Postacute Sequelae of SARS-CoV-2 Infection—Lessons Learned From a Coordinated Health System Response

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Abstract

Objective: To outline a consensus-designed process for triaging and managing patients with post-coronavirus disease (COVID-19) syndrome at Mayo Clinic.

Patients and Methods: We convened a central multidisciplinary team including members from the departments of general internal medicine, occupational medicine, physical medicine and rehabilitation, psychology, allergy and immunology, infectious disease, pulmonology, neurology, cardiology, and pediatrics and otorhinolaryngology with membership from all Mayo Clinic sites in Arizona, Florida, Iowa, Minnesota, and Wisconsin.

Results: Consensus recommendations were made for the best practice guidelines on triaging and managing patients. Several innovations were agreed upon, including a postacute sequelae of COVID-19-specific appointment request form for data collection, a bioregistry, a biorepository, and a postacute sequelae of COVID-19-specific treatment program.

Conclusion: Given that each clinical site had individual clinical practices, these recommendations were implemented using different models, which may provide broad applicability to other clinical settings.

S ince the initial identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late 2019, it has been identified in over 243 million people and has resulted in just under 5 million deaths globally as of October 2021. The World Health Organization has designated the clinical syndrome caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19), with its clinical spectrum ranging from asymptomatic individuals to severe disease resulting in death. Several risk factors have been associated with worse outcomes, including advanced age, cardiovascular disease, chronic obstructive pulmonary disease, cancer, diabetes mellitus, male sex, race or ethnicity, and obesity.[1-3] In a study of 355 patients who died of severe acute COVID-19, less than 1% had no associated risk factors.[4] In the United States, the risk of death is 12 times higher in patients with reported comorbidities (19.5%) than in those without (1.6%).[5] A recent meta-analysis of 69,762 patients found that age, cerebrovascular disease, and biomarkers such as C-reactive protein and lactate dehydrogenase are most strongly associated with mortality.[6]

Early during the COVID-19 pandemic in countries that were heavily impacted (ie, Italy, China, and France), observations were made that some hospitalized patients who survived the acute illness (<28 days) continued to have persistent symptoms. A case series of 143 individuals in Italy who had been hospitalized for severe acute COVID-19 described symptoms being present for more than 60 days from initial onset. A total of 87.4% of the patients (n=125) had persistent symptoms, including fatigue (53.1%), shortness of breath (43.4%), and joint pain (27.3%), when they were seen during posthospital

ambulatory follow-up.[7] A cohort study of 1733 hospitalized patients from China were assessed (with a median of 186 days after symptom onset) in the ambulatory setting after discharge. The most common persistent symptoms were fatigue or muscle weakness (63%) and insomnia (26%). In France, a study was conducted on 120 patients hospitalized for COVID-19 who survived and answered a follow-up telephonic questionnaire at a mean of 110.9 days after admission.[8] The most frequently reported persistent symptoms were fatigue (55%), dyspnea (42%), loss of memory (34%), lack of concentration (28%), and sleep disturbances (30.8%).[8] A few months later, studies reported persistent symptoms in patients who were not hospitalized for severe disease.[9] These studies estimated that between 10% and 30% of patients who recover from COVID-19 experience persistent symptoms that can last months after the resolution of acute disease.[9]

Mayo Clinic (MC) began to identify patients with persistent symptoms and complications after acute COVID-19 in a pattern similar to these early studies. In June 2020, we started a dedicated clinical and research program to both treat and study the long-term effects of COVID-19. To date, we have treated over 1000 patients in our combined post-COVID-19 clinics. The purpose of the present article was to define the post-COVID-19 spectrum of the disease and describe the various ambulatory clinical approaches (including treatment) that we used.

