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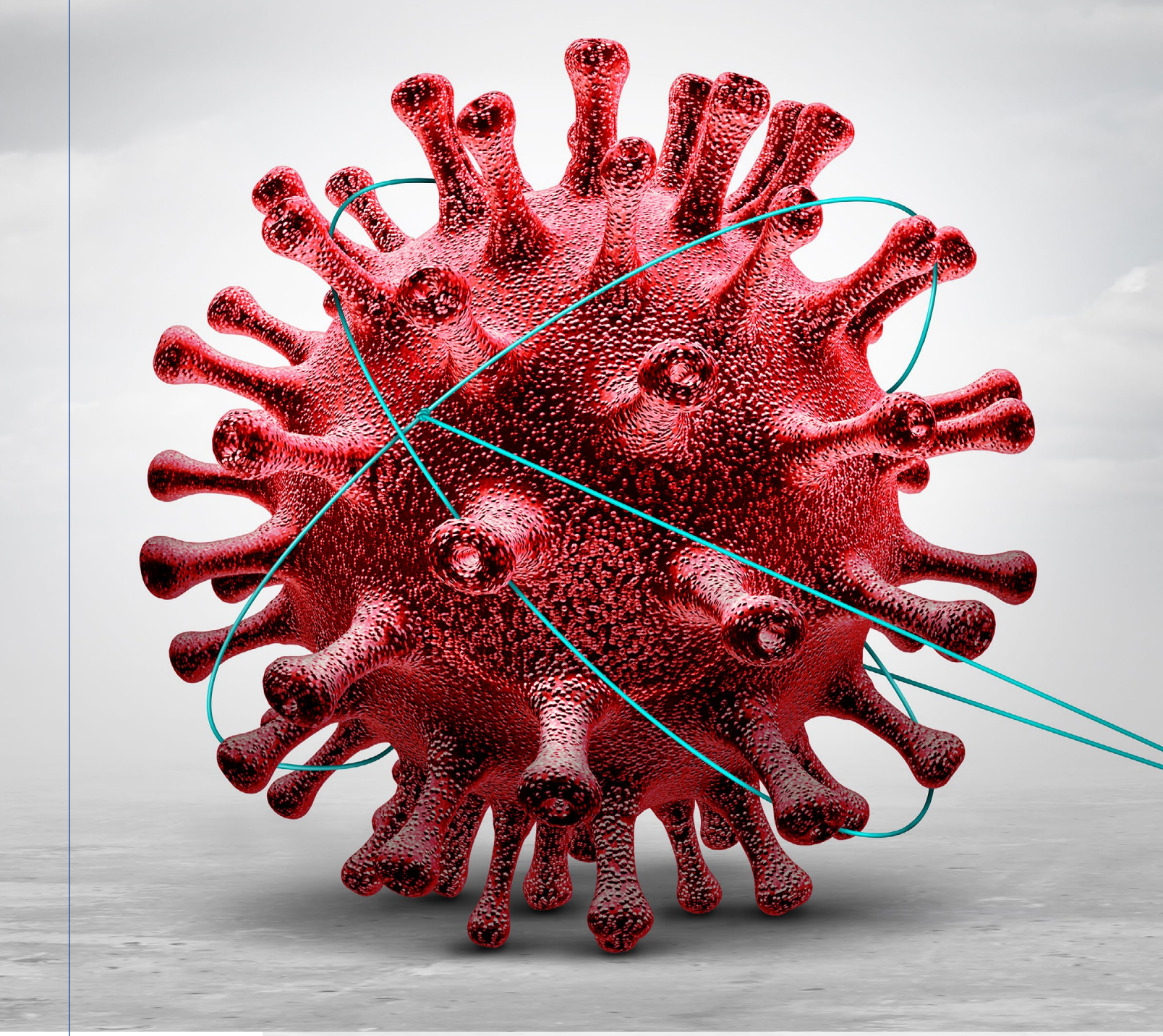
NUMBER 94 / VOL. 1, 2024

