Post COVID-19 Vaccination Chronic Injuries – Proposed Action

From: The Advisory Committee on Immunization Practices (ACIP) COVID-19 Immunization Workgroup

To: ACIP

This report was prepared by the ACIP COVID-19 Immunization Workgroup as part of its support of the ACIP work. It reviews published and unpublished information and knowledge related to chronic injuries post COVID-19 vaccination and SARS-CoV-2 infection and highlights related findings and proposed voting language of potential recommendations for further consideration and deliberations by ACIP.

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I. Report Summary

In a recent public survey, over a third of those acknowledged to be vaccinated against COVID-19 reported that they had experienced side effects, with 10% of those reporting major side effects (1). In another public survey, 24% of the participants reported that they knew someone who died from the adverse effects of COVID-19 vaccination (2). The sentiment emerging from these public surveys contrasts sharply with CDC's current public communications, which formally recognize only a limited set of rare, acute adverse events as being associated with COVID-19 vaccines, specifically, myocarditis, pericarditis, and anaphylaxis from the mRNA vaccines, and Guillain-Barré syndrome and thrombosis with thrombocytopenia syndrome (TTS) from the adenovirus-based vaccines (3).

In addition to the acute conditions that CDC has identified as associated with COVID-19 vaccination, numerous clinical studies document cases of severe, disabling chronic syndromes, often termed as *post-acute-COVID-19-vaccination syndrome* (PACVS). Patients suffering from PACVS present with heterogenous, prolonged symptoms that typically involve multiple organ systems, many of which overlap with chronic post SARS-CoV-2 infection syndrome, often referred to as *Long-COVID* (4). While the exact clinical definition and incidence of PACVS are not well characterized, existing prevalence estimates range from 0.003% of the general population to 0.9% of young and middle-aged persons (5).

Despite growing evidence including extensive patient and clinician testimonials, CDC and other public health agencies in the US do not currently recognize the existence of patients with PACVS. The US lacks an effective framework—supported by adequate pharmacovigilance and clinical infrastructure — to systematically recognize, diagnose, and longitudinally monitor chronic conditions arising post COVID-19 vaccination. The absence of diagnosis codes, diagnostic guidelines, awareness among healthcare providers, and appropriate pharmacovigilance surveillance systems have resulted in systematic under-recognition and under-reporting of PACVS. Consequently, there are only sparse data and limited knowledge on the epidemiology and clinical mechanisms of PACVS. Moreover, many vaccine-injured and particularly patients suffering from PACVS do not receive appropriate care and current vaccination policies underestimate true individual risks while overestimating the respective benefits. Indeed, many patients who experienced and reported PACVS-related symptoms after the first vaccine dose were advised - and sometimes even pressured - to continue vaccination with additional doses, causing rechallenge and significant worsening of their symptoms. These experiences undermine public trust.

This report is written with a sense of urgency. Immediate actions must be taken to rectify the failure to recognize and track PACVS, to acknowledge the individuals injured following CDC vaccination recommendations, and to actively promote data collection, analysis, reporting, and clinical development of pathways for care. This is fundamental and necessary to regain public trust in vaccination programs that have moral and bioethical obligation for solidarity, justice, and equity.

This report reviews existing published and unpublished literature related to PACVS and incorporates extensive input from PACVS patients and front-line physicians. It aims to provide a comprehensive analysis of the current systematic challenges faced by patients and physicians. The report then outlines several proposed operational recommendations and related voting language, for consideration and deliberation by ACIP, that are foundational to establishing the necessary pharmacovigilance and clinical infrastructures required to address the immediate needs of the COVID-19 vaccine injured, and transform the way related vaccine injuries are identified, monitored, and cared for. However, meaningful progress also requires a fundamental paradigm mindset change in how health authorities, the medical and scientific community, the media, and our society recognize, identify, and treat the vaccine injured. Those with vaccine injuries often suffer from systematic under-recognition by medical providers, suppression, abandonment, labeling as 'antivaxxers', and assertions that they 'imagine their injuries' or suffer from 'functional' disorders - a euphemism for psychosomatic symptoms.

The proposed recommendations for consideration by ACIP, outlined in this report, address three critical and interrelated domains that together form a cohesive framework for diagnostic classification, clinical guidance, research, and surveillance:

Proposed Recommendation I for consideration by ACIP: Establish comprehensive ICD-10 diagnosis codes for PACVS by domestically adopting the existing code instituted by the World Health Organization (WHO) in 2021 and creating additional codes that parallel the current coding system for Long-COVID. (See Section III.)

Proposed Recommendation II for consideration by ACIP: Develop diagnostic guidelines and training materials for medical providers to improve the diagnosis and clinical management of individuals with PACVS and Long-COVID. (See Section IV.)

Proposed Recommendation III for consideration by ACIP: Establish an international network of excellence centers focused on Long-COVID and PACVS, coordinated by CDC. This network will enable knowledge sharing, as well as research and development related to diagnosis, diagnostics, therapeutics, and best clinical practices for treating these syndromes. Additionally, the network should facilitate the implementation of the active surveillance systems required to support these objectives. (See Section V.)

II. Post-acute-COVID-19-vaccination syndrome (PACVS)

This section provides a review of published and unpublished literature related to PACVS, including testimonial and reports from patients and clinicians. Notably, the knowledge on PACVS is still evolving and significant knowledge gaps still exist. Long-COVID and PACVS are complex multisystem syndromes where multiple symptoms associated with different organ systems have been identified, with a wide range of phenotypes and presentations.

To align more closely with the current definition of Long-COVID, the definition of PACVS used in this report requires symptoms persisting for at least 12 weeks after vaccination that cannot be explained by other causes. The complexities of diagnosis and treatment of Long-COVID and PACVS are analogous to the diagnostic and treatment challenges historically faced by physicians diagnosing, managing, and treating multi-organ pathophysiology associated with Tuberculosis, HIV-AIDS, and Lyme disease. Studies have shown that symptoms and new onset of PACVS disease states mostly appear within days after vaccination but could potentially also appear weeks or even (in rare cases) months after vaccination (6–10). These persistent, unexplained post -vaccination symptoms have been observed and described across all types of COVID-19 vaccines in published case reports, and many of these patients do not recover, even with supportive care (11,12).