POSTACUTE SEQUELAE OF COVID-19

One of the major problems that health systems face in the management of postacute sequelae of COVID-19 (PASC) is the lack of a clear understanding of the etiology of persistent symptoms. An additional problem encountered was the lack of a clear definition to describe the persistent postacute COVID-19 patterns of symptoms. When chronic disease states lack a clear definition, it is very difficult to effectively treat patients or research their conditions. There are a number of terms in the literature and among the public that have been used to describe persistent symptoms, including post-COVID-19 syndrome (PoCOS), postacute coronavirus disease 2019, chronic COVID-19, long-haul COVID-19, persistent symptoms after COVID-19, and long

COVID-19.[10-12] All these terms have gained popularity. What defines each one has varied considerably depending on the source. For example, Greenhalgh et al[9] defined postacute COVID-19 as persistence for more than 3 weeks from the onset of the first symptom and chronic COVID-19 as extension beyond 12 weeks. A recent systematic review defined persistent COVID-19 symptoms as those persisting for at least 60 days after diagnosis, symptom onset, or hospital admission or at least 30 days after recovery from acute illness or after discharge from the hospital.

We developed an early working definition for persistent symptoms in June 2020 by drawing on the early experiences of taking care of patients with acute ambulatory COVID-19 from both teams such as the COVID-19 Frontline Care Team as well as our post-COVID-19 clinics.[13] The temporal definition was based on the normal infectious course of SARS-CoV-2, with the highest infectivity occurring just before symptom onset in up to 44% of patients and extending to a few days after symptom onset.[14] Viable virus is detected in culture up to 20 days after the onset of symptoms.[15] Although nonviable viral RNA shedding can occur up to 90 days after symptom onset, there is no evidence that this shedding can transmit SARS-CoV-2.[16] Seroconversion that is a shift from immunoglobulin M positivity to immunoglobulin G positivity occurs in most patients by 2 weeks after the onset of the first symptom. On the basis of this evidence, our initial definition of persistent post-COVID-19 symptoms included patients with at least 1 new symptom that persisted for 30 days or more after symptom onset. The time period of 30 days or more was chosen to allow for variation in the response characteristics of individuals and common postviral complications such as postviral cough.

Recently, the National Institutes of Health (NIH) introduced the term PASC to describe and define the persistent symptoms of COVID-19.[17] This definition accompanied a $1.15 billion dollar funding initiative over 4 years to support research on PASC and the prolonged complications of COVID-19. A 3-phase framework has been proposed to describe PASC, with the acute phase lasting 2 weeks from symptom onset and characterized by active viral replication and the initial host reponse.[18] The postacute hyperinflammatory illness involves a

Required:

- Timeline:
  - Viral prodrome[a] occurring after December 31st, 2019
  - Post-viral symptoms persisting >3 weeks
- Clinical stabilization or resolution of the viral infection/prodrome[b]

Major criteria:

- Positive PCR test **OR** rapid antigen test with a viral prodrome **OR** positive serology with a viral prodrome
- Viral prodrome involving symptoms more closely associated with COVID-19 infection, specifically anosmia, dysgeusia, or shortness of breath

Minor criteria:

- Two of six core systems:
  - Constitutional (fatigue, fevers, dizziness, sleep disturbance, photosensitivity)
  - Cardiac (tachycardia, palpitations, chest pain/tightness)
  - Respiratory (shortness of breath, cough)
  - Gastrointestinal (abdominal pain, nausea, vomiting, diarrhea)
  - Musculoskeletal (joint pain, myalgias, tenderness)
  - Neurological (parasthesias, weakness)
- Moderate or greater decrease in functional status
- Viral prodrome not including anosmia, dysgeusia, or shortness of breath

Exclusion criteria:

- Better explained by an alternative diagnosis, including pre-existing central sensitization syndromes

Probable:

Patients must have 2 major criteria and 1 minor criterion **OR** 1 major criteria and 2 minor criteria.

Possible:

Patients must have 1 major criterion and 1 minor criterion **OR** 3 minor criteria.