Long Covid: Where We Are Today

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LONG COVID: WHERE WE ARE TODAY

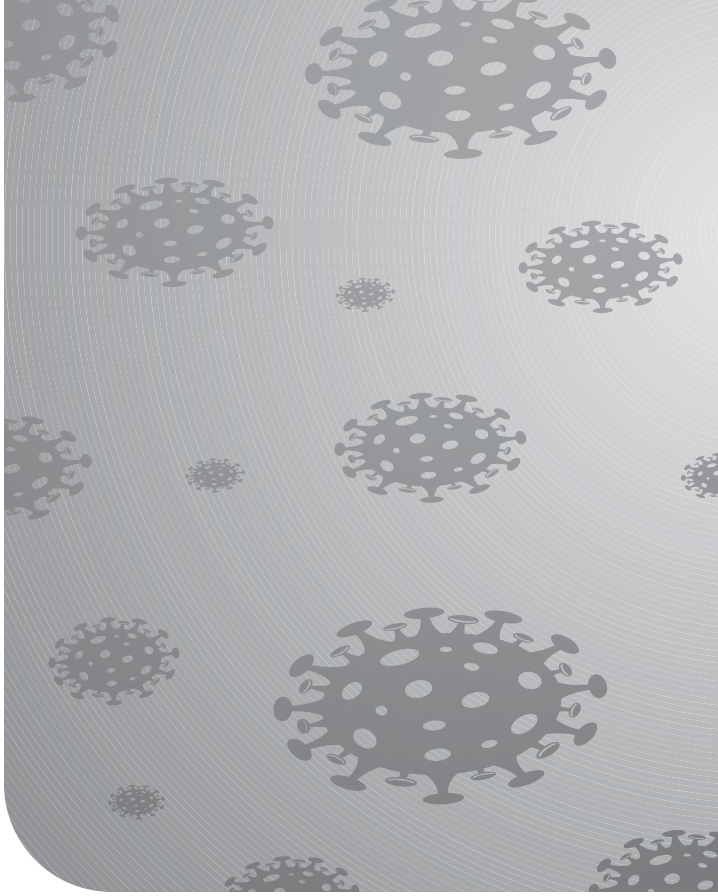
Sarah is a 58-year-old marketing professional and avid runner. She contracted COVID-19 in March 2020, experiencing mild symptoms initially, including fever, cough, and fatigue. However, after her initial illness subsided, Sarah's life took a frustrating turn. Months later, she continued to grapple with debilitating symptoms, including severe fatigue, chest pain, shortness of breath, and persistent brain fog. She struggled to walk around the block. She could do computer work in short sessions of 30 minutes once or twice a day. These symptoms disrupted her career, social life, and overall well-being, leaving her frustrated and searching for answers. Two years later she is finally back at work and considers herself mostly recovered.

Long COVID has emerged as a perplexing and debilitating condition affecting individuals after the initial acute phase of COVID-19 has passed. While much remains to be understood about this condition, this article aims to shed light on this troubling topic.

Long COVID is known by many names including Post-Acute Sequelae of SARS-CoV-2 Infection (PASC), Post-COVID-19 Syndrome, or Long-Haul COVID. Long COVID encompasses a wide range of symptoms that persist for weeks or months after the initial COVID-19 infection. These symptoms can affect various organ systems and significantly impact a person's quality of life.

Common symptoms include fatigue, shortness of breath, chest pain, cognitive impairment (often referred

to as "brain fog"), muscle and joint pain, loss of taste or smell, anxiety, depression and others (described in more detail below). A person with Long COVID may experience one or several of these symptoms.



Who Is Most at Risk for Long COVID?