Across peer-reviewed literature and pharmacovigilance reports from multiple nations, patients, clinicians, and researchers describe persistent post-vaccination multi-organ symptom clusters involving neurologic, cardiovascular, immunologic, endocrine, pulmonary, gastrointestinal, and autonomic systems (13–17). Documented complications include neuropathies, dysautonomia, cognitive impairment, immune dysregulation, complement activation, chronic fatigue, type 1 diabetes, gastrointestinal, neuro-endocrine, and autoimmune presentations, myocarditis, vaccine-induced thrombotic thrombocytopenia (VITT), venous and arterial thromboembolism, and other thrombophilia associated with clotting (6,14,18–25) .

PACVS is a heterogenous syndrome with diverse presentations. The typical pattern of multi-organ system involvement in this syndrome may be consequent to a cascade of dysregulated pathophysiological mechanisms (26,27). Consistent with this, survey and clinical cohort data suggest high healthcare utilization, prolonged impairment, and recurrent symptoms after vaccination, with many patients experiencing exacerbation of symptoms after subsequent doses (28). Studies and clinical experience have shown that Long-COVID and PACVS syndromes often evolve and change over time, which supports a hypothesized multi-organ dysregulation cascade (29).

In addition to the generalized symptoms observed in PACVS, several studies have also reported evidence indicative of multi-system syndromes that align with existing medical diagnoses, most notably small fiber neuropathy (SFN), postural orthostatic tachycardia syndrome (POTS), and myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) (30). Accordingly, there is need to identify subpopulations that might be more susceptible

to post-vaccine adverse effects, including those with pre-existing conditions, as well as those with certain demographic or genetic traits.

Accumulating evidence demonstrates a consistent pattern in which PACVS is associated with immune dysregulation and autoimmune mediated mechanisms. Correspondingly, multiple studies suggest that early recognition and appropriately targeted immunomodulatory treatment may improve clinical outcomes (12,23,31–34). In parallel, emerging data raise concerns regarding the potential pathogenic role of persistent biologically active vaccine-encoded spike protein or spike protein fragments in a subset of patients (26). Prolonged exposure to cell-associated and circulating spike-derived antigens as well as biologically active spike protein may contribute to the observed sustained immune activation, endothelial dysfunction, dysautonomia, and autoimmune phenomena, thereby perpetuating symptoms beyond the expected post-vaccination period. In the absence of supporting diagnosis codes and diagnostic criteria, it is challenging to conduct appropriate studies to substantiate these hypotheses regarding the involvement of chronic spike expression, and the currently limited available data have not supported the correlation with spike protein load and PACVS symptom burden (26,35).

Ongoing work seeking to characterize the clinical signatures of both Long-COVID and PACVS reports significant symptom overlap between these syndromes, suggesting similarities grounded in shared pathophysiology or with other prolonged inflammatory conditions (4). A common feature to both is patient exposure to endogenously-produced SARS-CoV-2 spike protein (35,36). Furthermore, it is possible that Long-COVID and PACVS represent heterogenous phenotypes that may require different clinical treatment protocols. For example, there is variable evidence regarding the impact of further COVID vaccination on Long-COVID patients. Patient surveys indicate that the COVID vaccines have no effect on Long-COVID symptoms for most patients (13,37,38), whereas other literature indicates that 12-29% of individuals with pre-existing Long-COVID may develop symptom amplification following COVID vaccination (13,37,39), while in one survey, more than half of respondents noted symptom improvement after COVID vaccination (38). The potential link between recurrent vaccination (rechallenge) and worsening (or improvement) of underlying illness needs to be consistently corroborated by robust epidemiological data (40).

Challenges Faced by Patients

Unfortunately, patients with PACVS often experience delayed diagnosis, misdiagnosis or diagnostic uncertainty. Consequently, PACVS patients rarely receive appropriate medical advice and care. Moreover, many patients and clinicians face months of repeated insurance denials and appeals, as medically necessary diagnostic evaluations and therapeutic interventions are routinely classified as off label.

There are several factors that contribute to repeated failures to clinically recognize, diagnose and treat presenting PACVS complaints (41).

First, the multi-symptom and multi-organ system involvement implies that PACVS does not fall into a well-defined discipline and specialty of medicine, and most physicians lack the awareness, training and diagnostic categories that would enable them to recognize the clusters of symptoms associated with PACVS. Moreover, patients with different initial symptoms may end up being seen by different specialists consequent to the current fragmented domestic medical system and therefore, receive no diagnosis or a different, often inappropriate, diagnosis reflecting biases inherent in different medical specialties (42–44).

Second, PACVS rarely fits into currently used diagnosis codes. The absence of appropriate ICD-10 diagnosis codes and limited experience of medical providers with this new syndrome further contribute to delays in diagnosis, difficulty in surveillance, and deleterious further vaccination. As a result, it is typical that PACVS patients often see many medical providers and face significant access barriers to subspecialty referral and appropriate therapeutics. This lack of accepted and socialized diagnosis codes and guidelines creates significant obstacles to recognition of disease, development of diagnostics, therapeutic advancement, and establishment of epidemiologic characterization of incidence and prevalence.

Third, another challenge to appropriately diagnose and document PACVS-related injuries is the fact that many of the symptoms PACVS patients experience overlap with commonly observed short-term post vaccination side effects. In particular, the current codes and surveillance cannot capture the fact that in PACVS patients, these symptoms may persist for prolonged periods of time (5).

Fourth, the inability of current diagnostic frameworks, routine testing technologies, and surveillance systems to identify persistent biological drivers—such as ongoing immune activation or antigen persistence—limits timely intervention and may allow potentially reversible immune-mediated injury to progress unchecked to chronic dysregulation. This problem further underscores the need for standardized diagnostic criteria, biomarker-guided evaluation, and evidence-informed treatment pathways.

Existing pharmacovigilance surveillance systems are inadequate to capture cases of PACVS due to gross under-reporting of vaccine injuries and because these systems primarily monitor and detect acute adverse events only, often neglecting long-term adverse effects (45). A recent survey among vaccine injured showed that only 11% of physicians logged the required adverse event reports to VAERS for COVID vaccine injuries. Of this subset of physician-observed events, 61% were published correctly, 22% were not visible and 12% were deleted (46).

It is critical to establish appropriate diagnosis codes, as well as standardized diagnostics guidelines and appropriate evidence-informed treatment guidelines, knowledge sharing, research and development, and surveillance infrastructures. Without those, PACVS patients will remain invisible within the healthcare system, hindering recognition, care coordination, disability assessments, epidemiological tracking, and research.