[a]*Stabilization/resolution characterized by symptom improvement x72 hours in the following, without NSAID or acetaminophen use: fever, chills, sweating, myalgia, diarrhea, cough, dyspnea, sore throat, chest tightness, nasal congestion, anosmia, dysguesia, fatigue; weakness, lightheadedness, headaches, nausea, or abdominal pain.*

[b]*Viral prodrome defined as: fever, chills, shortness of breath, anosmia, dysgeusia, muscle aches, fatigue, headache, congestion, cough, rhinorrhea, nausea, vomiting, or diarrhea.*
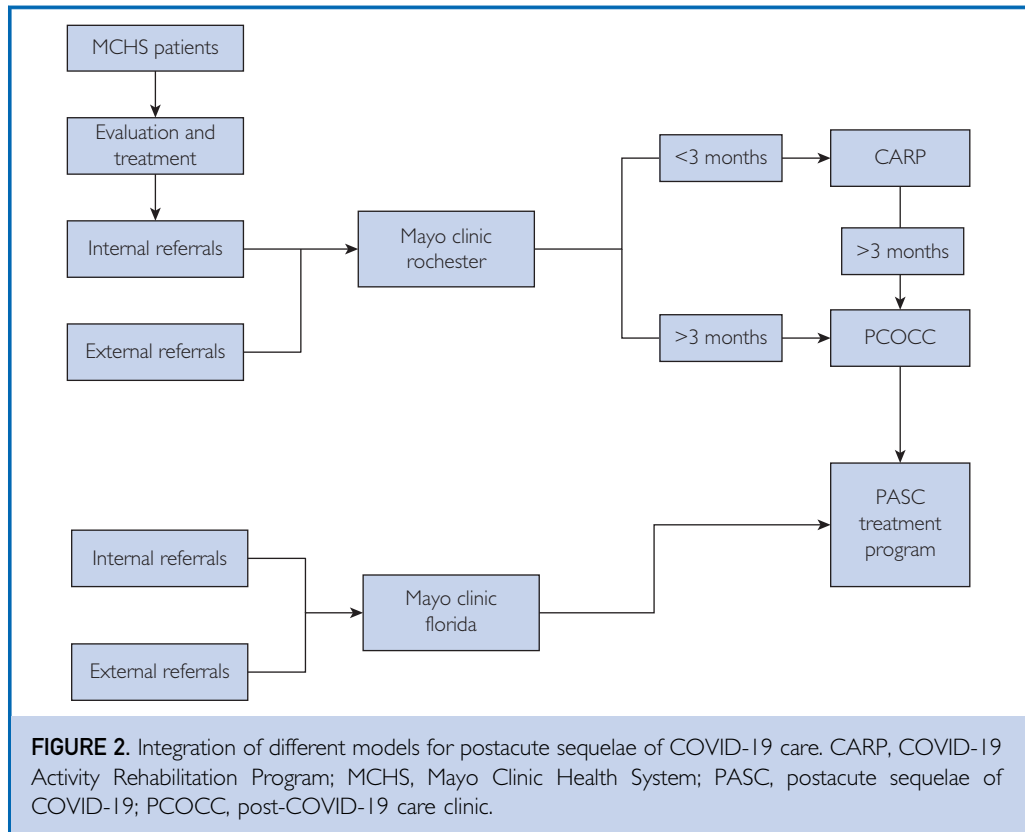
FIGURE 1. Proposed post-coronavirus disease 2019 syndrome diagnostic criteria. COVID-19, coronavirus disease 2019; NSAID, nonsteroidal anti-inflammatory drug; PCR, polymerase chain reaction.

dysregulated host response and can last between 2 and 4 weeks, and the late sequelae phase (>4 weeks) involves a number of persistent symptoms, determined without viable viral testing. The working PASC clinical definition that NIH has developed is as follows: a patient who is persistently symptomatic 30 days from the onset of infection. We agree with the definition, with the addition that the start of the 30-day time period begins with symptom onset during the acute phase. Additionally, we note that the definition of PASC is heterogenous, ranging from patients with only 1 persistent symptom, eg, anosmia to patients with multiple chronic symptoms, often co-occurring in a characteristic symptom cluster, which we described as post-COVID-19 syndrome.

