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COVID-19 and micronutrient deficiency symptoms — is there some overlap?

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1. Introduction

In December 2019, the first cases of a pneumonia of unknown cause were reported in Wuhan, China. The illness came to be known as coronavirus disease 2019 (COVID-19) and was found to be caused by the newly named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. SARS-CoV-2 is an RNA beta coronavirus [1]. The virus enters cells that produce receptors for the angiotensin-converting enzyme 2 (ACE2) by binding to these receptors on the cell membranes [1–3]. These cells then replicate the virus, leading to apoptosis and necrosis on a large scale [3]. Cells that express ACE2 receptors are found primarily in the lungs but are also found elsewhere throughout the body, such as in the nasal and intestinal mucosa [1–3]. It is believed that nasal and pulmonary epithelial cells are the main entry sites of the virus [4].

Normally, ACE2 is metabolized after binding to cell receptors, but when the receptors are blocked with SARS-CoV-2, ACE2 accumulates in the body which can lead to hypertension and lung or renal failure [5]. Further, infections with the virus can trigger the release of massive amounts of cytokines, referred to as a cytokine storm. These cytokines can cause a prolonged systemic inflammatory response (SIRS) [2,6–8]. SIRS contributes to the widespread effects of the virus on different organs of the body. It is known that the lungs are greatly affected by the SARS CoV-2 infection with acute respiratory distress syndrome (ARDS) being one of the most common complications. However, it has also been shown that the gastrointestinal tract, heart, liver, kidneys, and brain may all be affected as well [7,9].

COVID-19 has presented with every range of illness, from asymptomatic cases to intensive care unit (ICU) admissions...
[10–13]. Reports suggest about 80% of cases are mild enough to be managed at home, with up to 50% of those cases being completely asymptomatic [12,13]. The other approximately 20% of cases have resulted in hospitalization; a quarter being severe enough to require ICU admission [13]. Severe COVID-19 cases are characterized by the cytokine storm and SIRS mentioned above [2,6–8]. Neurological side effects can include encephalopathy, confusion, delirium, seizures, and even the augmentation or development of psychiatric or psychological disorders, such as depression [7,9–11]. Mild symptoms may include anorexia, nausea, abdominal pain, diarrhea, dyspnea, dysomnia, and dysgeusia which all affect nutrient intake [11].

2. Malnutrition risk and COVID-19

The systemic inflammation and effects of the cytokine storm can last for an undefined period of time after a patient is considered clinically resolved [6]. Individuals who suffer from COVID-19 related effects for at least a month after the acute phase of the illness has passed, are termed COVID long haulers. These continued symptoms last for at least a month and, in some literature, have lasted past three months [14,15]. The condition has also been referred to as chronic COVID, long COVID, or simply post–COVID [14]. The prolonged effects of COVID-19 do not seem to be affected by the severity of the acute case, though those with a greater number of symptoms in their acute phase may be more likely to develop post–COVID symptoms [15]. This prolonged inflammatory state can sustain anorexia and catabolism which, combined with the prolonged gastrointestinal and neurological symptoms, put COVID long haulers at increased risk of malnutrition, physical deconditioning, further prolonged recovery, and even hospital readmission [14,16–18]. COVID long haulers may need targeted nutrition interventions and physical therapy to rehabilitate and regain functional status [11,16] Long-term nutrition support may be necessary to help meet their needs [14].