III. ICD-10 Codes for PACVS

ICD-10-CM codes are essential for identifying, documenting, and tracking emerging health conditions. The US demonstrated leadership in this process with the adoption of '*U09.9 – Post COVID-19 condition'*, which enabled clinicians and researchers to systematically recognize Long-COVID even before consensus definitions were fully established. Early implementation of U09.9 improved case identification, facilitated disability and reimbursement pathways, supported research cohort development, enabled access to therapeutics, and strengthened public health surveillance.

A comparable infrastructure is urgently needed for patients experiencing persistent (chronic), multi-organ symptoms following COVID-19 vaccination. Under current US ICD-10-CM, coding of COVID-19 vaccine injuries relies on the general code '*T50.B95A - adverse effect of viral vaccines'*, which is nonspecific, limited to initial encounters, and inadequate for coding chronic or delayed sequelae. In practice, the absence of specific diagnosis codes prevent clinicians from accurately documenting PACVS, restricts access to appropriate diagnostic evaluations, and results in routine insurance denial of medically necessary therapeutics due to "off-label" classification. Moreover, patients with prolonged post-vaccination adverse conditions lack a diagnostic home, and the US currently lacks reliable surveillance data on these conditions. Consequently, many patients remain untreated or experience months-long delays in care despite persistent, function-limiting symptoms.

In contrast, in January 2021 the WHO instituted '*U12.9 – COVID-19 vaccines causing adverse effects'* in therapeutic use, which since then has been implemented by multiple countries. Germany's adoption of U12.9 enabled the characterization and formal recognition of PACVS, including population-level analyses not currently feasible in the US under current coding conventions. Comparable coding is needed for harmonization with international surveillance and to correct the present documentation gap in the US.

Without appropriate diagnosis codes, the US operates in a negative feedback loop exacerbating the problem:

1. No diagnosis codes exist;
2. Clinicians cannot reliably document or justify PACVS-related care;
3. Diagnostic testing and therapeutics are denied by insurers as off-label or non-covered;

4. Cases fail to appear in surveillance systems and no systematic research is conducted;
5. The related conditions and adverse events are perceived by regulatory agencies as rare or non-existing— reinforcing bias towards "functional" diagnoses and the absence of coding, clinical guidelines, recommended care pathways, and research to better understand the condition and develop effective therapies.

As mentioned above, the US has already demonstrated the feasibility and utility of adopting a new U-code for a novel post-infectious condition (U09.9). The same logic and public health justification apply to PACVS. Establishing dedicated diagnosis codes is a prerequisite for timely recognition, equitable access to care, appropriate therapeutic coverage, accurate surveillance, damages compensation, and responsible stewardship of vaccine safety monitoring.

Proposed ICD-10-CM Codes

Building on the WHO standards, and to enable full documentation of both acute and chronic presentations of adverse reaction post vaccination, the proposed recommendation is that CDC adopt the following:

- U12.90 – COVID-19 vaccines causing adverse effects in therapeutic use, unspecified (Parallel to WHO U12.9 for international harmonization.)
- U12.91 – Chronic condition following COVID-19 vaccination (a new code to capture Post Covid-19 vaccine chronic syndrome)

Similarly to the existing coding system for Long-COVID (U09.9), these codes should be paired with specific secondary manifestation ICD-10 codes when appropriate. Examples (not all-inclusive) include:

- G90.x – Autonomic disorders (e.g., dysautonomia/POTS)
- G62.x – Polyneuropathies (including small fiber neuropathy)
- R53.82 – Chronic fatigue
- I40.9 / I51.4 – Myocarditis
- H93.1 – Tinnitus
- G89.29 – Chronic pain
- D89.40 – Mast cell activation
- D89.9 – Disorder involving immune mechanism
- D68.69 – Other thrombophilia
- I77.9 – Disorder of arteries and arterioles, unspecified
- I87.2 – Venous disease
- Z15.89 – Genetic susceptibility to other disease
- M31.10 –Thrombotic micro angioplasty unspecified
- I20.89 – Non-coronary chest pain

For example, a case of a patient with PACVS who suffers from neuropathy, chronic fatigue and micro-clotting will be coded in the following manner:

- Primary: U12.91 – Chronic condition following COVID-19 vaccination
- Secondary: G90.1 (POTS), G62.81 (small fiber neuropathy), R53.82 (chronic fatigue), D89.40 (MCAS), D68.8 (micro-clotting)

Benefits of Implementation

Surveillance. Prospective and retrospective implementation of dedicated diagnosis codes will enable more accurate assessment of the prevalence of PACVS cases, recognition of temporal patterns, severity tracking, and early signal detection—capabilities currently impossible in the US.

Clinical care coordination. Standardized documentation can guide appropriate referrals, provide a framework for diagnostic evaluations, support clinical decision-making, and prevent harmful recommendations such as continued vaccination during stable or evolving adverse events. It will accelerate the clinician's ability to optimize therapeutic recommendations.

Disability, reimbursement, and patient support. Injured patients currently face major administrative barriers. A diagnosis code enables appropriate insurance processing, disability assessment, and access to evidence-based care.

Research acceleration and international harmonization. Coding enables cohort building, database linkage, and comparability between the US and international pharmacovigilance systems.

Conclusion and Proposed Recommendations

A growing body of clinical and scientific evidence, WHO precedent, international adoption, and established US coding for Long-COVID (U09.9) all support the implementation of a structured ICD-10-CM framework for post-COVID-19 vaccination conditions. Adoption of U12.90 and the addition of U12.91 (see above) are necessary to ensure accurate documentation, improve patient outcomes, enhance epidemiologic insight, and harmonize US surveillance with global standards.

Proposed voting language for Recommendation I for consideration by ACIP: CDC is recommended to establish comprehensive ICD-10 diagnosis codes for PACVS by adopting the existing U12.90 code instituted by the World Health Organization (WHO) in 2021 and a new code U12.91 code for chronic conditions parallel to the existing U09.9 system for Long-COVID.

IV. Post-Acute COVID-19 Vaccination Syndrome (PACVS) and Long-COVID: Guiding Principles of Diagnostic Framework

Background

The experience with vaccine-associated myocarditis illustrates the consequences of delayed recognition and the importance of diagnostic guidelines. Prior to FDA/CDC formal recognition and dissemination of diagnostic guidelines, cases were commonly missed, including fatalities (47–49). Once agencies issued guidance and clinicians were instructed to look for the pattern, cases were rapidly identified nationwide. Recognition improves safety and transparency—not only for affected individuals but for the entirety of the vaccination program.