POST-COVID-19 SYNDROME

Post-COVID-19 syndrome is very similar to other postviral syndromes after Epstein-Barr viral infection, severe acute respiratory syndrome, Q-fever, Zika viral infection, and chikungunya, wherein patients experience a

FIGURE 2. Integration of different models for postacute sequelae of COVID-19 care. CARP, COVID-19 Activity Rehabilitation Program; MCHS, Mayo Clinic Health System; PASC, postacute sequelae of COVID-19; PCOCC, post-COVID-19 care clinic.

similar constellation of persistent symptoms, including fatigue, pain, cognitive dysfunction, and postexertional malaise. Early on in the pandemic, we began to identify specific grouping of symptoms in patients with PASC and started to define their clinical phenotypes on the basis of symptom clusters and predominant symptomatology to help with treatment strategies. These phenotypes included fatigue, with postexertional malaise; orthostatic intolerance; cognitive impairment, including commonly reported "brain fog"; and myalgias or arthralgias. These chronic symptoms are similar to those experienced because of fibromyalgia (FMS), chronic fatigue syndrome (CFS), and postural orthostatic tachycardia syndrome (POTS). On the basis of these observations, physicians from our FMS, CFS, and POTS clinics retrospectively evaluated 465 patients presenting to our clinic who did not have pre-existing FMS, CFS, or POTS and had recovered from COVID-19.[19] Using the Delphi method, 42 patients (9%) were identified as likely having the characteristics of PoCOS, with the median age of these 42 patients being 46.5 years and 66.6% being women (n=28).[19] The predominant symptoms were pain (90.2%), fatigue (73.8%), dyspnea (42.9%), and orthostatic intolerance (38.1%). The duration of the symptoms ranged from 4 to 22 weeks (average, 11 weeks), with the cutoff in data collection being August 5, 2020.[19] On the basis of this small study, we formulated diagnostic criteria for PoCOS, which have helped us phenotype patients and rapidly triage them so that they can receive the appropriate testing and treatments (Figure 1).

DEVELOPMENT OF MC PASC AMBULATORY CLINICS

Mayo Clinic formed the Multidisciplinary Approach Guiding Post-COVID-19 Investigation, Education and Symptom Management in the latter half of 2020 to coordinate efforts and share clinical and research approaches to PASC. This multispecialty team comprises physicians, scientists, and allied health staff from the departments of general internal

medicine (GIM), occupational medicine (Preventative Medicine [Prev Med]), physical medicine and rehabilitation, psychology, allergy and immunology, infectious disease, pulmonology, neurology, cardiology, pediatrics and otorhinolaryngology with membership from all MC sites: Mayo Clinic Arizona (MCA), Mayo Clinic Florida (MCF), Mayo Clinic Rochester (MCR), and the Mayo Clinic Health System (MCHS) located in the Midwest. The Multidisciplinary Approach Guiding Post-COVID-19 Investigation, Education and Symptom Management team has created several novel initiatives, including a COVID-19 clinical triage system and multispecialty treatments, ranging from nursing delivered virtual education and gentle rehabilitative sessions, the use of wellness coaches in the longitudinal care of PoCOS, to smell retraining in patients with PASC-associated anosmia. Subspecialists experienced in acute COVID-19 and PASC see patients with signs of end-organ involvement.

Patient Entry

Patients present to our adult PASC clinics via self-referral (calling the Central Appointment Office) or physician referral. The patients are administered a 52-question appointment request form (ARF), which gathers information on the date of a positive test result and the timing or nature of their symptoms (Supplemental Material 1, available online at http://www.mcpiqojournal.org). The PASC triage team at each site reviews the ARF as the first step in phenotyping patients in order to develop an individual evaluation plan that may involve a multispecialty work-up coordinated by a member of the GIM or Prev Med teams. Since inception, MC PASC clinics have treated over 1500 patients with PASC, and the ARF has allowed us to efficiently direct patients to the appropriate individualized PASC work-up. In addition to optimizing PASC clinical care, the ARF and triage process may be used to drive recruitment for research. The general schema of our clinical evaluation program is outlined in Figure 2.

