilizing a multidisciplinary team will assist in more comprehensive care of the athlete.*
- *Raising awareness among clinicians, coaches, and athletic trainers will help identify more athletes at risk of REDs.*
- *Athletes need periodic check-ups for reassessment.*

## REFERENCES


1. Mountjoy M, Sundgot-Borgen J, Burke L, et al. The IOC consensus statement: beyond the female athlete triad — Relative Energy Deficiency in Sport (RED-S). *Br J Sports Med.* 2014;48(7):491-497.
2. Mountjoy M, Ackerman KE, Bailey DM, et al. 2023 International Olympic Committee's (IOC) consensus statement on Relative Energy Deficiency in Sport (REDs). *Br J Sports Med.* 2023;57(17):1073-1097.
3. Nickols R. What is Relative Energy Deficiency in Sport (REDs)? National Eating Disorders Association. March 4, 2024. Accessed May 4, 2026. https://www.nationaleatingdisorders.org/relative-energy-deficiency-in-sport-red-s/
4. Relative Energy Deficiency in Sport (REDs). Boston Children's Hospital. Accessed May 4, 2026. https://www.childrenshospital.org/conditions-treatments/reds
5. Kroshus E, Fischer AN, Nichols JF. Assessing the awareness and behaviors of U.S. high school nurses with respect to the female athlete triad. *J Sch Nurs.* 2015;31(4):272-279.
6. Logue DM, Madigan SM, Melin A, et al. Low energy availability in athletes 2020: an updated narrative review of prevalence, risk, within-day energy balance, knowledge, and impact on sports performance. *Nutrients.* 2020;12(3):835.
7. Wojnowich K, Dhani R. Care of the active female. *Am Fam Physician.* 2022;106(1):52-60.
8. Cabre HE, Moore SR, Smith-Ryan AE, Hackney AC. Relative Energy Deficiency in Sport (RED-S): scientific, clinical, and practical implications for the female athlete. *Dtsch Z Sportmed.* 2022;73(7):225-234.
9. Weiss Kelly AK, Hecht S; Council on Sports Medicine and Fitness. The female athlete triad. *Pediatrics.* 2016;138(2):e20160922.
10. Mountjoy M, Sundgot-Borgen JK, Burke LM, et al. IOC consensus statement on Relative Energy Deficiency in Sport (RED-S): 2018 update. *Br J Sports Med.* 2018;52(11):687-697.
11. Carl RL, Johnson MD, Martin TJ; Council on Sports Medicine and Fitness. Promotion of healthy weight-control practices in young athletes. *Pediatrics.* 2017;140(3):e20171871.
12. De Souza MJ, Nattiv A, Joy E, et al. 2014 female athlete triad coalition consensus statement on treatment and return to play of the female athlete triad: 1st international conference held in San Francisco, California, May 2012 and 2nd international conference held in Indianapolis, Indiana, May 2013. *Br J Sports Med.* 2014;48(4):289.
13. Melin A, Tornberg AB, Skouby S, et al. The LEAF questionnaire: a screening tool for the identification of female athletes at risk for the female athlete triad. *Br J Sports Med.* 2014;48(7):540-545.
14. Lundy B, Torstveit MK, Stenqvist TB, et al. Screening for low energy availability in male athletes: attempted validation of LEAM-Q. *Nutrients.* 2022;14(9):1873.
15. Foley Davelaar CM, Ostrom M, Schulz J, Trane K, Wolkin A, Granger J. Validation of an age-appropriate screening tool for female athlete triad and Relative Energy Deficiency in Sport in young athletes. *Cureus.* 2020;12(6):e8579.
16. Klein DA, Paradise SL, Reeder RM. Amenorrhea: a systematic approach to diagnosis and management. *Am Fam Physician.* 2019;100(1):39-48.
17. Klein DA, Sylvester JE, Schvey NA. Eating disorders in primary care: diagnosis and management. *Am Fam Physician.* 2021;103(1):22-32. Erratum in: *Am Fam Physician.* 2021;103(5):263.
18. Fehling PC, Alekel L, Clasey J, Rector A, Stillman RJ. A comparison of bone mineral densities among female athletes in impact loading and active loading sports. *Bone.* 1995;17(3):205-210.
19. Nattiv A, Loucks AB, Manore MM, et al. American College of Sports Medicine position stand. The female athlete triad. *Med Sci Sports Exerc.* 2007;39(10):1867-1882.



Kevin Pan, DO, MEd
Penn Medicine Lancaster General Health
538 N. Queen St., Lancaster PA, 17602
Kevin.Pan@pennmedicine.upenn.edu

Laura DiPaolo, MD, CAQSM
Penn Medicine Lancaster General Health
538 N. Queen St., Lancaster PA, 17602
Laura.DiPaolo@pennmedicine.upenn.edu

Minuette Laessig, MD
Penn Medicine Lancaster General Health
540 N. Duke St., Lancaster PA, 17602
Minuette.Laessig@pennmedicine.upenn.edu

Geoffrey Dreher, DO, CAQSM, FAOASM
Penn Medicine Lancaster General Health
538 N. Queen St., Lancaster PA, 17602
Geoffrey.Dreher@pennmedicine.upenn.edu

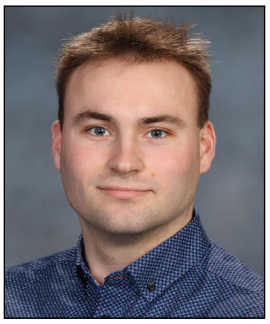
# Injury-Related Outcomes in Frail Geriatric Trauma Patients

**Nathan Schlessinger**
*Trauma Research Intern*
*Penn Medicine Lancaster General Health*

**Medoza S. Ameen, MPH**
*Trauma Research Associate*
*Penn Medicine Lancaster General Health*

**Julie M. Reichert**
*Trauma Research Associate*
*Penn Medicine Lancaster General Health*

**Lindsey L. Perea, DO, FACS**
*Research Director, Trauma and Acute Care Surgery*
*Penn Medicine Lancaster General Health*


Schlessinger


Ameen


Reichert


Perea

The National Institutes of Health defines frailty as an age-related increase in vulnerability due to worsened outcomes from everyday or acute stressors.[1] Low-energy mechanisms of trauma, classified as simple falls from a sitting or standing position, are more common in older adults. Physicians and hospitals should expect to see an increase in frail, geriatric trauma patients. It is important to characterize frailty early, as it will affect how a patient is treated.

The Trauma Service at Penn Medicine Lancaster General Health works closely with the Geriatric Medicine Service when caring for trauma patients aged 65 years and older. Our clinicians began implementing the Clinical Frailty Scale (CFS) in 2019 to better assess the needs of geriatric trauma patients. The CFS measures frailty on a scale from one to nine (see Table 1).[2]

Our research team in the Trauma and Acute Care Surgery Department conducted three retrospective studies on the effects of frailty, each utilizing the CFS looking at pelvic fractures, delirium, and rib fractures. Each study was approved by our organization's Institutional Review Board, and none received funding. Data were provided by the trauma registry and stored in a database management system to ensure the protection of all patient health information.

Table 1. **Dalhousie Clinical Frailty Scale**

| Frailty Score | Description |
|---|---|
| 1: Very Fit | Robust, active, energetic, motivated. |
| 2: Well | No active symptoms of disease, occasionally active. |
| 3: Managing Well | Medical problems are well controlled, not regularly active. |
| 4: Vulnerable | Independent, limited activity due to symptoms of disease. |
| 5: Mildly Frail | Evident slowness, requires assistance with daily activities. |
| 6: Moderately Frail | Requires assistance with all outdoor and housekeeping activities, may require assistance with routine personal care activities such as bathing and dressing. |
| 7: Severely Frail | Completely dependent on others for personal care due to either a physical or cognitive cause. |
| 8: Very Severely Frail | Completely dependent, approaching end of life. |
| 9: Terminally Ill | A life expectancy of less than 6 months. |

## Frailty and Geriatric Pelvic Fractures

Our first frailty study, "Frailty Is Associated with Worse Outcomes in Geriatric Pelvic Fractures,"[3] conducted in 2022, examined outcomes of frail, geriatric trauma patients with pelvic frailty fractures, defined by the World Health Organization as "a fracture that is caused by an injury that would be insufficient to fracture normal bone." In

the pelvis, these can occur as a result of low-energy trauma such as a ground-level fall[4] and are likely to increase as the population ages.

Geriatric patients are at an increased risk of frailty fractures.[4] Frail, geriatric patients sustaining pelvic fractures may have complications that their younger counterparts do not due to decreased bone density in the pelvis. Many pelvic fractures can be treated non-operatively if recovery and symptoms are closely monitored. There is limited research on frailty in geriatric patients and, more specifically, on frail patients with pelvic fractures. Therefore, we sought to determine if there was an association between frail, geriatric patients with pelvic fractures and worsened outcomes.

Our study included all geriatric patients who were aged 65 years and older presenting to our Level I Trauma Center between January 1, 2019, and September 30, 2021, who sustained a pelvic fracture and had a documented frailty score. Geriatricians at our institution utilize the Dalhousie Clinical Frailty Scale to assign patients a rating where 1 indicates a patient who is very fit and 9 indicates terminal illness.

Frailty scores are assigned based on a patient's pre-injury characteristics (see Table 1 on page 41).[2] For this study, patients were stratified into two groups: frail (CFS score >4) and non-frail (CFS score ≤4). Seventy patients met criteria to be included in this study. Of these 70 patients, 59% (n = 41) were frail and 41% (n = 29) were non-frail. All patients sustained a blunt mechanism of injury.[3]

As shown in Table 2, frail patients in this study were found to be older than their non-frail counterparts, and Glasgow Coma Scale was found to be lower in the frail group as was functional status at discharge. Frail patients were more likely to be discharged to a skilled nursing facility and less likely to be discharged to an acute rehabilitation center. We found no difference between frail and non-frail patients regarding their Injury Severity Score, emergency department (ED) length of stay, intensive care unit (ICU) length of stay, or hospital length of stay. Additionally, we found no difference in mortality between frail and non-frail patients.[3]

Although there was no difference in mortality between frail patients and non-frail patients who sustained pelvic fractures, frail patients had an overall worse outcome than their non-frail counterparts. Frail patients, on average, had a lower functional status at discharge, and nearly two-thirds of the sample were discharged to a skilled nursing facility.

Earlier studies have demonstrated a higher frailty score correlates with increased risk of mortality,[5] yet

**Table 2. Characteristics of Frail vs. Non-Frail Population**

| Characteristics | Not Frail (n = 29) | Frail (n = 41) | *p-value* |
|---|---|---|---|
| Gender[a] | 44.8 | 24.4 | 0.120 |
| Age[b] | 75 (69-84) | 87 (81-92) | <0.001* |
| Glascow Coma Scale[b] | 15 (15-15) | 14.5 (14-15) | 0.008* |
| Functional Status at Discharge[b] | 16 (16-18) | 14.5 (12-16) | 0.015* |
| Discharge Destination | | | |
| Skilled Nursing Facility[a] | 20 | 65.8 | <0.001* |
| Rehabilitation Center[a] | 52 | 15.8 | <0.004* |
| Injury Severity Score[b] | 10 (16-20) | 9 (5-12) | 0.118 |
| Length of Stay | | | |
| Emergency Department (minutes)[a] | 252 | 301 | 0.147 |
| Intensive Care Unit (days)[b] | 1 (0-1) | 0(0-1) | 0.302 |
| Hospital (days)[b] | 4 (3-7) | 4 (3-6) | 0.790 |
| Mortality[a] | 4 | 3 | 0.438 |

*Results reported as: a = n (% of population); b = median (IQR); * indicates a significant p-value (≤0.05). Functional status at discharge is scored out of a maximum score of 20 where 1 to 4 points are allotted from each of five domains: feeding, locomotion, expression, transfer mobility, and social interaction. A score of 1 indicates complete dependence and 4 indicates complete independence.*

Table 3. **Characteristics of Frail Patients Stratified by Delirium**

| Characteristics | No Delirium (n = 1,277) | Delirium (n = 40) | *p-value* |
|---|---|---|---|
| Age[b] | 80 (73-87) | 80 (76-88) | 0.545 |
| Gender: Male[a] | 575 (45%) | 20 (50%) | 0.629 |
| Hospital Length of Stay[b] | 3 (4-6) | 7 (6-12) | <0.001* |
| ICU Length of Stay[b] | 0 (0-1) | 1 (1-4) | <0.001* |
| Injury Severity Score[b] | 9 (5-13) | 10 (9-19) | 0.004* |
| Prescribed Benzodiazepine[a] | 247 (19.3%) | 19 (47.5%) | <0.001* |
| Prescribed Narcotic(s)[a] | 722 (56.5%) | 31 (77.5%) | 0.009* |
| Intubation[a] | 65 (5.1%) | 5 (12.5%) | 0.057 |
| Restraints Used[a] | 65 (5.1%) | 10 (25%) | <0.001* |
| Urinary Tract Infection[a] | 13 (1%) | 5 (12.5%) | <0.001* |
| Discharged to SNF[a] | 393 (30.8%) | 18 (45%) | 0.001* |
| Frailty Score[a] | 4 (3-5) | 4 (4-6) | 0.669 |

*Results reported as: a = n (% of population); b = median (IQR); * indicates a significant p-value (≤0.05). ICU: intensive care unit; SNF: skilled nursing facility.*

we did not find an increase in mortality; this could be due to our smaller sample size and stratification of patients into frail and non-frail categories. Further consideration and investigation are necessary to identify potential means to mitigate the increased risk of morbidity in this patient population.