Post-Acute COVID-19 Vaccination Syndrome (PACVS) and Long-COVID represent novel, complex, multisystem conditions characterized by neurologic, immunologic, endocrine, metabolic, autonomic, and vascular dysregulation following exposure to COVID-19 vaccination or the SARS-CoV-2 virus.

PACVS and Long-COVID are not characterized by a single biomarker, isolated organ pathology, or uniform clinical presentation. Instead, they represent heterogeneous clinical syndromes involving commonly measurable abnormalities that may vary among individuals, evolve over time, and fall outside traditional diagnostic reference ranges.

This section and corresponding appendices present an initial proposal of guiding principles and a preliminary diagnostic framework to support the systematic evaluation and management of affected patient populations. It is offered merely as an initial conceptual model, with the understanding that final and formal diagnostic guidelines will have to be developed over time through CDC's established processes and with the broad engagement of relevant stakeholders, extensive clinical validation, and cost-effectiveness considerations.

Clinical Presentation

Initial vaccine exposure may be associated with:

- No acute reaction
- Mild transient systemic symptoms
- On-going severe inflammatory or neurologic responses

Importantly, absence of an acute adverse reaction does **not** exclude subsequent development of PACVS. Symptom onset may occur immediately, within days to weeks, or after a delayed asymptomatic interval, like what has been observed in Long-COVID patients.

Symptoms may be intermittent or persistent, mild or severe, and frequently worsen with exertion or physiological stress. Caregivers should be aware of the range of symptoms involved with PACVS and Long-COVID. Common manifestations include:

- Post-exertional symptom exacerbation
- Persistent fatigue
- Cognitive impairment (“brain fog”)
- Difficulty with concentration or memory
- Headache or migraine
- Lightheadedness, presyncope, or tachycardia
- Sleep disturbance
- Dyspnea or air hunger
- Chest discomfort or palpitations
- Autonomic instability
- Gastrointestinal dysfunction (bloating, constipation, diarrhea)
- Altered taste or smell

PACVS and Long-COVID may manifest as new-onset disease, exacerbation of previously stable conditions, or unmasking of underlying susceptibility:

<u>Neurologic</u>

- Cognitive impairment
- Migraine disorders
- Mood and neuropsychiatric symptoms
- Small fiber neuropathy
- Central and peripheral neuroinflammation
- Autonomic
    - Postural orthostatic tachycardia syndrome (POTS)
    - Orthostatic intolerance
    - Hypocapnia with cerebral hypoperfusion
    - Other dysautonomias

<u>Immune-Mediated and Inflammatory Disorders</u>

- Mast cell activation syndrome
- Autoimmune disease (e.g., lupus, Sjögren’s syndrome, rheumatoid arthritis)
- Complement system dysregulation
- Persistent immune activation or immune exhaustion
- Immune deficiency (e.g., specific antibody deficiency)

<u>Cardiovascular and Vascular</u>

- Cardiac arrhythmias

- Endothelial dysfunction
- Microvascular ischemia
- Micro-thrombotic disease

Pulmonary

- Hypoxemia
- Impaired oxygen extraction
- Inflammatory or interstitial lung disease

Renal

- New or worsening chronic kidney disease

Metabolic and Endocrine

- Mitochondrial dysfunction
- Hyperlipidemia and insulin resistance
- Hormonal dysregulation

Contrary to assertions that PACVS lacks objective findings, reproducible abnormalities have been documented when appropriate diagnostic tools are employed, including:

- Complement system abnormalities
- IgG subclass deficiencies
- T-cell exhaustion and persistent immune activation
- Immunofluorescent fibrin micro-clot imaging
- Endothelial dysfunction testing (e.g., EndoPAT)
- Tilt-table testing demonstrating hypocapnia and cerebral hypoperfusion
- Reduced intraepidermal nerve fiber density on skin biopsy
- Elevated neurofilament light chain
- Persistent circulating spike protein or immune complexes
- Abnormal monocyte and lymphocyte phenotyping
- Mitochondrial metabolic derangements

Abnormalities involved with Long-COVID and PACVS are dynamic and often fluctuate over time, which implies that they may not be appropriately captured in a single snapshot. For example, cytokines, complement activity, mast cell mediators, coagulation markers, and immune cell phenotypes may vary with exertion, orthostatic stress, infection, repeat vaccination, or re-exposure, as well as hormonal cycling and exposure to medications (4,50–53).

Pathophysiologic Overview

Emerging clinical and translational evidence indicates that PACVS and Long-COVID are frequently driven by overlapping biological mechanisms, including:

- Immune dysregulation with concurrent hyper- and hypo-immune activity (6,54–57).
- Persistent antigen exposure or immune-complex signaling (58–61).
- Endothelial injury and microvascular dysfunction (62–69).
- Fibrinolysis-resistant fibrin amyloid micro-clots (70–73)
- Autonomic nervous system instability (74,75)
- Small fiber neuropathy identifiable by skin biopsy or QSART despite normal EMG/NCS (10,76,77).
- Secondary mitochondrial dysfunction and impaired cellular energetics (78–82).
- Neuroinflammation and microglial activation (83,84).

These processes predominantly occur at the **microvascular, cellular, and molecular level**, rather than as overt organ failure. Consequently, abnormalities are often not detected by existing routine laboratory testing or standard imaging modalities, and there is a need to identify diagnostic gaps, and correspondingly develop and clinically validate new diagnostic modalities. In the process of developing diagnostic guidelines, it is important to accept these advanced diagnostic tools and modalities as **clinically legitimate** as part of the needed exploratory process, even prior to comprehensive validation and dissemination into standard diagnostic and care pathways.

Primary Phenotype Domains

Evaluation should be guided by dominant clinical phenotypes, recognizing that overlapping across systems is common:

<u>Immunological</u>

- Hyperimmune activation (mast cell activation, autoimmunity, complement activation)
- Hypoimmune dysfunction (specific antibody deficiency, impaired innate signaling—TLR3)
- Mixed phenotypes may coexist

<u>Neurologic</u>

- Autonomic dysfunction
- Small fiber neuropathy
- Neuroinflammatory syndromes

Microvascular / Thrombotic

- Endothelial dysfunction
- Micro-clot pathology

Metabolic

- Mitochondrial dysfunction
- Microbiome dysbiosis
- Micronutrient deficiencies
- Hormonal dysregulation

The presence of objective abnormalities in **any single domain** is sufficient to establish biological disease, even if other domains appear normal.