Studies have shown that vaccination results in the reduction of the risk for Long COVID (Strain et al., 2022). For those people who have a breakthrough infection despite vaccination, findings suggest that mild COVID-19 in vaccinated people is significantly associated with reduced risk for labored breathing compared with unvaccinated patients up to three months after infection (Mitzrahi et al., 2023).

Older adults, particularly those over the age of 50, are more likely to experience persistent symptoms (Sudre et al., 2021). However, the highest percentage of diagnoses of Long COVID is in people between the ages of 36 and 50 years because they represent the largest population of people who had COVID-19 and survived (FAIR Health, 2022). Additionally, studies have shown that females are at a slightly higher risk than males for developing Long COVID (Mitzrahi et al., 2023; Osuchowski et al., 2021).

The severity of the initial COVID-19 infection is thought to be a predictor of Long COVID. Individuals who experience more severe initial symptoms, such as hospitalization or the need for intensive care, are at a higher risk for prolonged symptoms (Lopez-Leon et al., 2021). However, Long COVID is associated with all acute disease severities, and most Long COVID cases occur in non-hospitalized patients with a mild acute illness, since this is the larger population that gets COVID-19 (FAIR Health, 2022).

Individuals with pre-existing medical conditions such as obesity, diabetes, heart disease, and respiratory illnesses are thought to be more susceptible to Long COVID (Nalbandian et al., 2021). Conditions can weaken the immune system and make it harder for the body to recover fully after the acute phase of COVID-19.

Recovery

Recovery from Long COVID is a gradual process, and the timeline for improvement varies from person to person. The symptoms of Long COVID are diverse and can affect various organ systems; the most common symptoms tend to improve over time (Tenforde et al., 2020). Studies have provided some insights into the percentage of individuals who experience improvement in their symptoms at the six-month and one-year marks after the onset of Long COVID.

At the six-month mark, approximately 30 to 50% of individuals with Long COVID experience significant improvement in their symptoms (Huang et al., 2021; Sudre et al., 2021). At the one-year mark, further improvement is observed, with an estimated 50 to 70% of individuals experiencing significant relief from their Long COVID symptoms (Blomberg et al., 2021; Carfi et al., 2020). This improvement may continue beyond the first year, but the rate of recovery tends to slow down after this point.