## DELIRIUM AND GERIATRIC TRAUMA

The second study, "There's No Place Like Home: Delirium as a Barrier in Geriatric Trauma,"[6] conducted in 2024, focused on the effect of delirium in geriatric trauma patients. Delirium, a state of being in which a patient is confused for a period of time, is common among geriatric patients.[7] Although typically a temporary state of being, it can have a prolonged course with lasting effects. Delirium is also more common among those hospitalized for severe illnesses and requiring a higher level of care.

Many factors can increase the risk of delirium including infection, dementia, malnutrition, and admission to the ICU.[6-9] Delirium is commonly underdiagnosed and, if initially overlooked, can be more costly and often fatal.[7] Delirium can lead to longer hospital length of stay, increased hospital costs, and greater risk of in-hospital mortality.[7] Therefore, we conducted this study to understand the modifiable and non-modifiable factors associated with the development of delirium in the geriatric trauma population.

This retrospective chart review study included all geriatric trauma patients who were admitted to our Level I Trauma Center with a documented frailty score from January 1, 2019, to September 30, 2021. Frailty scores were assigned by a geriatrics provider utilizing the CFS outlined in Table 1 on page 41.[6] Patients were stratified into two groups: delirium (D) and without delirium (ND). A diagnosis of delirium was confirmed by a geriatrician.

As shown in Table 3, 1,317 patients met inclusion criteria of this study for having a documented frailty score and being aged 65 years and older. Of these, 3.04% of patients (n = 40) were found to have delirium.[6] There was no significant difference in age or gender between patients with delirium and patients without delirium, however patients with delirium stayed in the hospital for a median length of seven days, while the median length of stay for those who did not have delirium was three days. Those with delirium stayed in the ICU one day, while those

without delirium stayed zero days. The Injury Severity Score was found to be higher in those with delirium than those without (10 versus 9).

Additionally, those who experienced delirium as opposed to those who did not experience delirium were more likely to have had a benzodiazepine prescribed preadmission (47.5% versus 19.3%) and to have had a narcotic prescribed preadmission (77.5% versus 56.5%).

Patients who experienced delirium as opposed to those without delirium were more likely to be intubated (12.5% versus 5.1%), to be placed in restraints (25% versus 5.1%), to have a urinary tract infection (12.5% versus 1%), and to be discharged to a skilled nursing facility (45% versus 30.8%). When comparing frailty scores for the delirium group versus no delirium group, there was no significant difference in median frailty score.[6]

Women had longer stays in both the hospital (8 days, interquartile range [IQR] = 6.5-14.5, versus men: 6 days, IQR = 4.5-8, p = 0.022) and in the ICU (3.5 days, IQR = 1-5, versus men: 1 day, IQR = 0-3, p = 0.016). Furthermore, women were more likely than men to have a urinary tract infection (20.0% of women versus 5% of men, p = 0.049) and to be discharged to a skilled nursing facility (50% of women versus 40% of men, p = 0.007).[6]

Upon multivariable logistic regression to assess risk of delirium, we found an increase in hospital length of stay (adjusted odds ratio (AOR): 1.08, p = 0.016), positive urine drug screen (AOR: 2.587, p = 0.041), and documented urinary tract infection (AOR: 5.206, p = 0.018) were significant risk factors for developing delirium.

Surprisingly, delirium and frailty were not directly correlated in our study. What we found instead was that geriatric patients with delirium were more likely to be female and discharged to a skilled nursing facility.[7]

This reaffirms our hypothesis that delirium and frailty must both be considered when caring for a geriatric trauma patient and further highlights results from our pelvic fracture study, which found that frail patients were more likely female and more likely to be discharged to a skilled nursing facility.

## FRAILTY AND GERIATRIC RIB FRACTURES

For our third study, "Rib Fractures and Frailty in Geriatric Trauma Patients,"[10] also conducted in 2024, we examined the outcomes associated with frail, geriatric patients who present with rib fractures. In this retrospective chart review study, we included all geriatric patients (aged 65 years and older) with a documented frailty score and two or more rib fractures. Patients were stratified into multiple groups, including frail versus non-frail cohorts, and stratified based on number of rib fractures (≤3 versus >3).

As shown in Table 4, a total of 356 patients met inclusion criteria; of these, 44.38% of patients (n = 158) were frail. When stratified by the number of rib fractures, we found 56.75% of the 356 patients had >3 rib fractures. Frail patients were more likely to be female (60.76% versus 43.94%, p = 0.002) and older: median age of frail patients was 84 years; median age of non-frail patients was 76 years.

Frail patients, as opposed to non-frail patients, were less likely to live at home before their injury (72.6% versus 91.62%), were more likely to be discharged to a skilled nursing facility (50.63% versus 16.67%), and were more likely to have been receiving anticoagulants (43.67% versus 29.29%). Frail patients were also more likely to have had a fall as the mechanism of injury (89.87% versus 76.26%).

As in our first study, we found that frail patients, as opposed to non-frail patients, were more likely to have a lower functional status at discharge than their non-frail counterparts (16 versus 18). It is important to note that a lower functional status at discharge likely correlates with poorer outcomes.

Pain, Inspiration, and Cough (PIC) scores range from 3-10 and help describe the severity of symptoms in patients with rib fractures; lower scores correlate with more severe presentation. In our study, patients who were frail, as opposed to those who were not frail, were more likely to have lower — or more concerning — PIC scores (7 versus 8). Additionally, patients with >3 rib fractures, as opposed those with ≤3 rib fractures, were more likely to be admitted to the ICU from the ED (33.17% versus 18.18%).[10] Additional results of this study are further outlined in Table 4.

## CONCLUSION

Given the relative lack of studies on frailty in the geriatric trauma population, additional research must be done to gain more conclusive results. One study idea from our research team aims to investigate the correlation between traumatic injuries and osteoporosis in frail, geriatric females.

Table 4. **Characteristics of Patients Stratified by Frailty and Rib Fractures**

| Characteristics | Not Frail (n = 198) | Frail (n = 158) | *p-value* | ≤3 Rib Fractures (n = 154) | >3 Rib Fractures (n = 202) | *p-value* |
|---|---|---|---|---|---|---|
| Age[b] | 76 (71-83) | 84 (76-89) | <0.001* | 82 (73-88) | 78 (73-86) | 0.250 |
| Gender: Male[a] | 111 (56.06%) | 62 (39.24%) | 0.002* | 75 (48.70%) | 98 (48.51%) | 0.972 |
| Race: White[a] | 193 (97.47%) | 151 (95.57%) | 0.725 | 149 (96.75%) | 195 (96.53%) | 0.381 |
| PIC Score[b] | 8 (7-9) | 7 (7-8) | <0.001* | 8 (7-9) | 8 (7-8) | 0.03* |
| Home Prior to Admission[a] | 164 (91.62%) | 106 (72.6%) | <0.001* | 111 (77.62%) | 159 (87.36%) | 0.061 |
| Mechanism of Injury: Fall[a] | 151 (76.26%) | 142 (89.87%) | 0.05* | 140 (90.91%) | 153 (75.74%) | 0.003* |
| Number of Rib Fractures[b] | 4 (3-6) | 4 (3-5) | 0.036* | 3 (2-3) | 5 (4-7) | <0.001* |
| Injury Severity Score[b] | 10 (9-10) | 9 (9-10) | 0.163 | 9 (5-10) | 10 (9-10) | <0.001* |
| ED Glasgow Coma Scale[b] | 15 (15-15) | 15 (15-15) | 0.001* | 15 (15-15) | 15 (15-15) | 0.179 |
| Hospital Length of Stay[b] | 4 (2-7) | 5 (3-7) | 0.001* | 4 (3-7) | 4 (4-8) | 0.289 |
| Discharged from ED to ICU[a] | 50 (25.25%) | 45 (28.48%) | 0.577 | 28 (18.18%) | 67 (33.17%) | 0.009* |
| Received Anticoagulants[a] | 58 (29.29%) | 69 (43.67%) | 0.005* | 64 (41.56%) | 63 (31.19%) | 0.043* |
| Discharged to SNF[a] | 33 (16.67%) | 80 (50.63%) | 0.001* | 58 (37.66%) | 55 (27.23%) | 0.043* |
| Lower Functional Status at Discharge[b] | 18 (16-20) | 16 (15.5-18) | 0.001* | 18 (16-20) | 18 (16-19) | 0.721 |
| Had a DNR Order[a] | 38 (19.19%) | 80 (50.96%) | 0.001* | 53 (34.64%) | 65 (32.18%) | 0.626 |
| Mortality[a] | 5 (2.53%) | 3 (1.90%) | 0.692 | 0 (0.00%) | 8 (3.96%) | 0.012* |
| Readmission[a] | 16 (8.12%) | 11 (6.96%) | 0.919 | 11 (7.14%) | 16 (7.96%) | 0.027* |

*Results reported as: a = n (% of population); b = median (IQR); * indicates a significant p-value (≤0.05). PIC: Pain, Inspiration, and Cough; ED: emergency department; ICU: intensive care unit; SNF: skilled nursing facility; DNR: do not resuscitate.*

Another study idea includes preemptive frailty screening on patients who use anticoagulants to determine if they have increased frailty risk.[10] The continued study of frailty factors can be important in the prevention and treatment of the aging U.S. population.

Frailty must be considered by clinicians when caring for a geriatric population. Because a state of frailty can be caused by many physiological factors, research on this topic is vital in providing a deeper understanding of how to identify and reduce frailty in geriatric populations. If health providers in the United States take the necessary steps to prevent progression of frailty, we may be able to decrease the risk for medical complications and help keep our elderly patients healthy.

## REFERENCES


1. Xue QL. The frailty syndrome: definition and natural history. *Clin Geriatr Med.* 2011;27(1):1-15.
2. Church S, Rogers E, Rockwood K, Theou O. A scoping review of the Clinical Frailty Scale. *BMC Geriatr.* 2020;20(1):393.
3. Perea LL, Fort LS, Morgan ME, Brown CT, Wang S, Bradburn E. Frailty is associated with worse outcomes in geriatric pelvic fractures. *Am Surg.* 2022;88(7):1573-1575.
4. Rommens PM, Wagner D, Hofmann A. Fragility fractures of the pelvis. *JBJS Rev.* 2017;5(3):e3
5. Pecheva M, Phillips M, Hull P, et al. The impact of frailty in major trauma in older patients. *Injury.* 2020;51(7):1536-1542.
6. Toure A, Tadi R, Meagher M, et al. There's no place like home: delirium as a barrier in geriatric trauma. *J Surg Res.* 2024;293:89-94.
7. Aldemir M, Ozen S, Kara IH, Sir A, Baç B. Predisposing factors for delirium in the surgical intensive care unit. *Crit Care.* 2001;5(5):265-270.
8. Francis J. A prospective study of delirium in hospitalized elderly. *JAMA.* 1990;263:1097e1101.
9. American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2019;67(4):674-694.
10. Brown JH, LaRosa SK, Moore KG, Perea LL. Rib fractures and frailty in geriatric trauma patients. *Am Surg.* 2024;90(7):1971-1973.