It has been well established that adequate nutrient status is important for proper immune function. Micronutrients prevent excess damage from daily oxidative stress and adequate macronutrients prevent or minimize catabolism. Malnutrition frequently occurs in the presence of inflammation [18–22]. With such inflammation, COVID-19 may place patients into a hypermetabolic state [6,11,18,23]. Two studies using indirect calorimetry with COVID-19 patients in the ICU found measured resting energy expenditures of up to 200% of predicted needs [6,23]. Increased energy needs will also increase micronutrient needs. Adequate nutrient status is especially important during times of infectious disease so that cells can be replenished when injury has occurred [24]. A prospective, observational study of 68 adults admitted to the hospital under infectious disease care found that 32% of patients had multiple micronutrient deficiencies. The most prevalent micronutrient deficiencies included zinc (66.7%), selenium (46.6%) and thiamine (39.7%) [24]. A more recent study found that 94.4% of adults admitted to the ICU with COVID-19 and who met criteria for ARDS had undetectable vitamin C levels in their blood [25]. The role of micronutrients during times of pandemics has been discussed by experienced ICU researchers who have recommended therapeutic protocols. One protocol consisted of methylprednisolone, ascorbic acid, thiamine, heparin and a number of co-interventions and thus was called “MATH+” [26,27]. These experts recommended high dose vitamin C as an effort to downregulate the cytokine storm experienced by COVID-19 patients. Additionally, vitamin C can help repair tissue damage and can work synergistically with glucocorticosteroids that help with pulmonary function [26]. Thiamine was selected for use with the MATH+ therapeutic protocol for its antioxidant properties and reported evidence of increased needs during other viral diseases [26–29]. Additionally, when used together with vitamin C and glucocorticosteroids, thiamine may help reduce delirium. Delirium is a known symptom experienced during thiamine deficiency, it has also been reported as a symptom of COVID-19 [26]. Thiamine has a half-life of 9–18 days and the body can only store up to 30 mg (mg), making continual dietary intake important [30–32]. The recommended daily allowance for thiamine is 1.1 and 1.2 mg per day for men and women, respectively [33]. Requirements for thiamine proportionately increase with increased energy and carbohydrate needs, presenting yet another risk factor for deficiency [32].

The role of vitamin D in immune function has been well established now. Vitamin D has a role in both innate and adaptive immunity as well as a role in the antiviral response. The important roles vitamin D plays in immunity and infection have led to many studies conducted in COVID-19 patients. Ghelani et al. [34] reviewed 37 studies conducted in 2020 and 2021 worldwide. The authors summarized that most studies found positive outcomes associated with obtaining vitamin D levels within normal limits with or without supplementation. The overall recommendation is to treat all patients with vitamin D deficiency as soon as possible. The give preemptive supplementation to at risk populations. Supratherapeutic levels are not recommended [34–36]. This was stated more specifically in another recent review conducted by Borsche et al. [35] in which they merged and compared two diverse databases and determined a mathematical regression value of 50 ng/mL as a vitamin D3 level that prevents excess mortality. The authors also stated that with future variants and breakthrough infections approaching, the entire population should optimize its vitamin D3 level.

COVID-19 patients are at higher risk of malnutrition and weight loss independently of disease severity and hospitalization [20]. Symptoms such as anorexia, dysosmmn, dysgeusia, nausea, dyspnea, and fatigue can all lead to reduced food intake, leading to weight loss and suspected micronutrient deficiencies [14,16,20,37–39]. Further, decreased physical activity or bed rest during illness can contribute to losses in lean body mass, especially in the absence of adequate nutrient intake [11,18,20]. These factors, in addition to the hypermetabolic state promoted by inflammation, can put recovered infected individuals at high risk for malnutrition both in the hospital and at home [20]. There are few studies evaluating micronutrient status of patients who had mild cases of COVID-19 at home and continue to decline nutritionally in the recovery period. Symptoms of early micronutrient deficiencies often overlap with the symptoms of viral illnesses such as poor appetite, nausea, diarrhea, muscle weakness, pain, apathy, and confusion. These micronutrient deficiency symptoms are easily overlooked, and laboratory assessment is often not considered in hospital settings. Taking a proactive approach and treating suspected deficiencies of water-soluble vitamins and monitoring for improvement in signs and symptoms is the most common approach in hospital settings [30].

In addition to poor nutrient intake and increased nutrient needs during viral illness, common medications have also been shown to deplete several micronutrients, further increasing risk for deficiencies. Examples of these interactions include aspirin and vitamin C, diuretics and water-soluble vitamins, and oral contraceptives and B vitamins. This idea is further elaborated in Table 2. Drugs have been found to affect appetite, nutrient absorption, metabolism, and excretion, all affecting the need to either manage food and drug timing or nutrient needs [40]. The impact medications may have on patients presenting with COVID-19 who also have comorbidities will be highlighted in the following case reports.
Table 1

Nutrition-related assessment information for two cases with COVID-19.