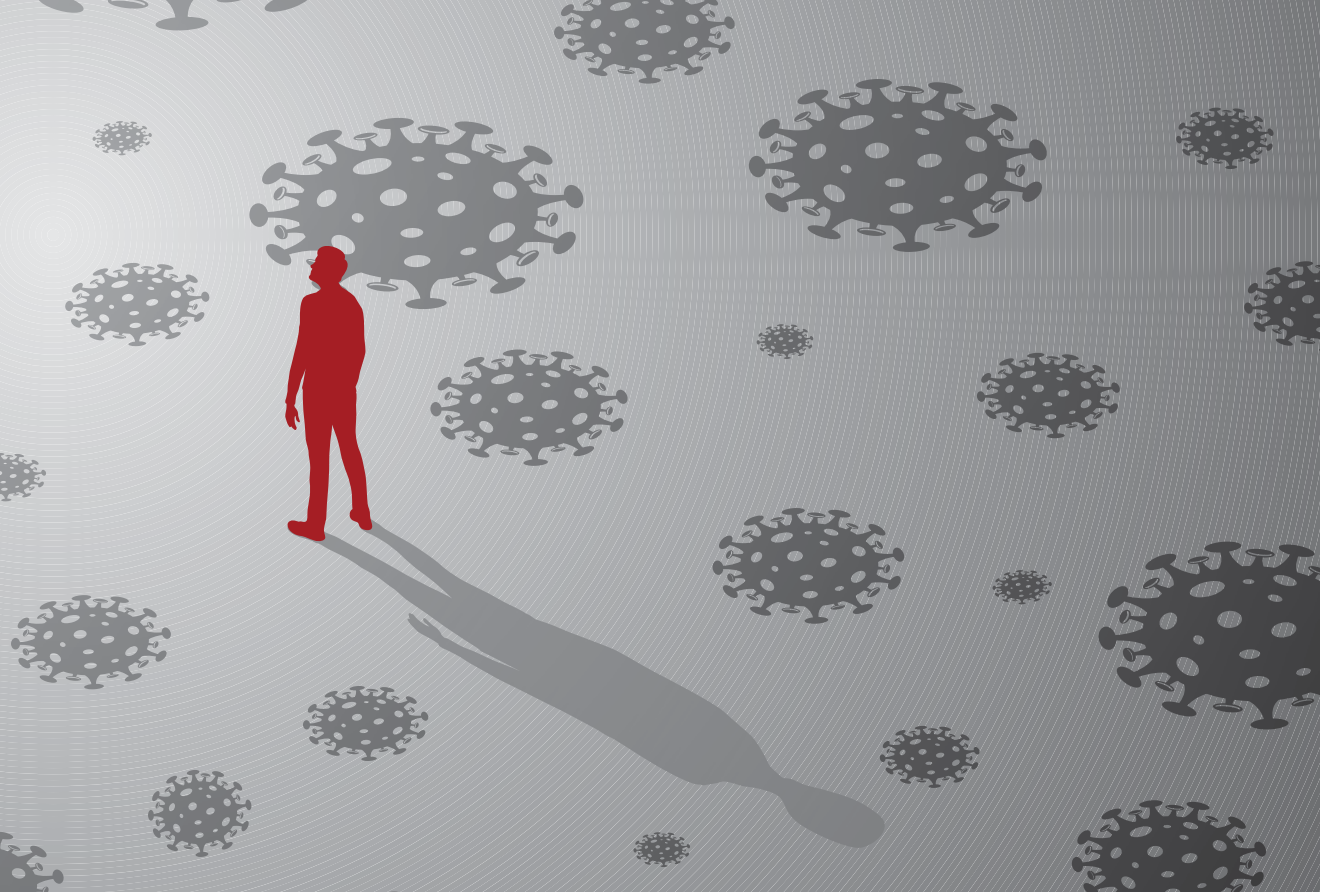
For some people, particularly those with new-onset of Myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS), symptoms can last for years (Demko et al., 2022).

General Treatment Options

It's crucial to emphasize that recovery from Long COVID can vary significantly from person to person. While many patients experience improvements in these symptoms, some face lingering issues or new challenges. An approach to treatment that includes medical, physical, and psychological support can greatly enhance the chances of a successful recovery (National Institutes of Health [NIH], 2021b).

While there is no one-size-fits-all treatment for Long COVID, management typically focuses on alleviating specific symptoms and improving overall well-being. Current Long COVID treatment is generally a combination of symptom management and the passage of time.

Structured advice regarding pacing and the gradual resumption of exercise can be beneficial, although



not curative. Rest is crucial for recovery, and for some, too much exercise should be avoided (Centers for Disease Control and Prevention [CDC], 2021). Many Long COVID patients benefit from judicious physical therapy to improve their muscle strength and flexibility. Occupational therapy can help individuals regain their independence in daily activities. For those with lingering respiratory symptoms, pulmonary rehabilitation can enhance lung function and breathing techniques. Gradually increasing physical activity can help avoid exacerbating symptoms.

Mental health support is essential for individuals with Long COVID, as many experience stress, anxiety, and/or depression. Therapy and support groups can provide valuable emotional assistance. A balanced diet and nutritional supplements may help boost energy levels and support overall recovery.

Sometimes antivirals such as Paxlovid or immune-modulating drugs are prescribed, depending on individual symptoms and needs. Healthcare providers often prescribe medications to address specific symptoms, such as pain relievers, medications to improve dizziness, or anti-inflammatory drugs.

Common Symptoms and Their Treatments

It is important to note that these symptoms can overlap and re-occur, making the management of Long COVID challenging for both patients and healthcare professionals. Theories are developing that may ultimately conclude that Long COVID consists of several different syndromes with overlapping presentations (see the section below).