Nathan A. Schlessinger
Penn Medicine Lancaster General Health, 555 N. Duke St., Lancaster, PA 17602
Nathan.Schlessinger@pennmedicine.upenn.edu

Julie M. Reichert
Penn Medicine Lancaster General Health, 555 N. Duke St., Lancaster, PA 17602
Julie.Reichert@pennmedicine.upenn.edu

Medoza S. Ameen, MPH
Penn Medicine Lancaster General Health, 555 N. Duke St., Lancaster, PA 17602
Medoza.Ameen@pennmedicine.upenn.edu

Lindsey L. Perea, DO, FACS
Penn Medicine Lancaster General Health, 555 N. Duke St., Lancaster, PA 17602
Lindsey.Perea@pennmedicine.upenn.edu


## CLARIFICATION

*In addition to those acknowledged in the original article, the authors of "Addressing Pain Catastrophizing in Elective Joint Replacement Surgery," which appeared in the Spring issue of* JLGH, *would like to thank the CAT Team nurses whose participation was instrumental in the success of the project. These are: Amy Adams, BSN, RN; Lisa Graham, BSN, RN; Staci Stoner, BSN, RN, CPAN; and Wendy Holler, MSN, RN, ONC, CRRN, ACNS-BC, FARN.*

# A Retrospective Review of Concomitant Use of Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors

**Alexis Jeschonnek, PharmD**
*Clinical Pharmacist, Penn Presbyterian Medical Center*

**Michelle Link Patterson, PharmD, BCACP, CDCES**
*Clinical Pharmacy Specialist, Main Line Health*

**Nafisa Khan, PharmD**
*Ambulatory Pharmacist Clinician, Penn Medicine Lancaster General Health*

**Jennifer I. Smith, PharmD, BCACP**
*Ambulatory Pharmacist Clinician, Penn Medicine Lancaster General Health*


Jeschonnek


Patterson


Khan


Smith

Estimates of the global burden of diabetes exceed 530 million adults with type 2 diabetes mellitus (T2DM), accounting for more than 95% of total cases worldwide.[1,2] In Lancaster General Health Physicians (LGHP) practices, there are approximately 32,000 patients living with diabetes. Over the past two decades, novel agents for management of T2DM have come to market, and the guidelines for management of individuals with diabetes have changed significantly as a result.[3,4] Two novel classes of medications acting on the incretin pathway are dipeptidyl-peptidase-IV (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

DPP-4 inhibitors are oral agents that improve glycemic control via inhibition of the DPP-4 enzyme, which decreases the breakdown of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP).[5] GLP-1 RAs, given orally or subcutaneously, directly activate the GLP-1 receptor to stimulate insulin secretion from the pancreatic beta cells.[5,6] Due to the overlapping pathway within the incretin system, concomitant use of DPP-4 inhibitors and GLP-1 RAs is considered a duplication of therapy.[3] When comparing simultaneous use of these agents versus monotherapy of either class alone, patients experience modest improvements in glycemic control and minimal additional weight loss.[7,8]

In one study, sitagliptin was added to liraglutide therapy, and although GLP-1 and GIP concentrations increased, marginal, non-significant changes were seen in glycemic levels.[5] Another published case series of patients with T2DM taking once-weekly GLP-1 RAs and simultaneous DPP-4 inhibitors demonstrated a median change in glycosylated hemoglobin A1c (HgbA1c) of –0.8% (interquartile range [IQR] = –4.3% to 2%). In the analysis, 28% of patients experienced gastrointestinal adverse reactions and 17% experienced hypoglycemia symptoms.[7]

As these two drug classes are more expensive compared to alternative non-insulin medications used to treat diabetes, the concomitant use of GLP-1 RAs and DPP-4 inhibitors can lead to excessive medication costs for both patients and the health care system.[5] For example, using the local zip code and price estimates from GoodRx, a four-week supply of brand dulaglutide costs $1,039 and 30 tablets of brand sitagliptin 100 mg cost $342, while a 30-day supply of extended-release metformin (at 2,000 mg/day) costs $8 and 30 tablets of glipizide ER 5 mg cost $9. Therefore, it is reasonable to review instances in which GLP-1 RAs and DPP-4 inhibitors are being used together with the intent of reducing the concomitant use of these drug classes.

Penn Medicine Lancaster General Health is a rural community health system located in Pennsylvania that serves Lancaster County as well as several surrounding counties. There are 15 ambulatory clinical pharmacists embedded within 12 of 28 LGHP Family Medicine practices; these pharmacists practice under collaborative drug therapy management (CDTM) agreements.

In the electronic health record (EHR), a duplicate therapy warning is triggered at the time of prescribing to discourage the concomitant use of GLP-1 RAs with

DPP-4 inhibitors. Prescribers must acknowledge the interaction to bypass the alert in order to prescribe two agents from these drug classes at the same time. They are able to enter additional clarifying information regarding why they are prescribing both classes together; this warning is therefore not a hard stop (see Fig. 1).

## METHODS

This single-center retrospective review was conducted across LGHP Family Medicine practices and was approved by the Lancaster General Hospital Institutional Review Board. An Epic SlicerDicer report was utilized to identify adult patients who had both a DPP-4 inhibitor and a GLP-1 RA or GLP-1/GIP dual agonist on their active medication list from January 1, 2023, to July 31, 2023.

Of the patients identified, the EHR dispense report was reviewed to determine if patients were actively filling both medications based on claim information from the dispensing pharmacy. Prescriber notes were reviewed to ensure appropriate inclusion of patients concomitantly prescribed and filling both agents.

Patients were included if they were over the age of 18 years and if the active prescriptions for the DPP-4 inhibitor and GLP-1 RA were both being filled simultaneously for at least one month. Combination products, such as those with a DPP-4 inhibitor plus metformin, were also included. Patients were excluded if they were seen by a primary care clinician outside of LGHP or if they were deceased.

Key data points collected include patient demographics and insurance type, primary care clinician and office location, whether the patient was seen by an ambulatory clinical pharmacist in the past year, the active medication list, time between initiation of first and second agent, outpatient pharmacy information, and pertinent glycosylated HgbA1c values.

Three HgbA1c values were reviewed. The first (HgbA1c #1) was obtained prior to initiation of the first agent; the second (HgbA1c #2) was obtained while on the first agent but prior to initiation of the second agent; the last (HgbA1c #3) was the most recent HgbA1c value obtained after initiation of the second agent. The minimum time between each HgbA1c was three months.

The primary outcome of this study was to determine the frequency of patients who were prescribed and filling both DPP-4 inhibitors and GLP-1 RAs. Secondary outcomes included the rate of occurrence at an outpatient practice with versus without an integrated CDTM ambulatory clinical pharmacist, impact of use pattern on HgbA1c, and adverse events potentially due to concomitant use of DPP-4 inhibitors and GLP-1 RAs. All outcomes were compared utilizing descriptive statistics (average, standard deviation).

At the conclusion of the study, ambulatory clinical pharmacists contacted the prescribers of these 28 individuals via the electronic health record and recommended discontinuation of the DPP-4 inhibitor.

## RESULTS

From the initial report, 138 patients were identified to have both a DPP-4 inhibitor and GLP-1 RA on their active medication list in the specified timeframe. Baseline patient demographics and characteristics are listed

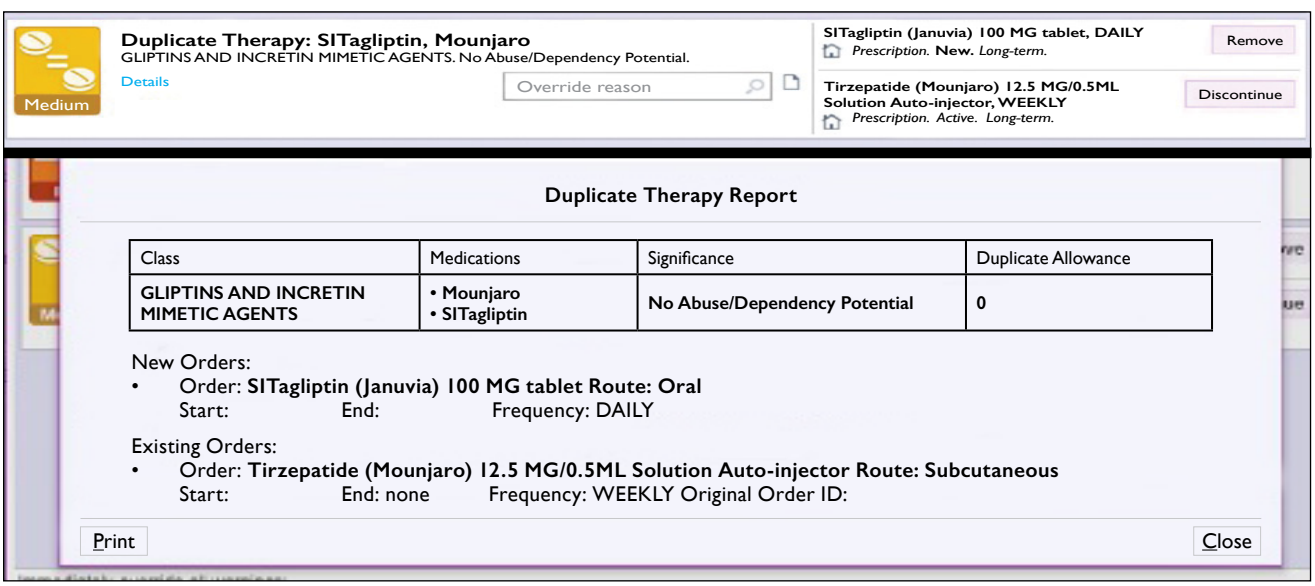



Fig. 1. Epic warning that fires when GLP-1 RAs and DPP-4 inhibitors are simultaneous active prescriptions.

in Table 1. Of the 138 patients identified to have both a DPP-4 inhibitor and GLP-1 RA on their active medication list, 28 (20%) were found to be actively filling both agents. The DPP-4 inhibitors, GLP-1 RAs, and combination products that were revealed to be co-prescribed during the review are detailed in Table 2 on page 50.

Sixteen (57%) of the 28 patients actively filling medications from both drug classes received care at a site without a CDTM ambulatory clinical pharmacist embedded within the practice. None of the patients were seen by an ambulatory clinical pharmacist or an endocrinologist within one year from the start of the enrollment period.

The majority of patients who had both drug classes on their active medication list were not actively filling both medications concomitantly but rather were transitioned from one drug class to the other. Notably, there was one patient identified to be actively filling and taking two DPP-4 inhibitors and one GLP-1 RA.

As seen in Fig. 2 on page 51, the median HgbA1c #1, HbgA1c #2, and HgbA1c #3 was 9.00% (IQR = 7.60-9.95), 9.10% (IQR = 7.98-9.53), and 7.65% (IQR = 6.85-9.05), respectively. The first agent prescribed in 25 out of 28 patient cases was a DPP-4 inhibitor. After the first agent was added, the median HgbA1c increased by 0.10%. After the initiation of the second agent, the median HgbA1c decreased by 1.45% to 7.65%.

The start of the first agent was recorded by either the first time the prescription was ordered or, if they were started on it outside of LGHP, the first time it was noted in the patient's chart. There was a median of 25.5 months (IQR = 34.7) from the time the first agent was started to the addition of the second agent, and there was a wide range of 3 months to 93 months. The duration of overlap of both agents was collected, and there was a median of 20 months (IQR = 52.3) of patients taking a DPP-4 inhibitor and a GLP-1 RA concomitantly.

Adverse events possibly attributable to the concomitant therapy of both a DPP-4 inhibitor and a GLP-1 RA were discovered in one patient, who reported experiencing diarrhea during a follow-up visit per clinician documentation. There was no additional documentation by the primary care clinician regarding symptom onset, and no changes were made to the patient's medication regimen. Based on this limited information, it is not possible to say if the patient's diarrhea was due to either agent alone or the combination.

