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Long COVID or Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) and the Urgent Need to Identify Diagnostic Biomarkers and Risk Factors

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

CDEF **Dinah V. Parums**

Science Editor, Medical Science Monitor, International Scientific Information, Inc., Melville, NY, USA

Corresponding Author: Dinah V. Parums, e-mail: dinah.v.parums@isi-science.com
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Long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC), also known as post-COVID-19 condition or post-COVID syndrome, can affect anyone infected with SARS-CoV-2, regardless of age or the severity of the initial symptoms of COVID-19. Long COVID/PASC is the continuation or development of new symptoms after three months from the initial SARS-CoV-2 infection, which lasts for at least two months and has no other identifiable cause. Long COVID/PASC occurs in 10-20% of patients infected with SARS-CoV-2. The most common symptoms include fatigue, cognitive impairment (brain fog), and shortness of breath. However, more than 200 symptoms have been reported. No phenotypic or diagnostic biomarkers have been identified for developing long COVID/PASC, which is a multisystem disorder that can present with isolated or combined respiratory, hematological, immunological, cardiovascular, and neuropsychiatric symptoms. There is no cure. Therefore, individualized patient management requires a multidisciplinary clinical approach. Because millions of people have had and continue to have COVID-19, even in the era of vaccination and antiviral therapies, long COVID/PASC is now and will increasingly become a health and economic burden that the world must prepare for. Almost five years from the beginning of the COVID-19 pandemic, this article aims to review what is currently known about long COVID/PASC, the anticipated increasing global health burden, and why there is still an urgent need to identify diagnostic biomarkers and risk factors to improve prevention and treatment.

Keywords: Long COVID • PASC • SARS-CoV-2 • Biomarkers • Risk Factors • Review

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Introduction

Long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC), also known as post-COVID-19 condition or post-COVID syndrome, can affect anyone infected with SARS-CoV-2, regardless of age or the severity of the initial symptoms of COVID-19 (**Table 1**) [1,2]. Long COVID/PASC is the continuation or development of new symptoms after three months from the initial SARS-CoV-2 infection, which lasts for at least two months and has no other identifiable cause [2]. Long COVID/PASC occurs in 10-20% of patients infected with SARS-CoV-2 [1,2]. The most common symptoms include fatigue, cognitive impairment (brain fog), and shortness of breath [3,4]. However, more than 200 symptoms have been reported [2,4].

As early as 2020, increasing numbers of case reports and small observational studies described long-term complications of coronavirus disease 2019 (COVID-19) following initial recovery from acute infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [5]. Initial reports described the prevalence of long COVID in 10-30% of patients with a recent history of SARS-CoV-2 infection, including pulmonary, renal, cardiovascular, immunological, hematological, neuropsychiatric, gastrointestinal, and dermatologic involvement, and chronic multisystem inflammatory syndromes in children and adults [5].

By 2022, the long-term clinical sequelae of SARS-CoV-2 infection in adults were recognized [6]. Also, children with asymptomatic or mild COVID-19 developed long-term symptoms, including fever, fatigue, and cough [7]. The pattern of the incidence and severity of some common childhood respiratory viruses was noted to have changed as the COVID-19 pandemic drove infectious hepatitis, respiratory syncytial virus (RSV), and adenovirus type 41 infection [7]. The terminology used for the long-term effects of SARS-CoV-2 infection varies, and the terms long COVID, post-COVID syndrome, and post-COVID-19 condition have been considered too simplistic [4,8]. There have been recommendations to replace the terminology with post-acute sequelae of SARS-CoV-2 infection (PASC) [2,4,8]. However, long COVID is still the most commonly used term (**Table 1**). In unvaccinated children and adults, some patients with severe COVID-19 developed an acute 'cytokine storm' up to four weeks following initial COVID-19, resulting in multiorgan damage due to hypercoagulation and vascular hyperpermeability [9]. This condition was identified as multisystem inflammatory syndrome in children (MIS-C) and multisystem inflammatory syndrome in adults [7]. Therefore, long COVID/PASC could represent a spectrum of hyperinflammatory diseases in terms of severity, duration, extent, and patient age [9]. There is no 'cure' for long COVID/PASC, and patients are managed symptomatically, requiring an individualized, multidisciplinary and holistic approach (**Table 2**) [1,2].