The most common symptoms of Long COVID are:

Fatigue. Fatigue is a hallmark symptom of Long COVID. Overwhelming and persistent exhaustion can significantly impact a person's ability to do their daily activities. Fortunately, patients often experience a reduction in fatigue levels as they continue to recover (Carfi et al., 2020).

When severe, the symptoms can be like those of ME/CFS, a syndrome that follows an infection and is characterized by brain and autonomic system abnormalities. People experience flu-like fatigue with constant achiness and exhaustion. They often experience post-exertional malaise (PEM), in which they feel worse following an exertion. Rest, pacing, improvement of the gut microbiome, and appropriate rehabilitation to avoid PEM crashes might help.

Shortness of Breath. Difficulty breathing, even during light physical activities, may be accompanied by chest discomfort. Many Long COVID patients initially experience shortness of breath, cough, or chest discomfort. With time, these respiratory symptoms often improve significantly. Research suggests that lung function gradually returns to normal in most cases (NIH, 2021b).

Brain Fog. Brain fog, memory issues, mental fatigue, and difficulty concentrating are common cognitive symptoms of Long COVID. Brain fog can refer to a range of symptoms such as difficulty thinking clearly, trouble concentrating, confusion, slow

thinking, forgetfulness, or simply not feeling sharp mentally. These symptoms can gradually improve with time, though it may take several months (Nalbandian et al., 2021). Cognitive testing may point to specific areas of dysfunction. Patients experiencing cognitive impairment may benefit from cognitive rehabilitation programs aimed at improving memory, concentration, and executive functioning. A variety of medications, exercises, and the passage of time can help.

Loss of Taste or Smell. A lingering loss or alteration of the sense of taste or smell is known as anosmia or dysgeusia. Loss of taste and smell is a frequently reported symptom of Long COVID. In most cases, these senses gradually return to normal, although it may take weeks or months (Lechien et al., 2020). There is currently no established treatment for this, although there are early reports of modest successes with certain medications (Chupp et al., 2022).

Chest Pain or Heart Palpitations. Irregular heartbeats or sensations of a racing heart or persistent chest pain or discomfort, which can sometimes mimic heart-related issues, are another symptom. While this symptom is less common than fatigue, some Long COVID patients continue to experience chest pain or discomfort. Fortunately, this symptom often improves as the body continues to heal (Chopra et al., 2021). Cardiovascular rehabilitation may be recommended.

Muscle, Joint, and Head Pain. Muscle and joint pain, akin to fibromyalgia or arthritis, can be part of Long COVID. Along with persistent and sometimes severe muscle and joint aches and pains, frequent and often severe headaches can occur and can be debilitating. These typically lessen with time, medications, and gentle physical therapy (Arnold et al., 2021).

Anxiety and Depression. Mood disorders and emotional disturbances, including anxiety, depression, and mood swings can happen with Long COVID. Anxiety and depression can be exacerbated by the physical and emotional toll of Long COVID. Psychological support, therapy, and medications can aid in improving mental health, which, in turn, can positively impact other symptoms (Taquet et al., 2021).

Heart Rate and Blood Pressure/ POTS. Some individuals experience fluctuations in heart rate and blood pressure as part of Long COVID. Autonomic nervous system symptoms, such as feeling lightheaded after standing up (orthostasis) can overlap with Postural Orthostatic Tachycardia Syndrome (POTS). Medications can be used to reduce orthostatic symptoms. These symptoms tend to stabilize as recovery progresses (Townsend et al., 2020), although it may last years for some.

Digestive Issues. Gastrointestinal symptoms such as nausea, diarrhea, or abdominal pain may occur. The gut microbiome has been found to be altered in patients with COVID-19 (Yeoh et al., 2021), and some of these bacteria population changes are strongly correlated with Long COVID at six months (Liu et al., 2022). Fecal transplants are being tried for people with Long COVID (Kazemian et al., 2021). Anti-nausea or anti-diarrhea medications may be prescribed for severe symptoms, as well as diet adjustments.