**Table 1. Baseline Demographics of Individuals Actively Filling Both Medication Types During Study Period**

| Baseline Characteristics of Patients | n = 28 |
|---|---|
| **Gender - # (%)** | |
| Female | 14 (50) |
| Male | 14 (50) |
| **Age (Median)** | 62.9 years |
| **Body Mass Index (Average)** | 34.3 kg/m$^2$ |
| **Diagnosis of Type 2 Diabetes Mellitus - # (%)** | 28 (100) |
| **Current Diabetes Mellitus Medications - # (%)** | |
| DPP-4 inhibitor | 28 (100) |
| GLP-1 RA | 26 (93) |
| GLP-1 RA/GIP | 2 (7) |
| Insulin, basal | 6 (21) |
| Insulin, bolus | 0 |
| Metformin | 16 (57) |
| Sodium-glucose cotransporter-2 (SGLT-2) inhibitors | 9 (32) |
| Sulfonylureas | 9 (32) |
| Thiazolidinediones | 0 |
| Meglitinides | 0 |
| **Insurance Type - no. (%)** | |
| Commercial | 11 (39) |
| Medicare | 14 (50) |
| Dual Medicare/Medicaid | 3 (11) |

## LIMITATIONS

This study had several limitations, including the retrospective nature of chart reviews within the EHR and the smaller sample size of patients included in the secondary evaluation. Reports of adverse effects were low, which could be due to a lack of documentation. In addition, regarding patients who were not started on therapy within this health system, the first HgbA1c value and the duration of therapy could only be collected based on first documentation of the agents in the chart. There was only one individual who did not have an accessible HgbA1c in the EHR prior to initiating the first medication.

Many patients in this review had been on both agents for several years. The decrease in some patients' HgbA1c values could be due to lifestyle modifications or the initiation of other additional agents, including insulin, during this time, but this cannot be known for

certain. It was also not known if the doses used for GLP-1 RAs were titrated appropriately. Knowing the doses of the medicines relative to the HgbA1c could have helped determine if the doses were titrated to target.

It is not known how many patients in these practices who had diabetes were strictly on treatment with one of these agents exclusive of the other class.

Despite these limitations, the data presented show a role for ambulatory clinical pharmacist intervention to improve the prescribing of these medication classes.

## DISCUSSION

Despite 138 patients being identified with a DPP-4 inhibitor plus a GLP-1 RA on their medication list, only 20% of them were filling both medications. This demonstrates the need for improved medication reconciliation practices to increase medication list accuracy. Pharmacists can play a vital role in the medication reconciliation process. It is possible that some prescribers may leave both drug classes on the medication list to allow for prior authorizations or for the patient to determine if the new medication is cost feasible. However, in many patients there was no follow-up to remove one of the medications from the list.

The first agent prescribed in 25 out of 28 patients (89.3%) was a DPP-4 inhibitor. This could be due to the timeline of market approvals in the United States (the first DPP-4 inhibitor was approved in 2006, versus 2009 for the first GLP-1 RA) and that DPP-4 inhibitors are oral agents while most GLP-1 RAs are injectable. The first oral GLP-1 RA (oral semaglutide) did not become available until 2019.

The average HgbA1c #1 (prior to initiation of the first DPP-4 inhibitor or GLP-1 RA) was 8.84% (SD ±1.73%). After the first agent was added, the average HgbA1c increased by 0.1%. This change is minimal given that most patients started with an HgbA1C >8% and most patients have an Hgb-A1C goal of either <7% or <8%.[3]

With the initiation of the second agent, which was typically the GLP-1 RA in this review, the average HgbA1c decreased to 7.86% (SD ±1.35%). While this is a reduction, it is not quite what would be expected by solely adding a GLP-1 RA to a patient's regimen. Since the doses of prescribed medicines were not noted during the course of this study, it is possible that the reduction in HgbA1c would have been of greater magnitude if GLP-1 RAs had been titrated to the maximally tolerated doses.

**Table 2. DPP-4 Inhibitor and GLP-1 RA Agents of Interest**

| DPP-4 Inhibitor Agents | GLP-1 RA Agents |
|---|---|
| Sitagliptin | Dulaglutide |
| Saxagliptin | Liraglutide |
| Linagliptin | Semaglutide |
| Alogliptin | Exenatide |
| | Lixisenatide |
| | Tirzepatide (dual GLP-1/GIP RA) |
| **Combination Products** | |
| Alogliptin and metformin | |
| Alogliptin and pioglitazone | |
| Dapagliflozin and saxagliptin | |
| Empagliflozin and linagliptin | |
| Empagliflozin, linagliptin, and metformin | |
| Empagliflozin and sitagliptin | |
| Linagliptin and metformin | |
| Saxagliptin and metformin | |
| Sitagliptin and metformin | |
| Insulin degludec and liraglutide | |
| Insulin glargine and lixisenatide | |

Historically, GLP-1 RAs lower HgbA1C by >1%, and some studies have shown HgbA1C-lowering potential as much as 2%.[3,9-11] This raises questions as to whether therapies were uptitrated according to the approved product labeling and if patients were adherent to their medications. Nonetheless, our results are consistent with the known greater glycemic-lowering potential of GLP-1 RAs compared to DPP-4 inhibitors.

After the identification of patients actively filling both medications, ambulatory clinical pharmacists contacted the prescribers to recommend discontinuation of the DPP-4 inhibitors.

While the cost of DPP-4 inhibitors and GLP-1 RAs is historically similar, clinicians should consider the preferential health outcomes that are associated with GLP-1 RAs. Several GLP-1 RAs have demonstrated cardioprotective effects including reductions in major cardiovascular (CV) events such as non-fatal myocardial infarction, non-fatal stroke, and CV death.[3,9,11-15]

Outcome trials of DPP-4 inhibitors have not demonstrated that these medicines lead to CV benefits, and while a potential increase in heart failure hospitalizations among individuals prescribed DPP-4 inhibitors has been shown, the data have not been consis-

tent; current guidelines recommend DPP-4 inhibitors not be used in patients with heart failure.[16-19] GLP-1 RAs promote more weight loss compared to DPP-4 inhibitors; this may be another reason to prefer this drug class, given the prevalence of obesity in patients with T2DM.[3,9] Deprescribing either medication will also reduce medication use burden and medication costs to the patient.

Based on the results of this medication use evaluation, ambulatory clinical pharmacists made 28 recommendations to primary care clinicians regarding duplication of therapy which resulted in an acceptance rate of 78.5%. One of the 28 recommendations was acknowledged without any change made; the remaining five were declined. In the cases of declination, clinicians cited no adverse effects and patient preference as justification to continue. In all cases that were accepted, the DPP-4 inhibitor was the medication that was subsequently discontinued.

One case of interest involved a patient who was prescribed two DPP-4 inhibitors in addition to one GLP-1 RA. In this case, there were no notes in the patient's chart from the clinician elucidating why the patient would be on this regimen.

The majority of the clinicians treating patients with both a DPP-4 inhibitor and a GLP-1 RA do not have an embedded clinical pharmacist in their practice. In our health system, clinical pharmacist involvement with diabetes management is dependent upon clinician referrals, and approximately half of the Family Medicine practices do not have a dedicated ambulatory clinical pharmacist. Due to the limited number of ambulatory clinical pharmacist full-time equivalents and competing priorities, many clinicians do not have access to or interact with pharmacist clinicians on a regular basis.

As described in this report, there is a role for ambulatory clinical pharmacists to promote evidence-based prescribing. It is well established that embedding pharmacists in primary care practices results in improved patient outcomes as well as decreased health care costs. One study identified a 1.75% decrease in HgbA1c for patients treated in a physician-pharmacist collaborative care group compared to an average 0.16% decrease in HgbA1C among patients treated in a usual care group without a pharmacist involved ($p < 0.05$).[20]

The ambulatory clinical pharmacists at LG Health who are embedded in Family Medicine practices manage diabetes for patients under a CDTM agreement. It is notable that no patients found to be taking drugs from both medication classes were seen by an ambulatory clinical pharmacist during the study period. With additional pharmacist resources, pharmacists would be able to provide medication management services to all Family Medicine practices and potentially reduce inappropriate prescribing.

Using available payor data, we calculated potential cost savings from recommended interventions for both LG Health and patients. The estimated cost to LG Health for the use of an unnecessary DPP-4 inhibitor over the course of a year is more than $5,000. From the data presented, if all interventions were accepted by the clinicians, then the health care system savings could exceed $180,000 per year. Some recommendations were accepted, and those pharmacist-initiated interventions resulted in an estimated cost savings of approximately $115,000 to the health care system per year and approximately $600 to each patient per year. Patient savings is valued based on an estimated monthly copay.

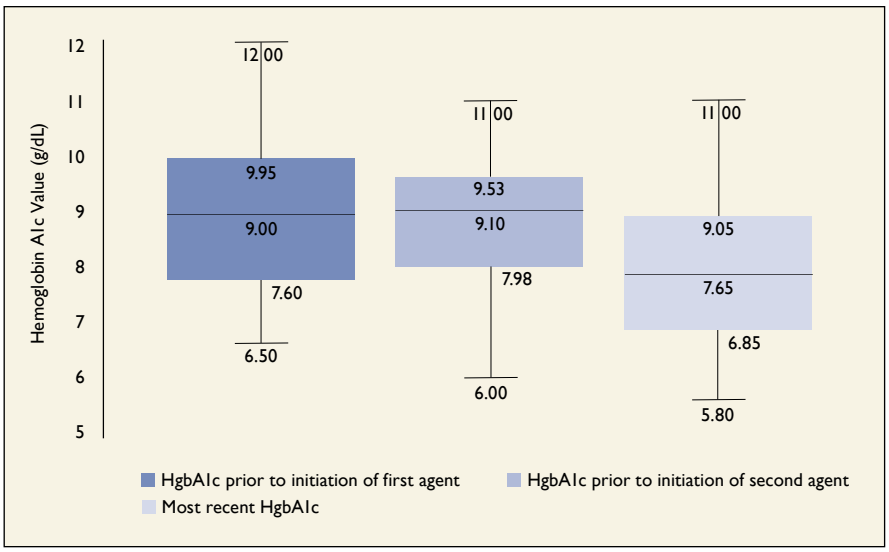



Fig. 2. Average glycosylated hemoglobin A1c (HgbA1c) at specified time points of individuals who were actively filling both medication types during the study.

## CONCLUSION

The results of this retrospective chart review demonstrate that despite guidelines and literature advising against concomitant use of GLP-1 RA and DPP-4 inhibitors, they are still prescribed together.