| Case 1 | Case 2 |
|--------|--------|
| Age    | 75 years old |
| Medical History | - COVID-19, clinically resolved |
| - CVA |
| - COPD |
| - CAD/HTN |
| Nutritively Relevant Medications | - Potassium Chloride |
| - Furosemide |
| Anthropometrics | Height: 181.6 cm |
| Weight: 96.8 kg |
| BMI: 29 |
| Weight Change: 12% loss – 1 month |
| Biochemical Data | Plasma Value Units Ranges |
| Na | 139 mmol/L 136–145 |
| K | 3.9 mmol/L 3.5–5.2 |
| Cl− | 107 mmol/L 98–109 |
| CO2 | 23 mmol/L 22–32 |
| BUN | 13 mg/dL 8–23 |
| Cr | 0.8 mg/dL 0.8–1.3 |
| Gluc | 156 H mg/dL 65–110 |
| Ca | 8.4 mg/dL 8.3–10.2 |
| Mg | 1.9 mg/dL 1.5–2.6 |
| PO4 | 3.0 mg/dL 2.3–4.3 |
| Albu | 3.2 L g/dL 4.0–4.9 |
| Folate | 7.6 ng/mL 5.4 |
| B-12 | >1000 pg/mL 218–1124 |
| Vit D | 24 L ng/mL 30–100 |
| CRP | 3.3 H mg/dL 0–1.0 |
| Nutrition Focused Physical Findings | - Moderate muscle wasting: temples, clavicle and scalpula |
| - Handgrip: 21.3 kg (borderline weak) |
| General Complaints | - Generalized weakness |
| - Mild anorexia |
| - Depression with new onset suicidal ideation |
| - Hypoactive delirium |
| - Waxing and waning mentation |
| - Irritability |
| Additional Results | - CT Thorax – bilateral ground glass opacities |
| - CT Head – encephalomalacia of the left thalamus and basal ganglia |
| - CT Head – hypodensity in right thalamus |
| - No infectious processes found to explain mental status changes |

3. Case reports

3.1. Case 1

A 75-year-old male with right sided hemiplegia and expressive aphasia from a prior cerebrovascular accident (CVA) 25 years ago and comorbidities including coronary artery disease, atrial fibrillation, hypertension, and chronic obstructive pulmonary disease complained of a dry cough during the COVID-19 pandemic. Six days after initial symptoms, he tested positive for COVID-19. Overall, his symptoms were mild, yet he complained of anorexia and poor nutrient intake. Two weeks from his initial symptoms, he complained of progressive weakness and functional decline, reporting that he could no longer care for himself at home. Symptoms at this point included anorexia, muscle weakness, magnified depression, irritability and agitation, and weight loss of 12% of his usual weight with muscle and fat wasting, resulting in a malnutrition diagnosis. Medication taken prior to admission included amiodipine, atorvastatin calcium, losartan, oxybutynin chloride, potassium chloride, furosemide, and metoprolol tartrate. Head computed tomography showed encephalomalacia involving the left thalamus and basal ganglia likely due to previous CVA. The esophagogastroduodenoscopy revealed normal gastrointestinal findings. Oral nutritional intake continued to be very poor for the first eight days of his hospital stay despite attempts to increase nutrition with oral nutrition supplements, modifications to meal patterns and frequent encouragement. During this time the patient’s neurological findings worsened with waxing and waning delirium, encephalopathy and increasing agitation. The interdisciplinary team determined that a nasogastric feeding tube would be placed to provide supplemental nutrition. Registered dietitians on the team determined that the patient was high risk for refeeding syndrome and recommended thiamine supplementation prior to initiating enteral nutrition with a standard enteral formula. Daily 100 mg intravenous thiamine was started and continued for the next seven days. Nutritional needs were met with enteral nutrition within 72 h of feeding tube placement. Within 48 h of nutrition intervention the patient was alert and oriented. Appetite had improved within four days of nutrition intervention and continued to improve over the next seven days. Nutritional needs were met with enteral nutrition within 72 h of feeding tube placement. Within 48 h of nutrition intervention the patient was alert and oriented. Appetite had improved within four days of nutrition intervention and continued to improve over the next seven days.