A current major concern is that many countries have now ceased recording cases of COVID-19. As of 18 August 2024, the World Health Organization (WHO) reported 238,416 cases of COVID-19 in the previous 28 days, representing an increase of 43,936 cases compared with the previous 28 days [2,3]. Systematic review and meta-analysis data had identified that up to 45% of patients who survived COVID-19 before 2023, regardless of hospitalization status, were experiencing a range of unresolved symptoms at 4 months [10]. It has become increasingly clear that patients who have recovered from symptomatic or asymptomatic SARS-CoV-2

Table 1. What's in a name? Current terminology and definitions.

Name	Definition	Attribution
Long COVID	Signs, symptoms, and conditions that continue or develop after initial SARS-CoV-2 infection and last more than 4 weeks	US Centers for Disease Control and Prevention (CDC). Department of Health and Human Services [1]
Post-acute sequelae of SARS-CoV-2 infection (PASC)	Ongoing, relapsing, or new symptoms or clinical conditions present at 30 or more days after SARS-CoV-2 infection	National Institutes of Health (NIH) Researching COVID to Enhance Recovery (RECOVER) Initiative [18]
Post-COVID-19 condition	Symptoms presenting 3 months from the onset of COVID-19 that last for at least 2 months and cannot be explained by other diagnoses	World Health Organization (WHO) [2]
Post-COVID syndrome	Symptoms that are unexplained by an alternative diagnosis and persist for more than 12 weeks after acute COVID-19	UK National Institute for Health and Care Excellence (NICE) [34]
Ongoing symptomatic COVID-19	Symptoms that are unexplained by an alternative diagnosis and persist for 4-12 weeks after acute COVID-19	National Institute for Health and Care Excellence (NICE) UK [34]

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Table 2. Current symptomatic treatment approaches for long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC) [1,2].

Symptom	Clinical features	Investigations	Management
Fatigue and post-exertional malaise	Fatigue that is not relieved by rest and is worse following stress or physical activity	History and examination with investigations to exclude treatable causes such as hypothyroidism, iron, B12, and folate deficiency, underlying malignancy, or ongoing chronic infections	Multidisciplinary and individualized 0holistic) symptomatic treatment, including using a diary to record symptom 'triggers' with rehabilitation and occupational therapy, if required
Chest pain and altered breathing patterns ('COVID squeeze')	Positional pain and pain on exertion with intermittent chest tightness	History and examination with investigations to exclude treatable causes, including ischemic heart disease, pericarditis, or pulmonary embolism	Multidisciplinary and individualized 0holistic) symptomatic treatment, including using a diary to record symptom 'triggers'
Exertional breathlessness	Shortness of breath associated with even mild physical activity	History and examination with investigations to exclude treatable causes, with lung function tests and lung imaging	Multidisciplinary and individualized 0holistic) symptomatic treatment, including using a diary to record symptom 'triggers'
Palpitations and dizziness ('COVID-induced autonomic dysfunction')	Symptoms associated with upright posture (orthostatic intolerance)	History and examination with investigations to exclude treatable causes, including blood pressure measurements and 24-hour ECG monitoring	Multidisciplinary and individualized 0holistic) symptomatic treatment, including using a diary to record symptom 'triggers'
Upper respiratory tract symptoms	Persistent sore throat, voice changes, and choking	History and examination with investigations to exclude treatable causes, including symptoms from gastroesophageal reflux disease and vocal cord pathology	Multidisciplinary and individualized 0holistic) symptomatic treatment, including using a diary to record symptom 'triggers'

infection can have long-term clinical complications, even in an era when vaccines and retroviral treatments are available [2]. According to current data, of the 675,619,811 people recorded as having recovered from COVID-19, the number of people with long COVID/PASC is unknown [2]. Almost five years from the beginning of the COVID-19 pandemic, this article aims to review what is currently known about long COVID/PASC, the anticipated increasing global health burden, and why there is still an urgent need to identify diagnostic biomarkers and risk factors to improve prevention and treatment.