## REFERENCES


1. Diabetes Statistics. National Institute of Diabetes and Digestive and Kidney Diseases. Published September 15, 2019. Accessed July 28, 2023. https://www.niddk.nih.gov/health-information/health-statistics/diabetes-statistics
2. Magliano DJ, Boyko EJ; IDF Diabetes Atlas 10th edition scientific committee. IDF DIABETES ATLAS [Internet]. 10th ed. Brussels: International Diabetes Federation; 2021.
3. American Diabetes Association Professional Practice Committee for Diabetes. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2026. *Diabetes Care.* 2026; 49(Supplement_1):S183-S215.
4. Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology consensus statement: comprehensive type 2 diabetes management algorithm-2023 update. *Endocr Pract.* 2023;29 (5):305-340. Erratum in: *Endocr Pract.* 2023;29(9):746. Erratum in: *Endocr Pract.* 2023;29(12):1025.
5. Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab.* 2016;18(3):203-216.
6. Razavi M, Wei YY, Rao XQ, Zhong JX. DPP-4 inhibitors and GLP-1 RAs: cardiovascular safety and benefits. *Mil Med Res.* 2022;9(1):45.
7. Lajthia E, Bucheit JD, Nadpara PA, et al. Combination therapy with once-weekly glucagon like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a case series. *Pharm Pract (Granada).* 2019;17(4):1588.
8. Nauck MA, Kahle M, Baranov O, et al. Addition of a dipeptidyl peptidase-4 inhibitor, sitagliptin, to ongoing therapy with the glucagon-like peptide-1 receptor agonist liraglutide: a randomized controlled trial in patients with type 2 diabetes. *Diabetes Obes Metab.* 2017;19(2):200-207.
9. Reid T. Choosing GLP-1 receptor agonists or DPP-4 inhibitors: weighing the clinical trial evidence. *Clin Diabetes.* 2012;30(1):3-12.
10. Berg JK, Shenouda SK, Heilmann CR, Gray AL, Holcombe JH. Effects of exenatide twice daily versus sitagliptin on 24-h glucose, glucoregulatory and hormonal measures: a randomized, double-blind, crossover study. *Diabetes Obes Metab.* 2011;13(11):982-989.
11. Tsapas A, Averinos I, Karagiannis T, et al. Comparative effectiveness of glucose-lowering drugs for type 2 diabetes. *Ann Intern Med.* 2020;173(4):278-286.
12. Violante R, Oliveira JH, Yoon KH, et al. A randomized non-inferiority study comparing the addition of exenatide twice daily to sitagliptin or switching from sitagliptin to exenatide twice daily in patients with type 2 diabetes experiencing inadequate glycaemic control on metformin and sitagliptin. *Diabet Med.* 2012;29(11):e417-e424.
13. Van Gaal L, Souhami E, Zhou T, Aronson R. Efficacy and safety of the glucagon-like peptide-1 receptor agonist lixisenatide versus the dipeptidyl peptidase-4 inhibitor sitagliptin in young (<50 years) obese patients with type 2 diabetes mellitus. *J Clin Transl Endocrinol.* 2014; 1(2):31-37.
14. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375(4): 311-322.
15. Blonde L, Klein EJ, Han J, et al. Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes Metab.* 2006;8(4):436-447.
16. Singh AK, Singh R. Heart failure hospitalization with DPP-4 inhibitors: a systematic review and meta-analysis of randomized controlled trials. *Indian J Endocrinol Metab.* 2019;23(1):128-133.
17. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* 2013;369(14):1317-1326.
18. Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet.* 2015;385(14):2067-2076.
19. Dunlay SM, Givertz MM, Aguilar D, et al. Type 2 diabetes mellitus and heart failure: a scientific statement from the American Heart Association and the Heart Failure Society of America: this statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. *Circulation.* 2019;140(7): e294-e324.
20. Norton MC, Haftman ME, Buzzard LN. Impact of physician-pharmacist collaboration on diabetes outcomes and health care use. *J Am Board Fam Med.* 2020;33(5):745-753.



Alexis Jeschonnek, PharmD
Ambulatory Care, Penn Presbyterian Medical Center
51 N. 39th St., Philadelphia, PA 19104
Alexis.Jeschonnek3@pennmedicine.upenn.edu

Michelle Link Patterson, PharmD, BCACP, CDCES
Department of Pharmacy, Main Line Health
Lankenau Medical Center, 100 E. Lancaster Ave., Ste. B11, Wynnewood, PA 19096
MLinkPatterson@gmail.com

Nafisa Khan, PharmD
Department of Pharmacy and IV Solutions, Penn Medicine Lancaster General Health
555 N. Duke St., Lancaster, PA 17601
Nafisa.Khan@pennmedicine.upenn.edu

Jennifer I. Smith, PharmD, BCACP
Department of Pharmacy and IV Solutions, Penn Medicine Lancaster General Health
555 N. Duke St., Lancaster, PA 17601
Jennifer.Smith2@pennmedicine.upenn.edu

NARRATIVE MEDICINE

# What Dementia Could Not Steal

**Kirsten Johnsen Martin, DO, FAAFP**
*Director of Osteopathic Education, Family Medicine Residency Program*
*Penn Medicine Lancaster General Health*

The morning after Thanksgiving in 2022, I helped move my mother into a secured memory care facility.

The contrast felt cruel. Just hours earlier, I had been surrounded by my husband's large family, stuffed full of turkey and all the fixings. Cousins had played together, while adults chatted or dozed off from the tryptophan surge and the sounds of football murmured in the background on the TV. The next morning, I was unpacking my mother's belongings in a new and unfamiliar space, one that I never imagined she would need.

Someone once told me that dementia is a terrible thief. At the time, I understood what that meant for them — someone grieving the loss of their own parent to dementia. But now I, too, live inside that truth.

Dementia has stolen my mother in pieces. Some days the process unfolds in slow motion, and other days bring sudden unmistakable change. But every year as Thanksgiving approaches, I feel that loss all over again. The holiday that once meant comfort and celebration now is associated with a different kind of remembering.

We had been told just two weeks earlier that my mother needed to transition to memory care. We should have seen it coming. Her confusion had worsened. She could no longer perform the simplest tasks of daily living, and she had started wandering in the early morning hours. The reality was that my mom's care needs had surpassed what my dad was able to provide on his own.

Even knowing that, the phone call felt like an ultimatum. And it left me numb and raw. Moving her was the right decision. Nonetheless, the messy emotional bundle of frustration and grief from the process still lingers even years later.

Fast forward to Thanksgiving 2025, another anniversary arrived. This time, I enrolled my mom in hospice care.

After years of relative stability, further evidence of her decline was apparent. She can no longer feed herself, although she will still eat if someone gently offers food to her lips. She especially loves ice cream, and watching her enjoy it reminds me of life's small pleasures. She sleeps much of the day and only rarely speaks. Her brain no longer reliably tells her feet how to move, so she depends on the assistance of two people to transfer from the bed to her wheelchair.

I am a family physician. I have spent years caring for aging patients and walking with families through the long journey of memory loss and the grief that accompanies it. I have tried to offer compassion, dignity, and honesty to patients whose lives are being rewritten by cognitive decline.

But nothing in medicine prepared me for watching my own mother disappear. While I understand dementia clinically, I did not until now know what it would feel like to become its daughter. The moment that shattered me came shortly before hospice care began. I gently removed her socks and saw pressure wounds on her heels. I had seen and treated wounds like that in numerous patients. I knew what they meant. But seeing them on my mother's frail body felt unbearable.

How had the woman who once cared for everyone else become so fragile that her own skin could no longer protect her?

As if losing my mother is not enough, dementia has begun to steal my father too. When my mother moved into memory care, my father faithfully visited her daily at 11:00 a.m. for lunch. For a long time, that ritual remained unchanged, but gradually his visits have become less predictable. Sometimes he arrives an hour or two early, sometimes not at all. If I call him after noticing he hadn't been there, he sometimes insists he has already seen her.

My phone alerts me whenever he leaves his apartment. AirTags tucked into his wallet and keys help me track where he is. Those small pieces of technology do not lie. They have become quiet witnesses to a truth I would prefer not to face — dementia is no longer

taking only one parent. I find myself grieving the slow but steady loss of two parents.

After visiting my parents, I often sit alone in my car for the long drive home. No music. No one else sitting beside me. The silence feels more honest. I find myself more reflective than usual, and the weight of it all catches up to me — anger, sadness, grief, and most certainly fear.

I recall the joyful times of yesteryear around the holidays — Christmas trees the day after Thanksgiving, family outings, concerts, meals, traditions that once felt permanent. I think about what my parents imagined for themselves in retirement, and all the years I imagined with them: lunch out with my mom on afternoons off, Sunday hikes, family trips, my children growing older with their grandparents beside them. Dementia has stolen those futures too.

As a physician, I was trained to try to fix what is broken — to intervene, to treat, to help. Over time, I have accepted that I cannot always restore what disease takes away. I have told families that there is both power and comfort in attending to grief, that suffering feels lighter when it is shared. Yet in my own family, I feel utterly powerless and often very alone.

For a long time, I searched my mother's face for signs that she recognized me. I wondered whether she knew my brother, her grandchildren, or even my father. Now I no longer ask myself that question as often. She has not spoken my name in well over a year. Most days she speaks little at all, and when she does, her words dissolve into sounds I cannot understand.

And still, parts of her remain. Even after dementia changed her so much, my mother continued to extend care and compassion toward others. Before her illness, she served as a chaplain. The way she had provided pastoral care to many remained beautifully woven into her personality, changed by disease but still shining through. In memory care, she still reached for other residents, offering quiet companionship even when language was gone. The staff often told us she remained a joy.

I cling to that. I cling to the sparkle that occasionally appears in her eyes. The way she still responds to a familiar hymn. The unexpected word that sometimes emerges from silence. And the flicker of recognition that feels like a gift, even if only for a moment. Those moments are brief. But they are still hers. They are still ours to share.

Thanksgiving now holds more than gratitude for me. It also holds grief, anger, fear, and longing for what has been lost. I resent the years we will not have, and I mourn the ordinary moments that once seemed guaranteed.

But grief and gratitude can coexist. That may be the most important thing my mother is still teaching me.

Dementia is indeed a terrible thief. It has stolen memories, language, independence, the future my family thought we would have. It has taken far more than I ever imagined it would. But it has not taken everything. I will continue turning my focus toward gratitude for who my mom was, all that she taught me, how she cared for me and my family, and how she touched the lives of so many others.

*"Grief and gratitude can coexist. That may be the most important thing my mother is still teaching me."*

Each Thanksgiving, I feel the ache of what dementia has taken from my family. I suspect I always will. But I am learning that gratitude does not require the absence of grief. Sometimes gratitude is simply choosing to hold tightly to what remains. And I am doing my best not to let dementia steal that too.

Kirsten H. Johnsen Martin, DO, FAAFP
Family Medicine Residency Program
Penn Medicine Lancaster General Health
540 N. Duke St., Lancaster, PA 17602
Kirsten.JohnsenMartin@pennmedicine.upenn.edu

SPOTLIGHT ON CLINICAL RESEARCH

# Justice & Equity in Research

**Heather Madara**
*Supervisor Research Regulatory and Outreach*
*Penn Medicine Lancaster General Health Research Institute*

It is no secret that injustice and inequity in research have long been a part of Western medicine, with marginalized groups the victims of decades of abuse, often in the name of "research." It is crucial to acknowledge transgressions before we can have conversations with the communities that have been targets of this abuse. And it is only with sincere efforts to rebuild trust that we can hope to conduct ethical, valuable, and relevant research.

This article offers brief snippets from our nation's past that are in no way meant to be comprehensive histories. Although no journal article could account for all the atrocities that have been committed, what follows is a brief introduction to some names and topics, presented with the hope that readers will look up more information from other reputable sources and that this will simply be the start of the conversation. References and recommended reading are provided throughout and at the end of this article.

## JAMES MARION SIMS

James Marion Sims is often referred to as the "Father of American Gynecology." Until 2018, he was immortalized with a statue in Central Park in New York City. A surgeon in the 19th century (1813-1883), Sims developed the first surgical treatment for a condition that impacted many Black and white women of the time: vesicovaginal fistula — an unwanted opening that forms between the bladder and the wall of the vagina, often due to difficult childbirth. This type of fistula impacted enslaved Black women at a much higher rate than it did white women, due to multiple factors including malnutrition — leading to underdeveloped bones and smaller pelvises — and age, because enslaved women gave birth on average three years earlier than white women.

Sims used enslaved Black women as test subjects. He performed surgeries without anesthesia and often invited others to view the surgeries. At that time, the only legal requirement for performing surgeries on enslaved women was the consent of their enslavers.

Historical records do not provide much information about the 12 enslaved women on whom Sims experimented. In many of his own records, he concealed their race, "portraying them as white in the illustrations that accompanied his accounts of the surgery."[1,2] We know the names of only three, all of them teenagers: Anarcha, Betsy, and Lucy. Anarcha was 17 years old when she underwent the first of her 30 surgeries.