MCF PASC CLINIC

Mayo clinic Jacksonville in Florida is a multispecialty clinic with a 304-bed acute care hospital that serves as a tertiary care center, with patients traveling from mostly the South Eastern United States. In response to the growing number of patients with persistent symptoms after COVID-19 infection, the institutional leadership convened a steering committee to develop and coordinate a PASC clinic at MCF. This steering committee adapted the framework suggested by the Enterprise workgroup to suit local practice preferences. The MCF PASC clinic is directed by the GIM department, with specialist support. This clinic has seen over 100 patients since May 2021. Patients who are being evaluated for PASC are triaged to ensure that they have symptoms after COVID-19 infection and that we can appropriately preschedule their evaluations. Additional previsit questionnaires are completed, including PROMIS, the World Health Organization Disability Assessment Schedule, and the Treatment Burden Questionnaire, to better delineate patient characteristics. Patients are initially seen during a virtual visit, followed by a face-to-face visit, appropriate medical work-up including specialty consultation as needed, and then a plan-of-care discussion visit at the end of their evaluation, at which time patients who do not have tissue damage to explain their symptomatology are recommended to undergo a specialized cognitive treatment program (the PASC Treatment Program) that is designed to assist patients with lifestyle-related approaches, including nutrition, exercise, sleep, stress, and anxiety, as they manage their recovery from PASC.

MCR COVID-19 ACTIVITY REHABILITATION PROGRAM

The COVID-19 Activity Rehabilitation Program (CARP) at MCR currently cares for patients with PASC within the first 1-3 months after the onset of COVID-19 symptoms. This clinic, directed by the Departments of Prev Med and physical medicine & rehabilitation, has seen more than 300 patients since June 2020.[20] The main goal of this clinic is to provide a comprehensive rehabilitation plan using individualized physical therapy, occupational therapy, or cognitive therapy. The patient data from the first 100 patients seen between June 1, 2020, and December 31, 2020, were recently published.[20]

The majority (75%) of the patients seen had not been hospitalized for COVID-19. On average, the patients seen were 45.4 years old, and 68% were women. The most common symptoms noted on initial presentation were fatigue (80%); respiratory complaints, including dyspnea (59%); and neurologic complaints, including headache (59%). The other common symptoms were subjective cognitive complaints, sleep disturbance, and mental health symptoms. Persistent anosmia and dysgeusia were not common in this cohort. Approximately one third (34%) of the patients reported having difficulties performing activities of daily living, and 84% of the patients reported trouble with household chores, exercise, driving, and/or completing tasks required at work. Thirty-seven percent of the patients were not back to work at the time of presentation to the program.
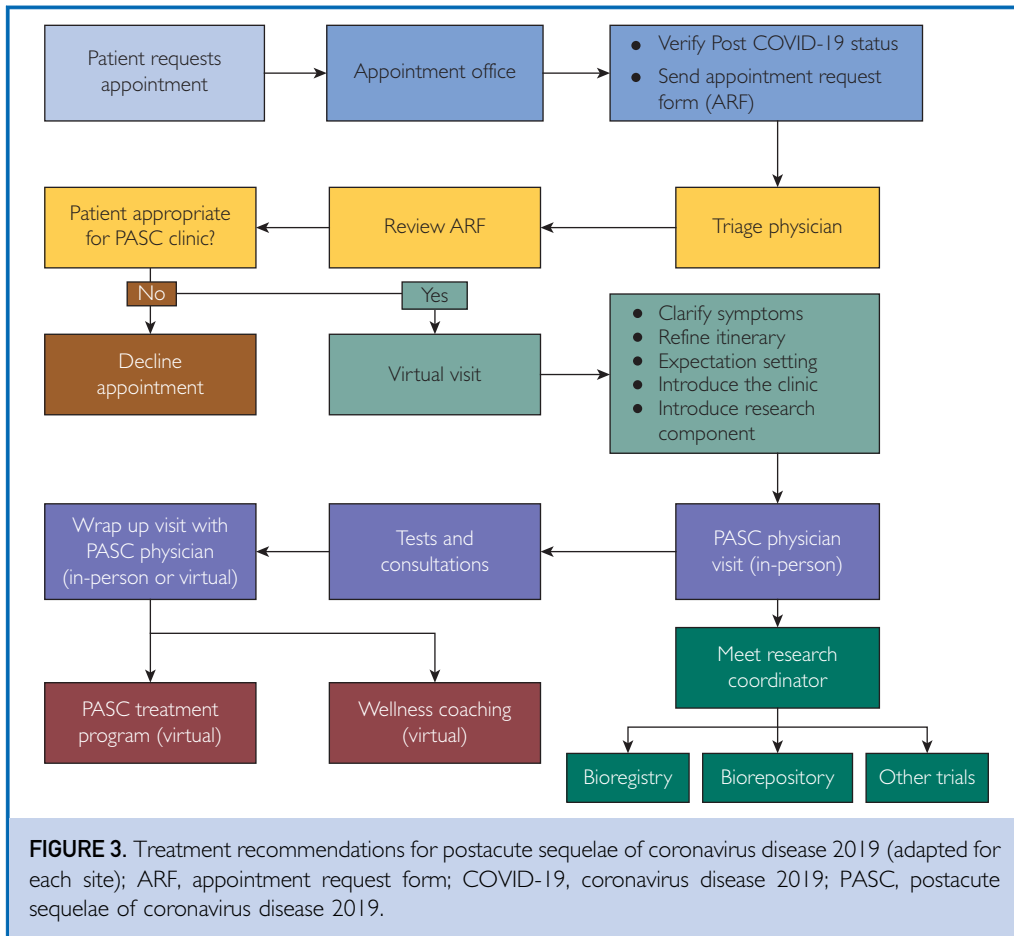
MCR POST-COVID-19 CARE CLINIC