Post-Acute Viral Infection Syndromes – a Historical Perspective

Several viral infections have known but rare post-acute syndromes of varying incidence and severity [11]. For example, following acute poliovirus infection and viremia, about 1% of patients develop paralytic poliomyelitis [12]. Poliovirus spreads to the central nervous system (CNS) and destroys motor neurons of the brainstem, spinal cord, and motor cortex, causing paralytic poliomyelitis [12]. Degrees of recovery vary with age at onset, the extent of CNS involvement, availability of supportive care, and proneness to complications, with younger patients being more capable of recovery [12]. Several decades after the polio epidemic, follow-up studies identified that between 25-40% of people who had recovered either fully or partially from poliomyelitis developed symptoms of motor neuron disease (MND) with features that were indistinguishable from sporadic motor neuron disease (MND) as a form of post-polio syndrome [12].

The 1917-19 global influenza pandemic ('Spanish flu') was associated with post-acute sequelae that included 'encephalitis lethargica' with symptoms of Parkinsonism and catatonia [13]. The 'Spanish flu' was caused by the H1N1 influenza virus [13]. Cases of encephalitis lethargica persisted in North America and Europe until 1929 [13]. In 2020, up to 2.5 million people in the US and 24 million people worldwide had myalgic encephalomyelitis (chronic fatigue syndrome) associated with herpesvirus and enterovirus infections [11]. In 2020, up to 1.9 million people in the

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US alone had post-treatment Lyme disease, which included neurological symptoms [14]. In 75% of patients who survive Ebola, fever, fatigue, and muscle aches persist for up to two years following infection [15]. Diarrhea and fatigue persist for up to a decade in up to 40% of people infected with *Giardia duodenalis* [16].

Long COVID/PASC in Adults – the Researching COVID to Enhance Recovery (RECOVER) Consortium

In 2023, the US National Institutes of Health (NIH) established the Researching COVID to Enhance Recovery (RECOVER) Consortium, a prospective longitudinal cohort initiative to study the long-term effects of COVID-19 [17]. As of 23 June, 2023, the RECOVER study enrolled 12,057 non-pregnant adults, 1,917 pregnant women, and 9,599 children with long-term symptoms after confirmed SARS-CoV-2 infection in 85 sites in 33 US states [17]. The study aimed to identify the symptoms present in SARS-CoV-2-infected individuals at six months or more after infection compared with uninfected individuals and to identify symptom-based criteria for PASC [17,18].

On 25 May, 2023, Thaweethai and colleagues reported the findings from data analysis of 9,764 adult participants in the RECOVER study [18]. There were 37 symptoms involving multiple systems identified as present more often in SARS-CoV-2-infected participants at six months than in uninfected participants [18]. The 9,764 study participants included 71% women, 16% Hispanic/Latino patients, and 15% non-Hispanic Black patients, with a median age of 47 years (range, 35-60 years) [18]. The most common symptoms included brain fog (64%), fatigue (85%), post-exertional malaise (87%), dizziness (62%), palpitations (57%), and gastrointestinal symptoms (59%), followed by chronic cough, change in smell or taste, changes in libido, thirst, chest pain, and abnormal movements [18]. Of 2,231 participants first infected with SARS-CoV-2 on or after 1 December, 2021, and enrolled within 30 days of infection, 10% (N=224) had long COVID/PASC at six months [18]. Among infected participants in the entire cohort, the proportions of PASC positivity were 39% (299/757) in hospitalized participants and 22% (1636/7387) in non-hospitalized participants during acute infection [18]. The proportions of long COVID/PASC positivity were 19% (442/2,377) in men and 25% (1,540/6,221) in women, 20% (885/4389) in patients aged 18-45 years and 28% (904/3175) in patients aged between 46-65 years [18].

In the RECOVER study data, four PASC cluster groups were identified [18]. Cluster 1 (N=477) included patients who reported changes in smell and taste (100%) [18]. Cluster 2 (N=405) included patients with post-exertional malaise (99%) and fatigue (84%) [18]. Cluster 3 (N=587) included patients with 'brain fog' or cognitive impairment (100%), post-exertional malaise (99%), and fatigue (94%) [18]. Cluster 4 (N=562) included patients with fatigue (94%), post-exertional malaise (94%), dizziness (94%), brain fog (94%), gastrointestinal symptoms (88%), and palpitations (86%) [18]. The heterogeneous nature of these long-term complications of COVID-19 is supported by findings from the National COVID Cohort Collaborative [19]. These findings highlight the importance of continued research to identify high-risk phenotypes and biomarkers for susceptibility to developing long COVID/PASC [4]. As of September 2024, more than 500 million people worldwide have now had COVID-19, which means that the long-term consequences of infection with SARS-CoV-2 will continue to have a significant health and economic impact worldwide [2,5,20].