These three young women were not only experimented on but also forced to learn how to medically care for one another. Some historians suggest that "they became skilled medical practitioners in their own right" because of this necessity, though they were never recognized for their skills.[3]

In her book chapter, "Mastering the Female Pelvis: Race and the Tools of Reproduction," author Terri Kapsalis states: "Sims' fame and wealth are as indebted to slavery and racism as they are to innovation, insight, and persistence, and he has left behind a frightening legacy of medical attitudes toward and treatments of women, particularly women of color."[4]

## HEPATITIS STUDIES AT THE WILLOWBROOK SCHOOL

From 1956 through 1971, residents at the Willowbrook State School for Children with Mental Retardation were infected with live hepatitis in order to develop a vaccine. Dr. Saul Krugman, the principal investigator of the study, argued that the good that would come from development of a vaccine would outweigh the anticipated minor harms to these children. He also argued that, due to the prevalence of hepatitis at the institution, the children were bound to be exposed to the same strains even if they were not in the study.[5]

Dr. Krugman, alongside Dr. Joan Giles, oversaw more than 50 children with mental disabilities in this study. These children, between the ages of 5 and 10 years old, were either "injected with the virus itself or made to drink chocolate milk mixed with feces from other infected children in order to study their immunity."[6]

In the 1950s, testing vaccines on children did not have the stigma it rightfully carries now. However,

while parents of these children did consent for their children to participate in the study, there remain questions about whether the permission letter adequately explained the study and its risks. Additionally, Dr. Krugman would offer the opportunity for families to skip the long wait lists for admission to Willowbrook if they agreed to permit their children to participate in his trials.

Dr. Krugman certainly faced criticism for the ethics of his study. The editors of *The Lancet*, who previously published Dr. Krugman's study results, wrote that "[t]he Willowbrook experiments have always carried a hope that hepatitis might one day be prevented, but that could not justify the giving of infected material to children who would not directly benefit."[6] Many others wrote regarding their opposition to his methods and/or protested his appearances at events. Despite all of this, Dr. Krugman became president of the American Pediatric Society in 1972, was awarded the John Howland award in 1981, and received the Lasker-Bloomberg Public Service Award in 1983.

### JEWISH CHRONIC DISEASE HOSPITAL STUDY[7]

Dr. Chester Southam was a "respected clinical investigator" at the Memorial Sloan Kettering Cancer Center when he had the idea to collaborate with the Jewish Chronic Disease Hospital (JCDH) in Brooklyn, New York, on a cancer trial to examine whether people with cancer lacked immunity to it. Patients at JCDH were chronically ill but, importantly, did not have cancer. To test his theory about immunity, Dr. Southam injected 22 patients at JCDH with cancer cells without their consent. He was concerned the patients would react negatively if they were told they would be receiving cancer cells, so he and his co-investigators told them they were being injected with a "cell suspension."

> **"Science without conscience is the soul's perdition."**
>
> — François Rabelais

Several other physicians had declined to participate in this study citing ethical concerns. When they learned that the study had moved forward, they resigned from JCDH. In addition, a member of the board of directors filed a lawsuit, which garnered attention from the media. Comparisons to Nazi experiments were quick to follow, along with a hearing before the Board of Regents of the University of the State of New York in 1964 that pointed to the Nuremberg Code, a set of medical standards created following the trials of Nazi physicians involved in atrocities during World War II, which unequivocally states: "the voluntary consent of the human subject is absolutely essential." This hearing resulted in a one-year probation but no suspension of licenses or any formal prosecution for those involved in the study. In fact, Dr. Southam was elected president of the American Association for Cancer Research in 1968, just two years after the Board of Regents' decision. Three years later, he returned to his alma mater, Thomas Jefferson University in Philadelphia, to become the head of the Division of Medical Oncology, where he remained until 1979.[8]

### TUSKEGEE STUDY

Researchers in Macon County, Alabama, began the Tuskegee Syphilis Study in 1932 to document the progression of syphilis in Black men. These researchers from the U.S. Public Health Service (PHS) and the Tuskegee Institute targeted "sick, desperately poor sharecroppers" for their study, telling the men that they would receive treatment for their "bad blood," even though no treatment yet existed for syphilis when the study began.[1] The men were also offered "free medical exams, free meals, and burial insurance."[9]

At least 600 Black men participated in the study, more than half of whom had tested positive for syphilis. Those who did not have syphilis were part of the control group. When penicillin was identified as a treatment for syphilis in 1943, treatment was still withheld from the 399 men in the study with the disease. Researchers met with local Black physicians to ask them not to treat men who were in the study, instructed military physicians not to provide treatment to the men if they were inducted into the military while in the study, and sent a list of the participants to the clinics nearby so that they would not receive treatment if they showed up there.

This study went on for four decades, only ending in November 1972 at the advisement of a Health and Scientific Affairs panel when the media became aware of the study's methods. A $1.8 billion class-action civil lawsuit was filed in 1973 to seek damages for the surviving participants and their heirs. When the lawsuit was settled, the payments amounted to "$37,500 for each living study participant, $15,000 for his heirs ... The living control-group members received even less."

A formal acknowledgement of this atrocity was not made until 1997 when then-President Bill Clinton

issued a formal apology to the eight surviving study participants. This apology was accompanied by the creation of the Tuskegee University National Center for Bioethics in Research and Health Care, which was funded in part by a grant from President Clinton and has the goal of "training and educating African Americans in bioethics."[1]

## CONCLUSION

We have a long way to go to earn back the trust of marginalized communities that view health care and research as tools of abuse and surveillance. Many more instances of harm have been committed by the health care community against marginalized groups in the United States. These include:

- The forced sterilizations of Black birthing people and birthing people with disabilities, covered in *Medical Apartheid* by Harriet A. Washington and *Menace to the Future* by Jess Whatcott.
- The exclusion of voluntary female participants in clinical research until 1993, as described in the NIH Revitalization Act of 1993.
- "Research" performed on incarcerated individuals, detailed in *All in Her Head* by Elizabeth Comen, MD, and *Menace to the Future* by Jess Whatcott.

These events have contributed to a pervasive and long-lasting mistrust of and skepticism toward health care systems and practitioners.

It is a harrowing reality that many of these horrific events yielded no or minimal consequences for the perpetrators. However, there have been critical safeguards put in place in the years since these events. While these are not infallible, they are valuable and foundational to ensuring health care and research are not sources of pain but of relief. These include:

- **Nuremberg Code:** This set of 10 standards was developed in August 1947 to help us judge reported abuses of human-subjects research.
- **Institutional Review Boards:** The National Research Act of 1974 led to the development of Institutional Review Boards, or IRBs. An IRB is a committee that reviews research studies to ensure that they comply with applicable regulations, meet commonly accepted ethical standards, follow institutional policies, and adequately protect research participants.
- **Belmont Report:** This summary of ethical principles published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974 forms the basis of acceptable human-subjects research. The three foundational principles established in the report are respect for persons, beneficence, and justice.
- **International Council for Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use:** This statement helped established several international standards of Good Clinical Practice for the development of pharmaceutical products.
- **U.S. Food and Drug Administration (FDA):** This agency of the U.S. Department of Health and Human Services is the part of the federal government tasked with regulating research that involves food, dietary supplements, drugs, as well as medical devices and electronic products, to ensure that the data collection during these investigations is gathered in an ethical, compliant, and sound manner. Products must be considered safe before they can be marketed and made readily available for commercial use.
- **Informed Consent:** This encompasses the ongoing process of obtaining an individual's and/or their legally authorized representative's agreement to participate in research before any study activities take place. This is one of the central protections provided for under Health and Human Services regulations and falls into the Belmont principle of respect for persons.

### Recommended Reading

- *Medical Apartheid: The Dark History of Medical Experimentation on Black Americans from Colonial Times to the Present* by Harriet A. Washington
- *American Sirens* by Kevin Hazzard
- *The Immortal Life of Henrietta Lacks* by Rebecca Skloot
- *All in Her Head* by Elizabeth Comen, MD
- *The Pain Gap* by Anushay Hossain
- *Sex Matters* by Alison J. McGregor, MD
- *Your Consent Is Not Required: The Rise in Psychiatric Detentions, Forced Treatment, and Abusive Guardianships* by Rob Wipond
- *Menace to the Future: A Disability and Queer History of Carceral Eugenics* by Jess Whatcott
- *The Viral Underclass: The Human Toll When Inequality and Disease Collide* by Steven W. Thrasher
- *Bodies and Barriers* edited by Adrian Shanker
- *The Remedy: Queer and Trans Voices on Health and Health Care* edited by Zena Sharman
- *And the Band Played On: Politics, People, and the AIDS Epidemic* by Randy Shilts
- *Sentenced to Silence: One Black Man's Story of Imprisonment in America* by Allen Hornblum

So, what does this mean for those of us in health care? What can we do to prevent occurrences like those described above from happening again? Individual actions will vary based on our roles, but at the most foundational level, the importance of education cannot be overstated. Each of us must take steps to learn about the history of health care and research in the United States if we have any hope of not repeating past transgressions.

Taking it a step further, one of the things that marginalized communities have long said is that they feel more comfortable with a clinician who looks like them. Diversity in medicine saves lives. Cherise Hamblin, MD, in a *JLGH* article[10] in 2021, provided data directly supporting this:

> A study in Oakland, Calif., showed that Black men who were seen by a Black doctor were much more likely to accept preventive and invasive services, and were more willing to talk about their health problems ... The authors estimated that "Black doctors could help reduce cardiovascular mortality by 16 deaths per 100,000 per year — leading to a 19% reduction in the Black-white male gap in cardiovascular mortality."[11]

Ciciley Littlewolf, MD, a Native American clinician in North Dakota, states: "It's so important that patients see doctors who look like them, come from the same cultural background, because it increases trust — but also that cultural awareness." According to Nicole Riddle, MD, a pathologist in Florida who uses a wheelchair: "For people with differing abilities, it's literally about trying to change the actual physical structure or architecture of a workplace — not only people's minds, opinions and actions."[12]

Staffing our health system with people who represent the communities we serve is critical.

More actions may include joining a community organization so we can be of service in situations that do not ask anything of the people seeking aid. It may look like creating a psychologically safe space within our teams to discuss events that team members have personally experienced or heard about from patients. It may be as simple as engaging with books, movies, or presentations from perspectives that differ from ours to broaden our empathy.

Recognizing what has been committed in the name of science can make people uncomfortable. Sitting with the discomfort and wrestling with our complicated thoughts and emotions that arise is important. Change is not always easy. But we owe it to one another's humanity to do the hard work, the necessary work of challenging our biases and speaking up when we see harm being done. It only takes one decision, one individual action, to spark change.

**Scan to access links to the safeguards listed in bold on page 57.**

## REFERENCES


1. Washington HA. *Medical Apartheid: The Dark History of Medical Experimentation on Black Americans from Colonial Times to the Present.* Paw Prints; 2006.
2. Hamblin C, Hill K. Book review: Medical Apartheid. *JLGH*. 2022; 17(2):57-58.
3. *Anarcha, Betsy, and Lucy.* The New York Historical; 2026.
4. Kapsalis T. Mastering the female pelvis: race and the tools of reproduction. In: Wallace-Sanders K, ed. *Skin Deep, Spirit Strong: The Black Female Body in American Culture.* HathiTrust; 2026:263-300.
5. DuBois JM. Hepatitis studies at the Willowbrook State School for Children. Bioethics Research Center at Washington University in St. Louis. 2020. Accessed April 30, 2026. https://bioethicsresearch.org/resources/case-studies/hepatitis-studies-at-the-willowbrook-state-school-for-children/
6. Rosenbaum L. The hideous truths of testing vaccines on humans. Forbes. Updated June 15, 2020. Accessed April 30, 2026. https://www.forbes.com/sites/leahrosenbaum/2020/06/12/willowbrook-scandal-hepatitis-experiments-hideous-truths-of-testing-vaccines-on-humans/
7. Lerner BH. Sins of omission — cancer research without informed consent. *N Eng J Med.* 2004;351(7):628-630.
8. Paid Notice: Deaths SOUTHAM, CHESTER MILTON. The New York Times. April 10, 2002. Accessed April 30, 2026. https://www.nytimes.com/2002/04/10/classified/paid-notice-deaths-southam-chester-milton.html
9. The Untreated Syphilis Study at Tuskegee Timeline. Centers for Disease Control and Prevention. September 4, 2024. Accessed April 30, 2026. https://www.cdc.gov/tuskegee/about/timeline.html?CDC_AAref_Val=https://www.cdc.gov/tuskegee/timeline.htm
10. Hamblin C. Diversity in medicine: why our patients can't wait. *JLGH.* 2021;16(3):86-88.
11. Alsan M, Garrick O, Graziani G. Does diversity matter for health? Experimental evidence from Oakland. *Am Econ Rev.* 2019;109(12):4071-4111.
12. Robeznieks A. Why does representation in medicine matter? AMA members speak out. American Medical Association. March 4, 2024. Accessed April 30, 2026. https://www.ama-assn.org/public-health/health-equity/why-does-representation-medicine-matter-ama-members-speak-out


Heather Madara
Penn Medicine LG Health Research Institute, 133 E. Frederick St., Lancaster, PA 17602
Heather.Madara@pennmedicine.upenn.edu

EDUCATIONAL QUIZ FROM URGENT CARE

# Ketogenic Diet-Associated Hypomagnesemia

**Madeline Cingle, PA-C**
*Physician Assistant, Urgent Care*
*Penn Medicine Lancaster General Health*

## CASE HISTORY

A 77-year-old male presents to an urgent care center with three days of intermittent dizziness, primarily positional. The episodes last 5-10 minutes, occurring when he is transitioning from lying to sitting; the episodes are most noticeable in the early morning. He denies syncope, chest pain, palpitations, dyspnea, headache, visual changes, focal neurological deficits, hearing loss, tinnitus, fever, or chills.