3.2. Discussion

Although the team did not suspect thiamine deficiency initially, it was determined that after sudden improvement in symptoms within days of intravenous thiamine, retrospective review of the patient’s symptoms aligned with thiamine deficiency. The overlap of symptoms expected with COVID-19 and malnutrition did not put
thiamine deficiency as a differential diagnosis and therefore no laboratory assessment was completed. This patient was also on furosemide which may have further put him at risk for thiamine de

### Table 2
COVID-19 symptoms that relate to micronutrient deficiencies and associated nutrient depleting medications [30–57].

| Symptoms                          | Associated Nutrient Deficiencies | Medications that may deplete associated nutrients |
|-----------------------------------|----------------------------------|--------------------------------------------------|
| Anxiety                           | Vitamin C                        | - Aspirin                                         |
| Apathy                            | Thiamine                         | - OHA/Diuretics/Antidepressants/Anticonvulsants/HRT/OC |
| Confusion                         | Niacin                           | - Antipsychotics                                  |
| Ataxia                            | Thiamine                         | - Diuretics/ACE inhibitors                        |
| Dizziness                         | Magnesium                        | - Acid-suppressants/Antibiotics/OC/Corticosteroids/Digoxin/HRT |
| Encephalopathy                    | Thiamine                         | - Diuretics/Digoxin/Anticonvulsants               |
| Headache                          | Pyridoxine                       | - Oral Contraceptives                             |
| Irritability                      | Biotin                           | - Aspirin/Antibiotics                             |
| Loss of Appetite                  | Niacin                           | - Antipsychotics                                  |
| Changes in ability to concentrate| Magnesium                        | - Aspirin/Antibiotics                             |
| Muscle Cramps                     | Magnesium                        | - Acid-suppressants/Antibiotics/OC/Corticosteroids/Digoxin/HRT |
| Muscle Pain/Tenderness            | Vitamin C                        | - Aspirin                                         |
| Paresthesia of Extremities        | Pyridoxine                       | - Aspirin/Antibiotics/OC/Corticosteroids/Digoxin/HRT |
| Sleep Disturbances                | Biotin                           | - Aspirin/Antibiotics                             |
| Shortness of Breath               | Vitamin D                         | - Cholesterol Lowering Meds                       |
| Weakness/Fatigue                  | Magnesium                        | - Acid-suppressants/Antibiotics/OC/Corticosteroids/Digoxin/HRT |
|                                  | Vitamin C                        | - Cholesterol Lowering Meds                       |
|                                  | Vitamin D                        | - Acid-Suppressants                               |
|                                  | Iron                              | - Acid-Suppressants                               |
|                                  | Magnesium                        | - Acid-suppressants/Antibiotics/OC/Corticosteroids/Digoxin/HRT |
|                                  | Zinc                              | - Diuretics/ACE Inhibitors                        |

OHA — oral hyperglycemic agents HRT — hormone replacement therapies OC — oral contraceptives

3.3. Case 2

A 77-year-old male with a history of congestive heart failure, chronic kidney disease and type 2 diabetes was admitted to the hospital for a suspected CVA. Nutrition specific findings included no reported weight loss, fair to good appetite, and long-term use of the following medications: atorvastatin calcium and aspirin. A nutrition-focused physical exam completed by the dietitian was positive for impaired skin integrity including a stage 1 pressure injury on left heel and ecchymosis on patients left forearm, mottled male nails, and corkscrew hairs found on patient’s forearms. Suspected vitamin C deficiency was identified by the nutrition team, and nutrition interventions included vitamin C 500 mg tab daily and high calorie high protein oral nutrition supplements twice
daily. CVA was ruled out and patient was discharged with vitamin C supplementation. There were no other significant findings during this admission and the diagnosis was undetermined encephalopathy. Full nutrition assessment findings for this initial hospital stay are found in Table 1. However, 8 days later the patient experienced a sudden onset of hypoxia and was admitted for low oxygen saturations, pneumonia and COVID-19 positive status. Supportive care was provided to this patient, and the patient was discharged after five days in the hospital. Patient continued to take vitamin C supplements. Unfortunately, over the course of the next month the patient developed anorexia that resulted in poor nutritional intake and weight loss. Sixty days following his COVID-19 diagnosis he was admitted to the hospital with failure to thrive, and a 33-pound weight loss (16.5% of usual weight) with worsened skin integrity, leukocytosis, left lower lung infiltrate and likely aspiration pneumonia, and a complicated urinary tract infection. Patient was also diagnosed with vitamin D deficiency and macrocytic anemia due to folate deficiency related to his severe malnutrition. Head computed tomography showed tiny focus of hypodensity in right thalamus. The patient continued to decline throughout admission with worsening mental status. The family declined enteral nutrition and requested hospice care, and the patient passed 4 days after admission and 10 weeks after his COVID-19 diagnosis.