Sleep Disturbances. While many people with Long COVID experience a wide range of symptoms, one prevalent issue is sleep disturbances. Insomnia is a common sleep problem in Long COVID patients. Individuals may have difficulty falling asleep and staying asleep, and may experience non-restorative sleep (Huang et al., 2021). In contrast, some Long COVID patients experience excessive daytime sleepiness, a condition known as hypersomnia (Mazza et al., 2021). This can result in daytime napping, which further disrupts the nighttime sleep cycle. Sleep disturbances may be treated with improved sleep hygiene practices such as the elimination of caffeine, going to bed at the same time, pre-bedtime rituals, daytime sunlight, or improved sleep settings. Relaxation, exercise, yoga, or medication may be useful as well.

Hair Loss. Hair loss, known as telogen effluvium, can occur for months in over 20% of people hospitalized with COVID-19 (Seyfi et al., 2022). This unexpected symptom can be very distressing for those individuals who experience it.

Prevention

Since Long COVID follows an acute infection of COVID-19, it makes sense to continue to take steps to avoid COVID-19 infections. A review of the many non-pharmaceutical interventions that were used to reduce the spread of COVID-19 showed that social distancing and face masks, especially high-grade masks such as N95s, worked the best. Enhanced ventilation was helpful and there was a lack of evidence for enhanced cleaning procedures or public screens (Mahase, 2023). While vaccinations are recommended, vaccines have unfortunately become a politicized issue and individuals will make their own decisions.

Medical Treatment Models

Some patients benefit from symptom-specific care from individual specialists who may or may not treat many people with Long COVID. Specialist care can work well, especially for someone with a limited set of symptoms. The specialist may be local and convenient.

Another option is to receive care at a Long COVID center. A center will have a variable array of healthcare

professionals well-versed in the condition's nuances. Medical specialists such as cardiologists, pulmonologists, physiatrists (physical medicine and rehabilitation), gastroenterologists, neurologists, and others may be available. Other professionals such as physical therapy, occupational therapy, speech-language pathology, behavioral health, cognitive (neuropsychiatric) testing, cardiopulmonary rehabilitation, nutritionists, and others may be available. The specific types of professionals available will vary by location.

Long COVID centers typically offer interdisciplinary care (professionals with different backgrounds actively integrating and coordinating their knowledge and findings) or multidisciplinary care (professionals with different backgrounds work in the same center but do not generally coordinate). The only way to know if a particular center offers interdisciplinary care is to inquire as to whether the professionals routinely meet for the purposes of care coordination and case discussion.

Long COVID clinics tend to be in big cities at academic medical centers. Examples of Long COVID clinics include the Post-Acute COVID-19 Clinic at John Hopkins in Baltimore, Maryland and the Center for Post-COVID Care at Mount Sinai, New York City. For the most up-to-date information, perform an online search using terms such as Long COVID or post-COVID clinic or center.

Leading Theories on the Causes of Long COVID and Its Subtypes

We don't fully understand what causes Long COVID. More research is needed. There are several leading theories regarding what causes Long COVID, and these theories are not mutually exclusive. As the medical community develops a better understanding of the causes, this should lead to improved treatments.

One of the leading theories behind Long COVID is immune dysregulation. The immune dysregulation theory suggests that the immune system's persistent activation leads to inflammation and tissue damage, affecting multiple organs and systems. Some researchers are concerned that this immune dysregulation can cause a reactivation of underlying pathogens such as the Epstein-Barr virus (Peluso et al., 2022). With immune dysregulation, the body's immune system remains too long in a heightened state of alertness, with immune cells, such as T cells (Klein et al., 2022) and B cells, continuing to circulate and fight off perceived threats even after the virus has been cleared (Tenforde et al., 2020). Multiple studies have found elevated levels of autoantibodies in Long COVID (Arthur et al., 2021). This prolonged immune response could contribute to the ongoing symptoms seen in Long COVID patients, such as fatigue, brain fog, and joint pain.