Role of Genetic Predisposition

Clinical experience and emerging evidence indicate that genetic susceptibility significantly influences disease expression, severity, and response to injury. Relevant modifiers include:

- Thrombophilia variants (e.g., PAI-1, Factor V Leiden, Prothrombin mutation)
- MTHFR variants affecting methylation and endothelial function
- HLA haplotypes influencing immune persistence and autoimmunity
- APOE genotype affecting neuroinflammatory vulnerability
- Hypermobility spectrum disorders and Ehlers–Danlos syndromes

Genetic testing may therefore serve an important role in risk stratification and phenotype explanation.

Principles for Diagnostic Evaluation

PACVS and Long-COVID may be diagnosed when symptoms or objective abnormalities are:

- Continuously or intermittently present for **at least 12 weeks**, and
- Either continuous from vaccination or delayed in onset.

Diagnostic guidelines should incorporate the following principles:

1. Absence of a single abnormal test does not exclude disease.
2. Normal routine laboratory results do not rule out immune, microvascular, autonomic, or mitochondrial pathology.

3. Advanced diagnostics, including ones currently not commercialized, are frequently required to identify objective disease correlates. It is likely that new diagnostic modalities will have to be developed, clinically validated, and made accessible over time.
4. Phenotype-driven, mechanism-based testing represents the preferred diagnostic standard.
5. Repeat testing, functional assessments, and provocation-based studies should be permitted when clinically indicated.

PACVS and Long-COVID share mechanistic overlap with recognized immune-mediated and post-infectious conditions—including vasculitis, autoimmune encephalitis, antiphospholipid syndrome, mitochondrial disease, dysautonomia, and mast cell activation disorders—where pattern recognition across clinical, laboratory, and imaging data is standard practice. PACVS and Long-COVID should therefore not be considered a diagnosis of exclusion.

Clinical and Public Health Implications

PACVS and Long-COVID can affect children and adults regardless of age, sex, socioeconomic status, disability, race, ethnicity, or geographic location. Symptoms may be resolved over months or persist for years and may substantially impair occupational function, educational participation, and activities of daily living.

Failure to develop and adopt an expanded diagnostic framework is likely to cause:

- Systematic underdiagnosis
- Misclassification as psychiatric or functional illness
- Delayed or denied care
- Psychological harm and stigmatization
- Continued exposure to biological triggers
- Potential progression to irreversible organ injury

Given the evolving scientific understanding and heterogeneity of PACVS and Long-COVID, diagnostic standards should prioritize clinical inclusion rather than exclusion, with flexibility to adapt as evidence advances. Appendices IA and IB illustrate the complexity of PACVS and Long-COVID presentations, demonstrate how standard evaluations may initially appear unrevealing, and highlight how advanced, mechanism-directed testing can identify underlying pathology and guide targeted therapeutic decision-making.

Conclusions and Proposed Recommendation

There is a critical clinical and ethical need for standardized, mechanism-informed diagnostic guidelines for Post-Acute COVID-19 Vaccination Syndrome and Long-COVID.

Guidelines should:

- Recognize PACVS and Long-COVID as a multisystem biological condition.
- Develop, clinically validate, and make accessible advanced and functional diagnostics.
- Support phenotype-driven evaluation.
- Permit repeat and dynamic testing.
- Incorporate genetic risk stratification.
- Be updated regularly as scientific evidence evolves.

Proposed voting language for Recommendation II for consideration by ACIP:
CDC is recommended to develop and disseminate formal diagnostic guidelines and clinician training materials to improve recognition, evaluation, and management of individuals with PACVS and Long-COVID.

V. Clinical and Pharmacovigilance Infrastructure

Existing COVID-19 Vaccine injury and Long-COVID surveillance and research do not address many concerns of patients. In particular, these concerns include prolonged multi-symptom cases or events (e.g., dysautonomia, immune dysregulation, severe cutaneous reactions like bullous pemphigoid, dysmenorrhea, and others). A new approach involving specialized care facilities, organized within a well-coordinated network, is needed for developing and implementing expert diagnosis, treatment, surveillance, and study of post vaccination adverse events and Long-COVID.

This approach can improve vaccine confidence as patients would have a place to be systematically evaluated with designated clinical infrastructure, where diagnostics and treatments can be successfully trialed. Over time, standardized treatment approaches can be developed, and new methods can be effectively evaluated compared to the standards. Existing clinical infrastructure and local expertise are not sufficient to address the challenges posed by syndromes like PACVS and Long-COVID. A new approach can ensure sufficient clinical data are collected for rigorous phenotyping and the collection of biospecimens for research into the underlying pathophysiology of COVID vaccine chronic injuries and Long-COVID.

The reason to consider combining both COVID-19 vaccine injury and Long-COVID in such centers is the overlapping related symptoms between the two conditions and the practical reality that many patients or their physicians may not understand if they are experiencing one or the other. Furthermore, many patients may both have been vaccinated and infected,

sometimes making it difficult to establish whether their symptoms are caused by vaccines or infection.

The creation and support of such specialized centers of excellence have proven effective for other newly emergent diseases (85). One notable relevant example has been the establishment and maintenance of Centers for AIDS Research (CFAR). Another example is the Children's Oncology Group (COG).

The Use Case of the Children's Oncology Group (COG)

To inform the implementation of appropriate clinical and pharmacovigilance infrastructure to address the needs of PACVS and Long-COVID patients, it is instructive to consider existing successful models.

The *Children's Oncology Group* (COG) is the largest clinical research network focusing on childhood cancer. Currently, over 12,000 clinicians in 220 children's hospitals in the United States, Canada, Australia, New Zealand, and Saudi Arabia collaborate within this network (86,87). The establishment of this network provided clinical and pharmacovigilance infrastructure that enabled several large-scale activities related to research, therapeutic development, and longitude surveillance systems, with demonstrable improved outcomes for patients.

Funding for COG is supported through National Cancer Institute (NCI) funding for the Network Operations Center, the Statistics and Data Center and the Biopathology Center. Additional network grants support specific programs. (For detail description of COG organizational structure see Appendix II.)

COG facilitates clinical trials. Such large-scale collaboration enables the investigation of rare pediatric cancers with sufficient sample size and power. COG currently supports over 100 active clinical trials, enrolling approximately 12,000 patients each year. The five-year survival rate of childhood cancers increased to over 85% from 30% in the 1960s, highlighting the importance of these multicenter collaborations for a rare disease like pediatric cancer (88).