4. Discussion

This unfortunate case calls providers to reflect on the relationship between nutrition status and immune function during this pandemic. This case is unique in that the patient presented as generally well-nourished but had two risk factors for vitamin C deficiency: type 2 diabetes mellitus and long-term use of aspirin. This patient had an uneventful hospital admission first for undetermined encephalopathy and then quickly followed with another short stay admission for COVID-19. During the months that followed, despite resolution of clinical COVID-19 symptoms, this patient developed decreasing nutrition intake that resulted in malnutrition and eventual death.

Tissue saturation of vitamin C is equal to 1500 mg, and the level at which clinical deficiency symptoms occur is 300–400 mg [43]. The body tightly controls tissue and plasma concentrations of vitamin C; with a moderate intake of 30–180 mg per day, 70–90% is absorbed [44]. Subclinical deficiencies of vitamin C are more common than once thought [45]. It takes 8–12 weeks of inadequate intake for vitamin C deficiency to begin showing symptoms [45]. Initial symptoms of vitamin C depletion include fatigue and inflammation of the gums [44]. As it progresses, symptoms such as petechiae, ecchymoses, purpura, joint pain, anemia, depression, poor wound healing, hyperkeratosis, and cork screw hairs [44]. If the disease continues to progress, the deficiency may be life threatening with anaarca, hemolysis, jaundice, and convulsions [45].

Repletion of vitamin C can be administered orally or intravenously. These different routes will produce different vitamin C concentration in the body when administering the same dose [46]. It was found in a study that vitamin C concentrations were consistently higher when given the same dose intravenously versus orally. In this case, the patient was given an oral administration of vitamin C, which produces more tightly controlled plasma values [46]. All aspects of the case should be considered such as severity of illness and ability to swallow when determining which route to administer vitamin C. Individuals with diabetes are reported to have lower vitamin C status [47,48]. This phenomenon of lower vitamin C status in individuals with diabetes was explained by three proposed reasons: decreased renal reabsorption of vitamin C, ascorbic acid uptake competition with glucose, and an increase in oxidative stress in individuals with type 2 diabetes mellitus [47].

The relationship between aspirin and vitamin C has been studied in human subjects and Guinea pigs as neither can endogenously produce vitamin C [40,49]. Aspirin is thought to impact the storage of vitamin C in the leukocytes by inhibiting uptake into these specific cells [40]. Interestingly, high doses of vitamin C may also lead to the body retaining more of the drug [50]. The short-term effect aspirin has on vitamin C depletion is well recognized, yet the long-term effects of aspirin on vitamin C status are not fully clear [40].

Vitamin C affects immune function in a number of ways: modulation of T cell expression of genes, supporting natural killer cell activity providing protection against viral attacks, supporting response of neutrophils, protecting against oxidative stress, and supporting humoral thymus immune antibodies and delayed hypersensitivity responses [51–53]. There have been cases of vitamin C deficiency following infectious epidemics which suggests infections may deplete vitamin C [43]. Patients with pneumonia and acute respiratory distress had significantly lower vitamin C levels when compared to controls; vitamin C status decreased as severity of the condition increased [43]. The same has been found with vitamin D deficiency. Based on the study conducted by Borsche and colleague [35] there is a strong inverse relationship with vitamin D3 levels and mortality when controlling for other factors. Case 2 had extremely low vitamin D3 levels.

Vitamin C has been shown to have preventative benefits considering infections. One study showed for COVID-19 prevention, the recommended daily dosage of oral vitamin C is 2000–3000 mgs per day [54]. This however conflicts with the United States tolerable upper limit of vitamin C in adults which is 2 g per day [54]. As for the therapeutic effects of vitamin C, a study showed that an oral dose of vitamin C, 2000–8000 mgs per day may be beneficial in reducing the incidence and duration of respiratory infections [55]. This same study also found that intravenous vitamin C of 6000–24,000 mgs per day produced lower mortality, intensive care unit, and hospital stays for patients with severe respiratory infections [55].