Long COVID/PASC in Children and Adolescents – the RECOVER-Pediatric Consortium

Most long COVID/PASC studies have evaluated adults, and the long-term effects in children and adolescents have only recently been studied [21]. Identifying phenotypes of individuals at risk of developing long COVID/PASC and biomarkers are awaited [1,2]. However, recent studies in children and adolescents, using data from the RECOVER-Pediatric Consortium, have begun to develop and apply clinical indices of risk and outcomes [9,22,23].

In August 2024, Gross and colleagues reported the findings from a study of children (6-11 years) and adolescents (12-17 years) with and without a history of SARS-CoV-2 infection [22,23]. There were 898 school children with a mean age of 8.6 years (51% male), including 751 children with a previously confirmed SARS-CoV-2 infection and a non-infected control group of 147 children [22,23]. This study aimed to analyze the RECOVER-Pediatrics cohort data to identify common prolonged long COVID/PASC symptoms in children and adolescents (6-17 years old), how these symptoms differed by age group, how symptoms could cluster into phenotypes, and what combination of symptoms could be used to develop an index to identify and assess the risk of long COVID/PASC [22,23]. The study included 11% Black or African American children, 34% Hispanic, Latino, or Spanish children, and 60% Caucasian children [22,23]. Gross and colleagues also studied 4,469 adolescents with a mean age of 14.8 years (52% male), including 3,109 adolescents with a previously confirmed SARS-CoV-2 infection and a non-infected control group of 1,360 adolescents [22,23]. The study included 13% Black or African American adolescents, 21% Hispanic, Latino, or Spanish adolescents, and 73% Caucasian adolescents [22,23]. The median time between the first confirmed SAS-CoV-2 infection and the symptom survey was 506 days for school-age children and 556 days for the

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adolescents studied [22,23]. Data analysis identified 14 symptoms of long COVID/PASC in both children of school age and adolescents who had a confirmed history of COVID-19 when compared with the controls [22,23].

In the recent data analysis study from the RECOVER-Pediatric Consortium, symptoms of long COVID/PASC were shown to affect almost every organ system of children and adolescents [22,23]. Combinations of symptoms associated with a history of COVID-19 were identified to form a PASC research index for each age group [22,23]. There were 89 prolonged symptoms in nine symptom domains [22,23]. In children of school age, neurocognitive symptoms, pain, and gastrointestinal symptoms were associated with reduced quality of life [22,23]. In adolescents, pain, changes in smell or taste, and fatigue-related symptoms were associated with reduced quality of life [22,23]. Data clustering analyses identified four long COVID/PASC symptom phenotypes in children of school age and three long COVID/PASC symptom phenotypes in adolescents [22,23]. This study developed research indices for characterizing PASC in children and adolescents. Symptom patterns were similar but distinguishable between the two groups, children and adolescents. [22,23]. These recent data highlight the importance of characterizing long COVID/PASC separately for different age groups [22,23].

Recent Studies to Develop a Long COVID/PASC Risk Index

Recently, population data and electronic health record (EHR) data have been used to investigate clinical and demographic factors associated with the risk of developing long COVID/PASC [23,24]. However, these provisional study findings that aim to produce a PASC index await application and validation studies.