COG enhances clinical care. With more than 220 member institutions in the United States, Canada, Australia, New Zealand, and Saudi Arabia, most children with cancer in these countries are treated at a COG site (86). Given the relative rarity of pediatric cancer, multi-institutional collaboration is essential to the timely conduct of research and COG is uniquely positioned to do this in many pediatric and adolescent/young adult cancers. Individual members come from 28 disciplines, and this encourages diverse perspectives and contributions to science with a common goal to enroll children with cancer onto clinical trials to improve outcomes. The collaborative, multidisciplinary approach to science functions to support research to continually improve outcomes for children with cancer.

COG facilitates active surveillance. Long-term effects of pediatric cancers and drug-induced toxicity from oncologic treatments remain a significant clinical challenge, especially for children. To address these concerns, the GOC has facilitated multi-institutional studies such as the *Childhood Cancer Survivor Study (CCSS)* to evaluate the long-term effects of childhood cancer and its therapies. The CCSS includes over 1,200 investigators across 31 participating centers in North America (89). A recent study from CCSS demonstrated a reduced incidence of severe late effects in the most recent cohort of childhood Hodgkin lymphoma survivors (90). With a centralized biorepository, COG facilitates the collection, storage, and distribution of over 100,000 biospecimens annually from clinical trial participants and non-study biobanking. COG has since developed comprehensive long-term follow-up guidelines that provide standardized screening recommendations and potential intervention strategies, continually updated to incorporate the latest evidence (91). This has resulted in the establishment of *Late Effects Clinics* across COG sites to monitor and manage pediatric cancer patients well beyond treatment.

Lessons Learned. Decades of experience in both the collection and use of data provide convincing evidence that outcomes can be effectively studied using conventional methods if countries and centers work together. Through networks of treatment centers and clinicians, clinical trial groups have formed to generate data within the US and selected other countries (86). Networks are the only way to generate sample sizes and standardized outcomes to study uncommon disease phenotypes with sufficient power and rigor. In the case of COG, focused coordination of data collection and analysis support clinical practice and policy changes for pediatric oncology in centers around the world.

The role COG serves in the context of enhancing pediatric oncology could inform a similar network structure to form international collaboration among experts in COVID-19 vaccine injury and long-COVID. A COG-like structure will accomplish stepwise advancements in diagnostics and care and the establishment of longitude active surveillance and data collection systems, including biospecimens.

Proposed PACVS and Long-COVID Network

Several existing infrastructures are relevant to consider as part of the concept development and implementation of the proposed network of excellence centers. Currently, Long-COVID clinics in the US are commonly offered by 43 of 50 (86%) of hospitals surveyed in the US. (92). However, these clinics do not operate within a coordinated network, and do not provide rigorous and consistent mechanisms for feedback between centers and with front-line clinicians. Consequently, it may be challenging to maintain, in each isolated center, the diversity and level of expertise needed to support the complexity of conditions like Long-COVID. It would be plausible to consider the integration of these existing centers as part of the newly proposed network. Another potentially relevant resource is the CDC Clinical Immunization Safety Assessment (CISA) project which began in 2001 but only includes eight centers in California, Georgia, Maryland, Massachusetts, New York, North Carolina, Ohio and Tennessee.

A network of clinics for treatment and study of COVID-19 vaccine-induced adverse events and Long-COVID would create a mechanism for care providers to share knowledge about vaccine injury and Long-COVID treatment strategies. This network could also serve to train clinicians and educate patients. Additionally, such a network would be able to facilitate the establishment of an active surveillance system to collect information about vaccine injuries from patients, collect biopsies and biomaterial for sequencing, DNA and other 'omic' analyses, and support sophisticated immunologic analyses involving flow cytometry or other advanced methods. Much as AIDS research greatly advanced knowledge of how viruses interact with the immune system, sophisticated assessment of PACVS and Long-COVID may advance understanding of a wide range of chronic inflammatory diseases such as Lyme. Importantly, it would give patients with reported injuries access to both experimental treatment protocols as well as validated specialized care and treatment methods that can be harmonized across the US through a standardized model of care. Moreover, it can advance such care over time through cooperative studies.

The proposed network activities would include (for more detail examples see Appendix II):

I. Long term surveillance (including data collection, surveys, biopsies, and sample collection) to map and better understand incidence, mechanisms and differential phenotypes.
II. Treatment of patients using current best practices and guidelines.
III. Development of diagnosis and new treatments approaches and assessment of their effectiveness.
IV. Identification of risk factors for the related injuries.
V. Development of multi-disciplinary centers of excellence (one-stop shop for patients) and expanding expertise through knowledge sharing and training.

Proposed network Operations. Operations like that of COG could be established. A streamlined proposed organizational structure is outlined in Figure 2. It will allow expedited training, sharing of data, and development of treatment protocols. Given that the symptoms of COVID-19 vaccine injury and Long-COVID can span multiple organ systems and areas of expertise, the need for multidisciplinary care is essential. Some member sites may contribute specific care expertise whereas others may include more than one area of expertise.

Roles of CDC. US CDC should be at the center of the proposed network and the related activities and manage the work with other agencies. The mission of the Network aligns closely with CDC's central public health responsibilities. In particular, because the network is designed to conduct surveillance and develop evidence-based treatment guidelines to the public, its goals fall squarely with the CDC's role in protecting and monitoring public health and translating data into actionable practice.

CDC is uniquely positioned to coordinate national surveillance and facilitate collaborations with other federal agencies. Accordingly, CDC's involvement as a central coordinating function of this network will ensure standardized data collection and

processing across clinics in the network and ultimately generate robust datasets that can inform CDC-led guideline development and public health recommendations.

Conclusions and Proposed Recommendations

Proposed voting language for Recommendation III for consideration by ACIP: CDC is recommended to establish, budget, and coordinate a COG-like network of PACVS and Long-COVID centers of excellence that will facilitate research related to the epidemiology of these conditions, diagnostics, and therapeutics, as well as the development of best clinical practices and implementation of longitude active surveillance systems.

The implementation of the proposed network should consider existing infrastructure (e.g., current Long-COVID clinics), patient eligibility for assessment, engagement and coordination with other relevant government agencies (e.g., NIH), mechanisms for budgeting and resource allocation, and management structure.