Unfortunately, in the current case example, the patient had three episodes of pneumonia in the last year of his life. It is unclear in this case example if the patient’s vitamin C or D deficiency had any impact on his immune system’s ability to recover from the illness. This question will remain unanswered but exploring the role of micronutrients and malnutrition in immunity may heighten provider awareness of how important nutrition may be for elderly patients with COVID-19.

Micronutrient deficiencies rarely occur in isolation. Clinical manifestations occur late in the course of micronutrient deficiency, and routine vitamin and mineral laboratory measurements are infrequent in many hospital settings. Many symptoms of deficiencies overlap with symptoms of other medical conditions. Table 2 outlines common clinical complaints that align with both micronutrient deficiencies and COVID-19. Medications commonly prescribed are also listed in Table 2.

Case 1 and Case 2 both had encephalopathy. Case 1’s encephalopathy resolved after thiamine infusion. Case 2 initially presented with a suspected CVA and was discharged with an undetermined reason for the encephalopathy. In hindsight, the authors suspect that other nutrient deficiencies may have been present and not yet diagnosed, as Case 2 had been on diuretics which placed him at risk of this deficiency. The signs and symptoms of encephalopathy may easily be mistaken for signs and symptoms of a stroke; indeed, ischemic strokes can result in encephalopathy [56]. Altered mental status, lethargy, muscle weakness, dysphagia, dysarthria, and nystagmus are symptoms common to both strokes and encephalopathy [56–58].

Both patients highlighted here experienced protein-calorie malnutrition shortly after a COVID-19 diagnosis. Although the
cases were mild and considered clinically resolved, their nutrition status worsened. The mutual relationship between protein-calorie malnutrition and immunity has been well-established in literature [59–62]. Protein-calorie malnutrition is believed to be the primary cause of immune deficiency worldwide [59]. Protein-calorie malnutrition can result in a decreased effectiveness of both innate and acquired immunity [61]. The gut-associated lymphoid tissue is the primary defensive barrier between the body and pathogens present in the gastrointestinal tract [62]. Protein-calorie malnutrition can lead to deterioration of the epithelial layer in the intestines, weakening the protection of the gut-associated lymphoid tissue [59–62] and possibly leading to bacterial translocation [60–62]. Moreover, when activated by an infection, the immune system requires supplies of protein and energy beyond the normal metabolic demands. A triggered immune response leads to immune cell proliferation, necessitating the multiplication of cellular components from protein-based nucleotides and organelles to lipid-based structural components. Protein is further demanded for the creation of Ig proteins, acute-phase proteins, and cytokines and their receptors [62]. In the presence of protein-calorie malnutrition, there may not be adequate provision of the substrates needed to meet these demands, resulting in a diminished response [59,60,62]. There may even be atrophy of lymphoid tissues when protein and energy supplies are scare [61].

Similarly, an impaired immune system can cause or exacerbate protein-calorie malnutrition, resulting in a vicious cycle [59–62]. Infections can lead to nutrient malabsorption and loss, such as in the incidence of diarrhea or emesis. An infection may result in anorexia which can in turn cause decreased nutrient intake, as was seen in Case 1. Infections can also have a catabolic effect, resulting in the loss of muscle and fat tissues as nutrients are directed towards the immune response [62]. The compounding effects of protein-calorie malnutrition, infection, and a weakened immune system cannot be overlooked in the discussion of these two cases of predicted micronutrient malnutrition.

5. Conclusion

Malnutrition, including micro- and macronutrient deficiencies, are common in elderly patients who have multiple comorbidities. The comorbidities themselves may deplete tissues of valuable nutrients, and the medications used to manage the comorbidities may increase urinary excretion or decrease absorption of the nutrients needed to weather an upcoming cytokine storm. While there are no definitive recommendations for micronutrient supplementation in the post-COVID period at this time, it is recommended that patients with COVID-19 be monitored in the post-COVID period to assess risk factors for nutrient depletion such as inadequate intake and nutrient-depleting medications. Provider education on the overlapping symptoms and a lower threshold for laboratory monitoring of micronutrients may be warranted.

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All authors developed the manuscript concept. S. Lewis conducted the analysis. S. Lewis wrote the first draft of the manuscript with input from Lora Chizmar and Sydni Liotta. All authors reviewed and commented on subsequent drafts of the manuscript.

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