In 2023, Hill and colleagues published the findings of factors associated with long COVID/PASC using data analysis from the US National COVID Cohort Collaborative (N3C) Data Enclave platform that includes patients who have been tested for or diagnosed with COVID-19 and the US RECOVER Consortium [25]. This retrospective case-control study included 31 health systems in the US from the N3C and 8,325 individuals with long COVID/PASC matched to 41,625 controls [25]. Patients with long COVID/PASC were coded and identified using the International Classification of Diseases, version 10 (ICD-10) code U09.9, or by a recorded long COVID clinic visit [25l]. Recorded risk factors included demographics, comorbidities, acute symptoms, chronic comorbidities, and treatment with data analysis using multivariable logistic regression analysis, random forest analysis, and XGBoost to determine the associations between possible risk factors and long COVID/PASC [25]. Of the 8,325 individuals with long COVID/PASC, the majority were >50 years of age (56.6%), female (62.8%), and were non-Hispanic Caucasian (68.6%) [25]. Logistic regression analysis identified middle age of 40-69 years, female gender, hospitalization with COVID-19, a long hospital stay of 8-30 days or more, a requirement for mechanical ventilation, and several comorbidities including depression, chronic lung disease, and obesity were associated with increased risk of a diagnosis of long COVID/PASC [25]. Factors significantly associated with a lower risk of a diagnosis of long COVID/PASC included younger age of 18-29 years), male gender, non-Hispanic of Black race, and lack of comorbidities (including substance abuse, psychosis, dementia, and cardiomyopathy [25]. This national study identified important risk factors for the diagnosis of long COVID/PASC [25]. However, these findings require clinical and epidemiological validation and an increased understanding of the pathogenesis of long COVID/PASC. Also, the effects of vaccines and antiviral agents in changing the course of long COVID/PASC still await study.

Zang and colleagues recently aimed to characterize long-term COVID/PASC using the EHR data from two large Patient-Centered Clinical Research Networks (PCORnet) that include INSIGHT and OneFlorida+, with data from 11 million patients with a history of SARS-CoV-2 infection in the New York City area and 16.8 million patients in Florida, respectively [24]. Data analysis, including inverse probability of treatment weighting, identified factors associated with both increased and reduced risk of long COVID/PASC for patients 30-180 days after the laboratory-confirmed SARS-CoV-2 infection when compared to non-infected individuals [24]. This study identified more long COVID/PASC diagnoses in New York City than in Florida [24]. This study determined that dementia, pressure ulcers, hair loss, pulmonary fibrosis, pulmonary embolism, dyspnea, chest pain, cardiac dysrhythmias, malaise, and fatigue were risk factors replicated in both cohorts [24]. These findings differ from those identified in other population or EHR-based studies and highlight the potentially heterogeneous risk factors for long COVID/PASC in different populations [24].

Cardiovascular Disease and Long COVID/PASC

Cardiovascular disease was one of the first recognized acute and long-term effects of SARS-CoV-2 infection and is an example of a category of long COVID/PASC that does not conform to current risk indices. In 2020, the effects of COVID-19 on the cardiovascular system began to be realized [26]. SARS-CoV-2 enters infected host cells following the binding of the viral spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor [27,28]. The ACE2 receptor is expressed by endothelial cells, cardiac myocytes, and vascular smooth muscle cells [27,28]. By February 2022, Lu and colleagues reported the findings from a large US cohort of patients diagnosed with COVID-19 and control cohorts to evaluate the effects on

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the cardiovascular system at 12 months [29]. The study group with a history of confirmed COVID-19 had a 72% increased risk of a diagnosis of heart failure, a 63% increased risk of myocardial infarction (MI), and a 52% increased risk of ischemic stroke when compared with the control group [29]. These results were independent of race, gender, age, and cardiovascular risk factors, including hypertension, hyperlipidemia, diabetes, and obesity [29]. Similar findings were reported in February 2022 by Xie and colleagues, who studied data from the US Department of Veterans Affairs database that included a cohort of 153,760 individuals diagnosed with COVID-19 between March 2020 and January 2021 and included two control cohorts [30]. Xie and colleagues identified that at 30 days after confirmed SARS-CoV-2 infection, there was a significantly increased risk of myocarditis, cerebrovascular disease, dysrhythmias, pericarditis, ischemic and non-ischemic heart disease; thromboembolic disease and heart failure [30]. Individuals who had COVID-19 had an increased risk of heart failure (72%), myocardial infarction (63%), and an increased risk of ischemic stroke (52%) when compared with controls [30]. These results were independent of patient gender, race, age, and other cardiovascular risk factors [30]. Importantly, the risk and disease burden were significantly increased even for non-hospitalized individuals during the acute phase of SARS-CoV-2 infection [30].