The patient reports initiating a ketogenic diet approximately three-and-a-half weeks ago, resulting in a 17-pound intentional weight loss from 212 pounds to 195 pounds. He reports adequate hydration.

His past medical history includes gastroesophageal reflux disease (GERD), hypertension, benign prostatic hyperplasia, chronic gout, arthritis, bladder cancer that is now in remission, and atherosclerosis of the aorta.

His regular medications include omeprazole, allopurinol, amlodipine-benazepril, red yeast rice, tamsulosin, tadalafil, a multivitamin, and simethicone.

The vital signs are notable for a blood pressure of 154/86 mmHg but otherwise are within normal limits. A neurological exam is unremarkable, and there is no evidence of orthostatic hypotension. A Dix-Hallpike maneuver reproduces dizziness without nystagmus, making benign paroxysmal positional vertigo less likely.

An electrocardiogram shows sinus rhythm with a first-degree atrioventricular block.

Given that there is a concern for electrolyte abnormalities in the setting of his recent ketogenic diet, a laboratory evaluation is obtained, revealing a critically low serum magnesium level of 0.8 mg/dL. The patient is immediately referred to an emergency department, where he receives intravenous magnesium replacement with rapid resolution of his symptoms. His borderline hypokalemia (initially 3.5 mmol/L) is also corrected.

He is discharged home with a prescription for oral magnesium supplementation and dietary counseling. He is encouraged to remain hydrated and to continue close outpatient laboratory follow-up with his primary care clinician, including a discussion of the role of his proton pump inhibitor and whether/how that should be reduced.

At the time he is discharged from the emergency department, the patient reports complete resolution of dizziness.

## QUESTIONS

1. What is the differential diagnosis for positional dizziness in an older adult?
2. What electrolyte abnormalities are associated with ketogenic diets?
3. What are the clinical manifestations of hypomagnesemia?
4. What factors increase the risk of hypomagnesemia in patients following a ketogenic diet?
5. How should severe hypomagnesemia be managed?
6. What counseling should be provided to patients considering ketogenic diets?

## ANSWERS

1. The differential diagnosis for dizziness that increases with position change includes benign paroxysmal positional vertigo, orthostatic hypotension, dehydration, electrolyte abnormalities, medication side effects, cardiac arrhythmias, and central neurologic causes such as stroke or transient ischemic attack.[1]
2. Ketogenic diets are associated with an increased risk for hypomagnesemia, hypokalemia, hyponatremia, hypocalcemia, and metabolic acidosis, particularly within the first four weeks of the diet.[2] Hypomagnesemia is among the most common early-onset complications.
3. Clinical manifestations of hypomagnesemia include dizziness, weakness, muscle cramps, tremors, neuromuscular irritability, and fatigue. Severe deficiency may lead to seizures, cardiac arrhythmias, torsades de pointes, and refractory hypocalcemia or hypokalemia (see Table 1 on page 60).[3]

4. Risk factors increasing the risk for hypomagnesemia include inadequate dietary magnesium intake, rapid weight loss, dehydration, renal magnesium wasting, concurrent hypokalemia or hypocalcemia, and medications such as proton pump inhibitors.[4]
5. Severe or symptomatic hypomagnesemia should be treated with intravenous magnesium sulfate followed by oral supplementation.[3] Coexisting electrolyte abnormalities must be corrected, and underlying contributors such as medications or dietary patterns should be addressed.[3]
6. Patients should be counseled about the risks associated with rapid weight loss, that they should maintain adequate hydration, along with the need for routine electrolyte monitoring. Patients should be taught to recognize warning symptoms. Many patients will need magnesium supplementation and alternative dietary approaches if deficiencies occur.[2,5]

## DISCUSSION

A ketogenic diet is characterized by high fat intake and marked carbohydrate restriction, inducing a state of ketosis that promotes rapid weight loss.[6] While effective for certain therapeutic indications and increasingly popular for weight management, this diet significantly alters electrolyte balance, particularly during early phases of initiation.[3,5]

Hypomagnesemia is among the most frequently observed electrolyte disturbances associated with ketogenic diets. Dietary restriction of magnesium-rich foods such as whole grains, legumes, fruits, and certain vegetables contributes to inadequate intake.[3] Additionally, ketosis and associated diuresis may increase renal magnesium losses. Dehydration, commonly reported during early ketogenic dieting, further exacerbates electrolyte depletion.[2]

Clinical recognition of hypomagnesemia is challenging due to its nonspecific symptoms, which may be misattributed to benign "keto flu." Importantly, severe hypomagnesemia can lead to life-threatening cardiac arrhythmias and neurologic complications.[3] Magnesium deficiency also impairs parathyroid hormone secretion and action, leading to refractory hypocalcemia unless magnesium is corrected.[3]

The concomitant use of proton pump inhibitors (PPIs) further increases the risk of profound hypomagnesemia. Long-term PPI use is associated with impaired intestinal magnesium absorption, making patients on both ketogenic diets and PPIs particularly vulnerable.[3,4]

This case highlights the importance of understanding the dietary history in patients presenting with nonspecific dizziness or neuromuscular symptoms. Early laboratory evaluation, prompt treatment, and targeted counseling can prevent significant morbidity.

**Table 1. Serum Magnesium Levels**

| Classification | Serum Magnesium | Clinical Significance[3] |
|---|---|---|
| Normal | 1.7-2.4 mg/dL | Asymptomatic; normal physiological function. |
| Mild Hypomagnesemia | 1.2-1.6 mg/dL | Often asymptomatic; may have nonspecific symptoms (lethargy, muscle cramps, weakness). |
| Moderate Hypomagnesemia | 1.0-1.2 mg/dL | Increased symptom likelihood; fatigue, tremor, muscle fasciculations. |
| Severe Hypomagnesemia | <1.2 mg/dL | Neuromuscular irritability (carpopedal spasm, seizures, tremors), cardiac arrhythmias (including torsades de pointes), refractory hypocalcemia/ hypokalemia. |

Madeline Cingle, PA-C
LG Health Urgent Care
1701 Cornwall Rd.
Lebanon, PA 17042
Madeline.Cingle@pennmedicine.upenn.edu

## REFERENCES

1. Alla S, Rao MY, Aslam SM. Clinical profiles of elderly patients presenting with persistent dizziness. *Ochsner J.* 2020;20(3):218-224.
2. Kang HC, Chung DE, Kim DW, Kim HD. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. *Epilepsia.* 2004;45(9):1116-1123.
3. Touyz RM, de Baaij JHF, Hoenderop JGJ. Magnesium disorders. *N Engl J Med.* 2015;373(19):1853-1863.
4. Perazella MA. Proton pump inhibitors and hypomagnesemia: a rare but serious complication. *Am J Med Sci.* 2013;345(3):171-174.
5. Dyńka D, Rodzeń Ł, Rodzeń M, et al. The ketogenic diet is not for everyone: contraindications, side effects, and drug interactions. *Ann Med.* 2026;58(1):2603016.
6. Ahmad Y, Seo DS, Jang Y. Metabolic effects of ketogenic diets: exploring whole-body metabolism in connection with adipose tissue and other metabolic organs. *Nutrients.* 2024;16(10):1900.

# C-Reactive Protein, HPV Vaccination, Delirium, Measles

**Alan S. Peterson, MD**
*Emeritus Director, Environmental and Community Medicine*
*Walter L. Aument Family Health Center*

## NEW CARDIOLOGY GUIDELINES PROMOTE C-REACTIVE PROTEIN TESTING

The leading cause of death in the United States is cardiovascular disease (CVD). Evidence from the past two decades demonstrates that the biomarker C-reactive protein, which signals the presence of low-grade inflammation, is a better predictor of risk for CVD than cholesterol.[1]

As a result, late last year the American College of Cardiology (ACC) published a statement with new recommendations for universal screening of C-reactive protein levels in all patients, alongside measuring cholesterol levels. According to the ACC:

> High-sensitivity C-reactive protein (hsCRP) is an inexpensive and widely available blood test. While there has been debate within the medical community regarding the utility of hsCRP, this statement details the data confirming its value in clinical decision making in primary and secondary prevention. In patients with known CVD, hsCRP level is at least as predictive of future events as LDL cholesterol levels, even in patients treated with statin therapy.[2]

C-reactive protein is created by the liver in response to infections, tissue damage, chronic inflammatory states from conditions like autoimmune diseases, and metabolic disturbances like obesity and diabetes. Inflammation plays a crucial role at every stage in the development and buildup of fatty plaque in the arteries, which causes atherosclerosis that can lead to heart attacks and strokes.[1]

The ACC emphasizes the important role of lifestyle interventions to reduce systemic inflammation. These include at least 150 minutes per week of regular exercise, along with following a Mediterranean or DASH diet including mindful intake of omega-3 fatty acids.[2] Dietary fiber from foods like beans, vegetables, nuts and seeds, as well as berries, olive oil, green tea, chia seeds, and flaxseeds, have been shown to lower C-reactive protein levels as well.[1]

Finally, the statement discusses current challenges and opportunities based on new evidence, exploring topics like the advancing field of cardio-immunology and areas for further research, such as the interplay between inflammation and key physiological systems, the role of novel special pro-resolving bioactive lipid molecules in promoting the resolution of inflammation and CVD risk reduction, and more.[2]

Knowing a patient's LDL cholesterol level alongside their C-reactive protein, apolipoprotein B, and lipoprotein(a) levels, paints a comprehensive picture of risk that can hopefully help motivate long-term commitment to the fundamentals of heart disease prevention.

## STUDIES SHOW HPV VACCINES HAVE "DRAMATIC" IMPACT ON CERVICAL CANCER

HPV-related cancers cause more than 350,000 deaths per year worldwide. A raft of studies involving millions of people over the 20 years since the approval of the first human papilloma virus (HPV) vaccine show that HPV vaccination is safe and dramatically lowers women's risk of cervical cancer. Findings of two updated Cochrane reviews on the impact of HPV vaccination — one looking at population levels of cervical and other HPV-related cancers, and the other a network meta-analysis of clinical trial data — bring together these conclusions.[3]

The population studies, involving over 132 million people in total, show that the benefits of the vaccination for cervical cancer prevention are unequivocal. Based on data covering 4.5 million person-years, vaccination by age 16 is associated with an 80% reduction in the risk for cervical cancer (relative risk [RR], 0.20; 95% CI, 0.09-0.44).[3]

In a separate study, published in *JAMA Oncology*, a Swedish cohort of 780,000 women showed that HPV vaccination resulted in a 37% lower incidence of high-grade vulvovaginal lesions, with the strongest protection seen in those vaccinated before age 17 years.[4]

Currently, groups such as the American Cancer Society and the American Academy of Pediatrics recommend routine HPV vaccination for all children starting between the ages of 9 and 12. Guidance from the Centers for Disease Control and Prevention is similar.

As for safety, the Cochrane team specifically looked for population data supporting any potential link between HPV vaccination and a list of adverse events — including postural orthostatic tachycardia syndrome, chronic fatigue syndrome, infertility, and paralysis; there is no such evidence. There is also no evidence that HPV vaccination encourages earlier sexual activity, a concern often raised on social media.