Appendix IA: Two Examples of Phenotype-Driven Diagnostic Pathways

The following examples illustrate potential approaches a clinician may use when conducting a diagnostic evaluation. Given the heterogeneity of presentations and the breadth of reported symptoms, assessment can be challenging and clinicians may be uncertain where to begin. Initial screening studies are frequently unrevealing, which may result in evaluation stopping prematurely. Moreover, in the absence of consensus, guidelines different physicians may vary in their approaches.

These examples are intended to demonstrate a stepwise approach—beginning with initial screening tests and progressing to more targeted secondary evaluations based on patient history, dominant clinical phenotypes, and findings from earlier assessments. Not all patients will require every test described, and inclusion of a test in the example should not be perceived as an indication that the test is part of recommended universal guidelines. Diagnostic strategies should be individualized and specific guidelines will have to be developed over time. Moreover, some of the mentioned tests are currently available through specialized labs and did not go through comprehensive clinical validation and cost-effectiveness evaluation. These tests are included in the discussion below because standard diagnostic modalities often fail to address the challenges of appropriately diagnosing PACVS and Long-COVID patients. Addressing these gaps will likely require development of new diagnostic approaches and their commercialization through a rigorous evaluation process.

When standard diagnostics end after negative initial testing, patients may experience delayed diagnosis, fragmented care, and disengagement from the healthcare system—often leading to increased downstream utilization and cost. While advanced testing carries upfront expense, the cost of missed or delayed diagnosis is frequently greater. This should motivate an approach that allows experimentation with new diagnostic approaches, subject to rigorous evaluation.

The subsequent examples are representative frameworks intended to support clinical reasoning. They are not exhaustive, prescriptive, or intended to function as a diagnostic "cookbook."

Example 1: Phenotype Driven Diagnostic Pathway: Microvascular / Thrombotic Endothelial Phenotype

1. Clinical Entry Point:
    - Presenting symptoms (common real-world scenario):
        - Severe fatigue with post exertional malaise
        - Brain fog, headaches, pressure sensation
        - Chest tightness or air hunger with exertion
        - New or worsened dysautonomia (tachycardia, lightheadedness)
        - Cold or painful extremities, livedo, leg heaviness

- History of COVID-19 infection and/or COVID-19 vaccination temporally preceding symptoms

Key principle:

Symptoms suggest circulatory failure rather than primary cardiopulmonary disease, prompting evaluation for microvascular, endothelial, and coagulation pathology, even if routine testing is unrevealing.

2. Initial Standard Testing (often nondiagnostic but necessary)
   - These tests are not sufficient but establish baseline safety and exclude alternative explanations:
     - CBC with differential, CMP, ESR, hs-CRP, PT/INR, aPTT,D-dimer, Troponin, BNP
     - Resting EKG and Basic echocardiogram

   Common outcome:

   Results are frequently within reference range or only mildly abnormal. This does NOT exclude disease and should not terminate evaluation.

3. Expanded Coagulation & Endothelial Assessment (triggered by temporal relation to SARS-CoV2 vaccine or SARS-CoV2 infection, increased symptom burden, and inadequate explanation from routine labs):
   - Advanced coagulation markers:
     - Fibrinogen, Fibrin monomer, Thrombin–Antithrombin complex (TAT), Factor VIII, von Willebrand factor (antigen & activity), ADAMTS13 activity,
   - Endothelial activation markers:
     - VEGF-A, sVCAM-1, sICAM-1, Endothelin-1, TGF-β, MMP-9

   Interpretation principle:

   Elevation of any subset supports endothelial injury or thrombo-inflammatory activation, even if D-dimer is normal.

4. Micro-clot & Fibrinolysis Assessment (critical step often omitted in conventional care)
   - Immunofluorescent fibrin amyloid micro clot imaging:
     - Qualitative presence and quantitative burden
   - Platelet hyperactivation assessment (if available)

   Possible findings: Dense fibrin amyloid structures, resistance to fibrinolysis, entrapped inflammatory proteins (NETs). Objective evidence of microvascular obstruction, even in absence of macroscopic thrombosis.

5. Genetic & Predisposition Layer: (explains susceptibility, persistence, and severity)
   - PAI-1 genotype, Factor V Leiden, Prothrombin mutation, MTHFR variants,
   - Other thrombophilia panels as indicated

   Purpose: Not to "blame genetics" but to:

   Explain disproportionate response to spike exposure.
   Guide intensity and duration of therapy.
   Support medical necessity of advanced testing and treatment.

6. Functional Vascular Testing (demonstrates real-world impact of microvascular disease)
   - EndoPAT / ENDOPAT-2000,
   - Reduced Reactive Hyperemia Index (RHI),
   - Laser Doppler flowmetry or laser speckle imaging, etc.

   Key concept:

   Confirms functional endothelial failure, bridging lab abnormalities with patient symptoms.

7. Targeted Vascular Imaging: (used selectively, not indiscriminately)
   - If neurologic or head pressure symptoms:
     - MRV brain and neck
       - Cerebral venous outflow obstruction
       - CVST
       - Jugular compression / Eagle syndrome
   - If lower extremity or pelvic symptoms:
     - MRV abdomen and pelvis
       - Iliac vein compression (May-Thurner)
       - Pelvic venous congestion
     - Lower extremity venous duplex with reflux

   Principle: Imaging is phenotype-guided, not routine, and seeks flow abnormalities, not just clots.

8. Diagnostic Synthesis:
   - At this stage, diagnosis is made based on convergent evidence, not a single test:
     - Symptoms consistent with microvascular ischemia.
     - Laboratory evidence of thrombo-inflammation and endothelial activation
     - Objective micro clot detection
     - Functional endothelial dysfunction

- ± Genetic susceptibility
- ± Imaging showing impaired venous outflow

Diagnosis example:

Post-COVID / Post-COVID-19 Vaccination Syndrome with dominant microvascular thrombotic-endothelial phenotype

9. Why This Pathway Matters:
   - Without this expanded pathway:
     - Patient is told "labs are normal"
     - Symptoms are misattributed to anxiety or deconditioning
     - Disease progresses untreated
     - Patient may be re-exposed to triggers (exertion, repeat vaccination)
     - Long-term vascular and neurologic injury risk increases
   - With this pathway:
     - Disease becomes measurable
     - Care becomes defensible and reimbursable
     - Treatment can be targeted to a specific mechanism
     - Surveillance and research become possible

Example 2: Phenotype Driven Diagnostic Pathway: Dysautonomia / Autonomic Circulatory Phenotype

1. Clinical Entry Point:
   - Presenting symptom cluster:
     - Orthostatic intolerance (lightheadedness, presyncope, syncope).
     - Inappropriate tachycardia or bradycardia.
     - Fatigue disproportionate to exertion.
     - Brain fog, visual dimming, head pressure.
     - Heat intolerance, sweating abnormalities.
     - Symptoms of GI dysmotility (nausea, constipation, early satiety)
     - Temperature dysregulation, blood pressure lability.
     - Symptoms worsen with standing, exertion, heat, or post-viral/post-vaccine exposure

Key principle:

Symptoms suggest failure of autonomic regulation and circulatory compensation, not anxiety or primary cardiac disease.