Biomarkers for Long COVID/PASC

Currently, there are no validated clinical biomarkers for long COVID/PASC, and it does not look likely that any will be identified [2,3,31]. In August 2024, Erlandson and colleagues RECOVER-Adult cohort participants with or without SARS-CoV-2 infection with a study visit and laboratory measures six months after the index date (or at enrolment if >6 months after the index date) [31]. Participants were excluded if the six-month visit occurred within 30 days of reinfection [31]. Among 10 094 participants, 8746 had prior SARS-CoV-2 infection, 1348 were uninfected, 1880 had a PASC index of 12 or higher, and 3351 had a PASC index of zero [31]. After propensity score adjustment, participants with prior infection had a lower mean platelet count (265.9×10^9 cells/L [95% CI, 264.5-267.4×10^9 cells/L]) than participants without known prior infection (275.2×10^9cells/L [CI, 268.5-282.0×10^9 cells/L]), as well as higher mean hemoglobin A1c (HbA1c) level (5.58% [CI, 5.56-5.60%] vs 5.46% [CI, 5.40-5.51%]) and urinary albumin-creatinine ratio (81.9 mg/g [CI, 67.5-96.2 mg/g] vs 43.0 mg/g [CI, 25.4-60.6 mg/g]) [31]. Although differences were of modest clinical meaning among participants with prior infection, no significant differences in mean laboratory values were found between those with a PASC index of 12 or more and those with a PASC index of zero [31]. Importantly, there was no evidence that the 25 routine clinical laboratory values assessed in this study could be a clinically useful biomarker of long COVID/PASC [31].

Future Directions to Address Unmet Needs

The treatment of long COVID/PASC requires a multidisciplinary approach that is individualized to the many and varied types and degrees of clinical effects (**Table 2**) [32]. In 2023, McCorkell and Peluso, writing in the journal *Nature*, emphasized the loss of momentum in research to identify biomarkers, risk factors, and effective treatment and prevention strategies for long COVID/PASC [32]. Research on long COVID/PASC needs more coordination and a collaborative multidisciplinary approach to research and patient management [32]. There are few clinical trials for evaluating interventions, a need for more momentum for implementing clinical trials, and a lack of long-term resourcing that should be addressed [32]. McCorkell and Peluso proposed that the US Government invest at least US$1 billion annually over the next ten years to focus on long-term COVID/PASC research, as they did in 2016 when more than $1.8 billion was allocated to the 21st Century Cures Act, mainly for cancer research [32]. According to the US CDC, around 6% of US adults are experiencing symptoms of long COVID/PASC [1]. There have also been estimates that 18 million adults in the US [2] and 65 million people worldwide are affected by long COVID/PASC [7]. In the US alone, the economic burden of long COVID/PASC is estimated to be $3 trillion over the next five years [20].

Ongoing research in the US, South Africa, and the UK has shown that SARS-CoV-2 can alter clotting proteins and induce autoimmune reactions [7]. SARS-CoV-2 can alter mitochondrial function, which might explain why many people with long COVID/PASC experience fatigue and malaise [7]. There is also evidence that SARS-CoV-2 is not a transient viral infection, as viral fragments can be found in the body for more than six months after the initial infection [33].

McCorkell and Peluso have suggested six main priorities for research and development in long COVID/PASC [32]. First, there still needs to be more agreement on the definition, terminology, and distinction from long-term comorbidities (**Table 1**) [32]. Second, more collaborative and multidisciplinary research and clinical teams are required [32]. Third, curate data from the early years of the COVID-19 pandemic, including the effects of SARS-CoV-2 variants, reinfections, and the number, timing, and types of SARS-CoV-2 vaccine doses [32]. Fourth. Accelerate research on biomarkers or combinations for long COVID/PASC [32]. Fifth, invest in preclinical and clinical research and clinical trials [32]. Currently, of 240 trials classed as interventional, only 91 are recruiting, and only 12 are testing pharmacological interventions [32]. Finally, McCorkell and Peluso recommend that diverse populations seeking care should be involved in research programs to ensure that any treatment advances are delivered to patients in the clinic [32].

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Conclusions

No phenotypic or diagnostic biomarkers have been identified for developing long COVID/PASC. This multisystem disorder can present with isolated or combined respiratory, hematological, cardiovascular, and neuropsychiatric symptoms. Therefore, individualized patient management requires a multidisciplinary clinical approach. Because millions of people have had and continue to have COVID-19, even in the era of vaccination and antiviral therapies, long COVID/PASC is now and will increasingly become a health and economic burden that the world must prepare for.

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