In terms of discussing the HPV vaccine with parents and young people, the advice to clinicians is to keep the focus on its ability to prevent cancer.

## PSYCHIATRIC ASSOCIATION OVERHAULS DELIRIUM GUIDELINE

The American Psychiatric Association (APA) has released an updated practice guideline for preventing and treating delirium, providing clinicians with evidence-based strategies to improve detection, management, and patient outcomes for a condition that affects tens of thousands of hospitalized adults each year. It's the first time this information has been upgraded in 26 years.

Delirium — a sudden decline in attention, awareness, and mental function — develops rapidly, often over hours, and typically lasts two to three days. It can arise from numerous factors, including advanced age, prior episodes of delirium, medical conditions such as pneumonia, urinary tract infection, psychiatric conditions like cognitive impairment, medications with anticholinergic properties or opioids, metabolic disturbances, vitamin deficiencies, sensory impairments, and sleep disruption.

The updated APA guideline includes 12 evidence-based recommendations across clinical settings and three suggestions covering assessment, nonpharmacologic interventions, and transitions of care; it provides clinicians with a practical framework to improve patient outcomes. It goes beyond detection and treatment and includes steps aimed at prevention.

One key recommendation is that patients with, or at risk for, delirium undergo regular structured assessments using validated tools. These tools measure factors such as awareness, language comprehension, and confusion, and their use varies by clinical settings. The guideline recommendations include the following:

- **Patients should receive baseline neurocognitive testing and a detailed review of factors that can contribute to delirium.** While medication reviews are routinely performed, the guideline emphasizes that they should specifically focus on drugs that worsen cognitive status.
- **Antipsychotics should only be used to address severe agitation or psychosis in delirium.** They should not be considered first-line medicines but may be used after deescalation strategies have failed, contributing factors have been addressed, and when the behavior poses a risk for harm.
- **Benzodiazepines should *not be prescribed* for patients with, or at risk for, delirium unless there is a specific indication.** This also applies to individuals with preexisting cognitive impairment. Benzodiazepines may cause sleepiness and confusion and can make delirium worse. They can also affect balance, potentially increasing the risk for falls.
- **The intravenous sedative dexmedetomidine can be used when patients are at high risk for delirium and undergoing major surgery or receiving mechanical ventilation.** The guideline advises *against* using melatonin or ramelteon — a sedative commonly prescribed for insomnia — to prevent or treat delirium. Melatonin is not an FDA-approved supplement.
- **Physical restraints should *not be used* except when a patient poses an imminent risk for harm to themselves or others.** Patients being discharged or transferred to another health care setting should receive a detailed medication review, medication reconciliation, and reassessment of the indications for medications.

The executive summary was published online in the *American Journal of Psychiatry*. This version targets not only psychiatrists but also specialists in internal medicine, family medicine, and critical care nursing.

Scan the QR code at right to access the full guideline. The APA is also developing supporting resources to help clinicians understand and implement the recommendations, including training slides, a clinical guide, a patient and family guide, webinars, and case vignettes.

## NEW MEASLES CASES THREATEN NATION'S ELIMINATION STATUS

In 2025, a total of 2,284 confirmed measles cases were reported in the United States, according to the Centers for Disease Control and Prevention (CDC).[5] By January 2026, that number had only slightly dropped to 2,140.

The case totals — signaling the largest outbreak since 1991 — mean the nation faces the prospect that

it could lose its measles elimination status. Elimination status is dependent on at least 12 months without continuous local virus transmission and a functional and healthy public health system.

In a recent Medscape commentary, Demetre C. Daskalakis, MD, MPH, an infectious disease specialist and former program director at the CDC, explained the problem:

> Before the introduction of the first measles vaccine in 1963, measles was widespread in the United States, with more than 90% of children infected by age 15 and roughly 4 million cases annually.... The elimination of measles deaths in America was not achieved by nonspecific interventions — it was measles vaccines that drove measles cases down to where deaths became unheard of from measles.[6]

The two-dose vaccine schedule has increased vaccine effectiveness to 97%, reducing infections in vaccinated children, as has the creation of Vaccines for Children, a program that effectively closed the equity gap in vaccine access in the United States, creating access for uninsured and underinsured children as well as Native American and Alaskan Native children.

"Vaccines have become topics of political debate rather than the routine life-saving interventions of primary care or the tools to prevent illness and death in our vulnerable populations," says Dr. Daskalakis. "Health agencies have been decimated and communications from them have been compromised by ideology."

In a recent analysis of data from 44 states and the District of Columbia, the share of U.S. counties where 95% or more of kindergarteners were vaccinated dropped from 50% before the COVID-19 pandemic to 28%.[7]

Dr. Daskalakis concludes, "Public health as an institution and the peoples' health as a mission are in trouble."

## REFERENCES


1. Scourboutakos MJ. One protein is a better predictor of heart disease than cholesterol. Science Alert. December 22, 2025. Accessed March 16, 2026. https://www.sciencealert.com/one-protein-is-a-better-predictor-of-heart-disease-than-cholesterol
2. Mensah GA, Arnold N, Prabhu SD, Ridker PM, Welty FK. Inflammation and cardiovascular disease: 2025 ACC scientific statement: a report of the American College of Cardiology. *J Am Coll Cardiol.* Published online September 29, 2025. Accessed March 16, 2026. https://www.jacc.org/doi/10.1016/j.jacc.2025.08.047
3. Parkinson M. New research confirms HPV vaccination prevents cervical cancer. November 24, 2025. Accessed March 16, 2026. https://www.cochrane.org/about-us/news/new-research-confirms-hpv-vaccination-prevents-cervical-cancer
4. Deng Y, Wu S, Ask LS, et al. Quadrivalent human papillomavirus vaccine and high-grade vulvovaginal lesions. *JAMA Oncol.* 2026;12(2):177-184.
5. Measles Cases and Outbreaks. Centers for Disease Control and Prevention. Updated March 13, 2026. Accessed March 16, 2026. https://www.cdc.gov/measles/data-research/index.html
6. Daskalakis D. Measles elimination is a public health vital sign: we are about to code. January 21, 2026. Accessed March 16, 2026. https://www.medscape.com/viewarticle/measles-elimination-public-health-vital-sign-we-are-about-2026a10001w1
7. Weber L, Gilbert C, Moriarty D, Lott J. U.S. vaccination rates are plunging. Look up where your school stands. The Washington Post. December 31, 2025. Accessed March 19, 2026. https://www.washingtonpost.com/health/interactive/2025/measles-vaccine-schools-outbreaks-public-health/


Alan S. Peterson, MD
Walter L. Aument Family Health Center
317 Chestnut St., Quarryville, PA 17566
Alan.Peterson@pennmedicine.upenn.edu

### Museum Exhibit Highlights Nurses of 1940s-Era LGH

Among the many treasures housed at the Lancaster Medical Heritage Museum are photographs by industrial photographer William Rittase that document daily life and nursing practices at Lancaster General Hospital during the 1940s. These historical images provide significant insight into the role of nurses in mid-20th-century health care.

Lancaster native Jocelyn Wagner, who graduated from Millersville University in May 2026, worked at the museum as an intern. She spent part of her time investigating the collection of Rittase prints. She was particularly interested in how the images feature women playing key roles at the hospital at a time when professional opportunities were limited.

"I was tasked to look into and analyze the individuals in the pictures and figure out their stories and their impact in the medical field in Lancaster County," explains Wagner. "But it was tough to find the nurses featured in the pictures. Many of the captions in the archived newspaper clippings do not include the names of the women, only referring to them as 'a nurse.' Though the work proved challenging, I enjoyed the opportunity to learn about the medical history in Lancaster."

The museum — including its collection of Rittase prints and Wagner's findings — is located at 410 N. Lime St., Lancaster. Admission is free to LG Health employees with a badge and children under 3; $8.00 for all others. Visit the museum website at **lancastermedicalheritagemuseum.org** for additional information and hours of operation.

NARRATIVE MEDICINE

# "Why Would I Want That?"

**S. Scott Paist, MD**

During my brief time as a geriatric consultant, I was asked to see a 94-year-old man who had fallen off his tractor and broken his right arm. He was living with his son's family; his son had found him under the tractor and brought him to the emergency room.

He apparently needed some sort of hardware to fix his arm, so the anesthesia service was asked to see him before he went to surgery. An EKG was performed, and it showed some sort of potentially ominous rhythm. The cardiology service was consulted by the anesthesiologist and recommended the placement of an implantable defibrillator; they subsequently asked me to see the patient. While the patient's son had already consented to defibrillator placement, the cardiothoracic team wanted my opinion regarding whether he was a reasonable candidate for their services.

The hospital record indicated that Mr. Landis was "demented and confused." I entered his room and introduced myself. He stared at me, alert but mute. I reached out with my left hand to shake his, and he took it readily with a firm grip. Heartened, I spoke in my nursing home way, several decibels louder than my conversational tone. He said, "What?" I got within a foot of one of his ears and shouted, "How are you doing?" He brightened and replied, "Everybody I can."

In those days, I carried a small amplifier with earphones sold by Radio Shack as an "eavesdropping device." I plugged the phones into his ears, turned the amplifier up to 10, and shouted into the device's microphone. We then had a normal, albeit very loud, conversation, and he scored 28 out of a possible 30 on the Folstein Mini-Mental State Examination.

I explained that the proposed defibrillator placement would prevent his heart from stopping both during his orthopedic surgery and from then on. He listened carefully and thought about it. "Wait a minute," he said, "you mean that if my heart stops, this thing will start it up again?" I told him that it most likely would. He was aghast. "Why would I want that?"

The defibrillator placement was canceled, his arm was fixed without incident, and he returned home to his tractor, where he resumed mowing the yard once his cast was removed.

*S. Scott Paist, MD, is a retired family physician who spent 30 years caring for patients in Lancaster County. Regarding the names used in this article, Dr. Paist states: "They are, in every sense of the word, fictitious."*

THE JOURNAL OF
LANCASTER GENERAL HOSPITAL
*Owned and published by*
*Penn Medicine Lancaster General Health*

*The Journal of Lancaster General Hospital* is published quarterly by Lancaster General Hospital, a nonprofit, community hospital in Lancaster, PA. The hospital and its parent, Lancaster General Health, are members of the University of Pennsylvania Health System (Penn Medicine). The journal is sent to the medical staff of Lancaster General Hospital, to physicians and others involved in delivery of health care in our service area, and to the administrative and medical leadership of Penn Medicine.





**Correspondence Email**
Maria.Boyer@pennmedicine.upenn.edu

**Mailing Address**
540 N. Duke Street | P.O. Box 3555
Lancaster, PA 17604-3555

**Website:** JLGH.org



**ISSN 1940-2813**


*Cover photo taken in the gardens of the Ann B. Barshinger Cancer Institute by David Lang, physician assistant with Union Community Care HIV Care and the School-Based Health Clinic at Carter & MacRae Elementary School, Lancaster.*

## INTERESTED IN WRITING FOR *JLGH*?

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

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

**Please contact the managing editor, Maria M. Boyer, via email at Maria.Boyer@pennmedicine.upenn.edu to discuss submitting an article or for further information.**

Penn Medicine

*The Journal of Lancaster General Hospital*
555 N. Duke St.
Lancaster, PA 17602

# EARN CME CREDIT

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

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

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

← Scan to access your eeds account.

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

## CME Offerings at LG Health

**Pediatric Grand Rounds**
July 14, August 11, September 8
7:00-8:00 a.m.

**Research Grand Rounds**
September 3
12:00 noon-1:00 p.m.

**Connect with the CME Department for a direct link to access CME On-Demand courses.**

Kristy Askey, CME Program Manager
Kristy.Askey@pennmedicine.upenn.edu

Olivia Reiver, CME Compliance Specialist
Olivia.Reiver@pennmedicine.upenn.edu

*Coming This Fall*

### In-Person Act 31 Training

The LG Health CME Department will offer an in-person Act 31 Child Abuse Prevention Training session this fall.

Details will be announced via email once the date is confirmed.

For more information on this session or a virtual option, contact the CME Department.