Another hypothesis regarding the causes of Long COVID involves viral persistence, where remnants of the SARS-CoV-2 virus linger in the body after the initial infection has resolved (Gaebler et al., 2021). These viral remnants potentially hide in areas of the body less subject to immune responses like the brain, or they may exist in a dormant state, avoiding detection by the immune system. Viral persistence could trigger a chronic inflammatory response, damaging tissues and leading to the prolonged symptoms seen in Long COVID. Researchers are actively investigating antiviral treatments that eliminate these persistent viral particles.

Other studies suggest that mitochondrial dysfunction could play a significant role in the development of Long COVID (Varghese & John, 2021). Mitochondria are often referred to as the "powerhouses" of our cells, responsible for generating energy to fuel various cellular functions. The mitochondrial dysfunction theory proposes that either the virus itself or the body's response to it damages the mitochondria in affected cells. This damage results in reduced energy production, leading to the fatigue and muscle weakness often reported by Long COVID patients. Additionally, mitochondrial dysfunction can disrupt other cellular processes, potentially causing symptoms like brain fog and muscle pain.

As part of ongoing research, different subtypes of Long COVID are being identified. Whether the symptom-based classifications (such as neurologic or respiratory), existing syndrome-based classifications (such as POTS, ME/CFS), or some other classification will be the final word is yet to be determined.

A greater understanding of Long COVID, its causes, and its subtypes is crucial for tailoring treatment approaches and providing better care for affected individuals. Researchers are actively working to classify and characterize these subtypes, aiming to identify distinct biomarkers and therapeutic targets for each (Davis et al., 2021).

Ongoing Research and National Funding

Understanding and treating Long COVID has become a top priority in the medical community, and substantial research funding is being channeled towards this cause. Long COVID is a complex puzzle, and uncovering its mysteries will take time. It is challenging to predict when definitive answers will emerge.

The NIH is at the forefront of Long COVID research funding. They have launched multiple initiatives to support research on the causes and treatments

of Long COVID. This includes the NIH Research Initiative on Long COVID, aimed at uncovering the underlying mechanisms of Long COVID and developing effective interventions (NIH, 2021a).

The CDC has also allocated resources for Long COVID research. They have funded studies to investigate the prevalence, risk factors, and outcomes of Long COVID among various populations, providing valuable insights into the condition (CDC, 2023).

Additionally, the Patient-Centered Outcomes Research Institute (PCORI) has supported research projects focusing on patient-centered approaches to Long COVID, with the goal of improving the quality of life for those affected by this condition (PCORI, n.d.).

An Ongoing Effort

Long COVID remains a challenging and enigmatic multisystemic illness that affects a diverse group of individuals worldwide. While research continues to advance our understanding of its causes, risk factors, and treatment options, much work remains to be done.

People like Sarah, who grappled with persistent symptoms for many months, serve as a reminder of the urgency to unravel the mysteries of Long COVID. As we await more answers, specialized clinics and ongoing research efforts offer hope for improved care and outcomes for those affected by this condition. With the concerted efforts of the global scientific community, we can hope for a brighter future where Long COVID is better understood and more effectively managed. •CSA



Dr. Gerda Maissel is a physician and former health system leader who brings a unique perspective to personal patient advocacy. She specializes in guiding people with complex medical problems through their stays in the hospital or rehabilitation facility. She loves being an advocate and says that it is the most satisfying work she's ever done. Dr. Maissel is a Board Certified Patient Advocate (BPCA), Board Certified Physical Medicine and Rehabilitation physician, and a Certified Physician Executive (CPE). Reach her at gm@mymdadvisor.com.

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