The GIM post-COVID-19 care clinic (PCOCC) at MCR cares for patients with PASC who have had symptoms persisting for more than 3 months after the onset of COVID-19 symptoms. One key feature of the MCR PCOCC is that this clinic aims to treat patients with PoCOS who have been either triaged directly into the clinic or referred by the CARP team or an MCHS primary care physician. For most of the patients, there was no evidence of tissue damage on testing, and these patients likely had a central sensitization phenotype, including fatigue, myalgia, and orthostasis. For the treatment of the central sensitization phenotype, we created a virtual treatment program aimed at patient education using elements of cognitive behavioral therapy, health coaching, and paced rehabilitation. This program is 8 hours long, delivered as two 4-hour segments, and accompanied by health coaching and nursing follow-up for 6 months. As a part of the PCOCC evaluation, the team developed a standardized evaluation to be ordered for any patient presenting to the clinic. This included basic laboratory testing (complete blood count, complete metabolic panel, erythrocyte sedimentation rate, and C-reactive protein), testing for the markers of COVID-19-associated inflammation (ferritin, D-dimer, and interleukin 6), autoimmune screening (antinuclear antibody and cyclic citrullinated

peptide with reflex to a full panel if either was present), a 6-minute walk test, and pulmonary function tests and chest imaging if the patient had dyspnea.

The data for the first 107 patients have been published.[21] A total of 75% of the patients seen at the clinic were women (n=80), with a median age of 47 years. Six phenotypes were identified on the basis of the primary predominate symptom they presented with, which included fatigue (n=68), dyspnea (n=23), myalgia (n=6), orthostasis (n=6), chest pain (n=3), and headache (n=1). Of these, the patients who had predominant dyspnea or chest pain were not likely to experience the other syndromic symptoms seen with PoCOS.

MAYO CLINIC HEALTH SYSTEM

The Mayo Clinic Health System is a regional health system affiliated with MC across 4 4 regions, including Southwest Minnesota, Southeast Minnesota, Northwest Wisconsin, and Southwest Wisconsin. This health system serves a large number of rural patients who would prefer to be treated locally rather than coming into a tertiary medical center for evaluation. In order to facilitate this, the Enterprise post-COVID-19 group met with the MCHS leadership and physicians in order to explore solutions that would allow for providing care to these patients closer to home. Thus, a model was created to facilitate the needs of patients experiencing post-COVID-19 symptoms within MCHS by capitalizing on the expertise of the MCR post-COVID-19 treatment teams. This was performed using an Extension for Community Healthcare Outcomes model, wherein we identified physician champions from each region to undergo additional training from CARP and PCOCC providers for evaluating symptoms that persist beyond the initial infection after COVID-19.[22] Available specialty care providers in the regions were also queried about what treatments they would be able to offer to patients with post-COVID-19 symptoms, and a list of available services in each region was compiled. Furthermore, CARP and PCOCC clinic referrals were still available for patients who necessitated that level of care if they could manage the necessary logistic factors to participate in the program. This model is useful for health

FIGURE 3. Treatment recommendations for postacute sequelae of coronavirus disease 2019 (adapted for each site); ARF, appointment request form; COVID-19, coronavirus disease 2019; PASC, postacute sequelae of coronavirus disease 2019.

care systems that, like ours, have a community health program affiliated with a larger tertiary referral center.

MAYO CLINIC ARIZONA
Mayo Clinic Arizona opted not to proceed with developing a dedicated PASC clinic at this time, and this effort is being coordinated as a part of their primary care clinics in a manner similar to that employed by MCHS. The PASC clinical teams from MCF and MCR (both CARP and PCOCC) have met with primary care clinics in MCA to disseminate knowledge and the best practices. These different models are displayed in Figure 3.

Research
In novel conditions, such as during post-COVID-19 syndrome, research is needed to better understand the behavior and physiology associated with the illness in order to inform clinical practice guidelines. Mayo

Clinic convened an Enterprise-wide group comprising physicians, scientists, and researchers from all 3 campuses and MCHS in order to develop a protocol for collating clinical experiences and care with research initiatives. This group established post-COVID-19 research goals that span basic science (disease mechanisms), clinical services, health services, population health, health disparities, and patient-reported outcomes. In order to better understand the disease process, we developed an institutional review board-approved bioregistry and biorepository to capture clinical data and scales as well as biological samples from the serum, the plasma, peripheral blood mononuclear cells, DNA, urine, and stool at multiple time points. This allows our group to follow-up patients longitudinally, which has the benefit of detecting temporal trends in illness trajectory and the effect of therapies. Every patient presenting to one of the PASC clinics at MCF or

MCR is approached and recruited to be included in the voluntary bioregistry and biorepository. In addition to maintaining these registries, the Enterprise workgroup reviews the rapidly evolving medical literature regarding post-COVID-19 syndrome and attempts to harmonize research efforts across the multiple sites in an effort to optimize and maximize resources, enhance meaningful collaborations, and minimize redundancies.

As mentioned above, NIH has started investigations into post-COVID-19 syndrome with a promise to invest upward of a billion dollars toward this research. Although this process is getting underway, it is important to collect and synthesize clinical data and observations on patients being seen with post-COVID-19 syndrome in order to provide a basis for their further investigations. This interim research will also likely be of the greatest value to changing care for patients who currently experience post-COVID-19 syndrome while we await the benefit of further larger trials.

CONCLUSION
Here, we presented the MC experience of defining post-COVID syndrome as a subphenotype of PASC and establishing multispecialty clinics to evaluate and treat PASC. Although we described a central schema that was agreed upon by the Enterprise workgroup, this was adapted to suit the clinical practice of the different regions, thus leading to 5 distinct PASC clinics—1 focusing on early rehabilitation and return to work (CARP), 1 focusing on PoCOS (PCOCC), 1 that sees all patients with PASC (MCF PASC), 1 that operates on the Extension for Community Healthcare Outcomes model (MCHS), and 1 that is entirely run by primary care without central specialty support (MCA). Additionally, we developed tools to enhance our patient evaluation and assessment, including the ARF and disease severity scales, and connected these to research via a PASC biorepository and bioregistry. We hope that this schema and the models will assist other health systems develop practice models to address the PASC epidemic.

POTENTIAL COMPETING INTERESTS
The authors report no competing interests.

SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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