2. Initial Safety & Screening Evaluation:
   - CBC, CMP, TSH, Ferritin, B12, ESR, CRP

- Resting EKG and echocardiogram

Common outcome: Results are frequently normal or mildly abnormal. Normal screening tests do not rule out dysautonomia and must not terminate evaluation.

3. Orthostatic Physiology Assessment:
    - Minimum evaluation (often underperformed):
        - Orthostatic vitals (10-minute active stand test if possible)
    - Diagnostic clues:
        - Exaggerated postural tachycardia (HR increase ≥30 bpm in adults, ≥40 bpm in adolescents in the absence of orthostatic hypotension)
        - Inappropriate sinus tachycardia (average 24-hr HR >90 bpm)
        - Classic orthostatic hypotension (sustained BP drop ≥ 20/10 mmHg within 3 minutes of upright posture)
        - Delayed orthostatic hypotension (sustained BP drop ≥ 20/10 mmHg within after 3 minutes of upright posture)

    If symptoms are significant or findings equivocal pursue further testing

4. Comprehensive Autonomic Testing:
    - Autonomic reflex screen:
        - Tilt table test with continuous beat-to-beat BP
        - Heart rate variability (deep breathing)
        - Valsalva maneuver
        - QSART (sudomotor function)
        - Consider skin biopsy if symptoms of SFN present
    - Key findings may include:
        - POTS, Orthostatic hypotension, neurocardiogenic syncope, inappropriate sinus tachycardia
    - Establishes objective autonomic failure, not functional illness.

5. Vascular & Venous Return Evaluation:
    - Preload failure to right ventricle; indications:
        - Severe orthostatic intolerance
        - Leg heaviness, venous pooling
        - Worsening with standing or exertion
    - Testing:
        - Lower extremity venous duplex with reflux
        - MRV abdomen/pelvis:
            - Iliac vein compression (May-Thurner)
            - Pelvic venous congestion
            - Renal vein compression

Identifies mechanical contributors to preload failure. Notably, compression syndromes are controversial and not universally recognized as sources of preload failure. This area requires further investigation and research.

6. Immune & Mast Cell Overlay Assessment
    - MCAS is a common dysautonomia amplifier:
        - Histamine, Tryptase, Prostaglandin D2, Leukotriene E4, DAO activity
        - IgG, IgA, IgM, IgE
        - Complement Activation Labs

    Rationale: Mast cell activation and immune dysregulation exacerbate autonomic instability.

7. Microvascular and Endothelial Contribution:
    a. Labs that link dysautonomia to vascular and endothelial pathology:
    - Fibrinogen, fibrin monomer, TAT
    - von Willebrand factor, Factor VIII
    - Micro-clot imaging (if available)
    - Supports circulatory dysautonomia rather than primary anxiety.

8. Comprehensive Neurological Motor and Sensory Exam & Small Fiber Evaluation:
    - If pain, sensory changes, or severe autonomic features are present)
        - Skin biopsy
        - QSART
        - EMG/NCS (to rule out large-fiber disease)

    Key principle: Normal EMG does not exclude autonomic small fiber neuropathy.

9. Diagnostic Synthesis: Diagnosis is pattern-based and unable to be defined by a single test.
    - Diagnosis is established based on:
        - Reproducible orthostatic symptoms
        - Objective autonomic testing abnormalities
        - Cerebral hypoperfusion and/or hypocapnia
        - ± Venous return impairment
        - ± Immune or microvascular abnormalities

    Example diagnosis: Post-COVID / Post-COVID-19 Vaccination Syndrome with dominant autonomic-circulatory dysautonomia phenotype (POTS / orthostatic intolerance with hypocapnic cerebral hypoperfusion)

10. Why This Pathway Matters:
    - Without this pathway:

  - Symptoms labeled anxiety
  - Patients advised to “exercise more”
  - Repeated syncopal episodes
  - Worsening disability.
  - Loss of employment/schooling.
- With this pathway:
  - Disease is objectively documented.
  - Treatment is targeted to underlying mechanisms and pathology.
  - Prognosis improves.
  - Surveillance data become accurate.

Dysautonomia in Long-COVID and PACVS is measurable, reproducible, and physiologic when appropriate autonomic, vascular, and metabolic diagnostics are applied.

Appendix IB: List of Labs and Imaging Modalities

The following list summarizes diagnostic tests and modalities that may be available for consideration. These tests are not intended to be performed universally in all patients. Rather, the list serves as a comprehensive reference to assist clinicians in identifying evaluations that may be appropriate based on an individual patient's clinical presentation, history, and dominant phenotypes.

The intent is to provide a structured framework outlining potential diagnostic options. Tests should be ordered only by clinicians with appropriate expertise to interpret the results accurately and apply findings meaningfully within the clinical context.

It is recognized that some tests included in this list may not be currently clinically validated, widely available, or incorporated into standard diagnostic pathways and guidelines. These tests are included because standard diagnostic modalities often fail to address the challenges of appropriately diagnosing PACVS and Long-COVID patients. Addressing these gaps will likely require development of new diagnostic approaches and their commercialization through a rigorous evaluation process.

- **COVID Vaccine Injury and Long-COVID Diagnostic Laboratory Panel:** These establish the physiologic footprint common in spike-related illness, endothelial inflammation, immune dysregulation, mitochondrial stress, and coagulation activation.
  - Basic Panels:
    - CBC with differential, CMP, Vitamin D, Fe panel, B12, folate, fasting lipid panel
  - General Inflammation
    - hs-CRP
    - ESR
    - IL-6 and TNF-α (93–95) [Inflammatory and Anti-inflammatory Cytokine panel]
    - LDH
  - Endothelial Injury/ Microvascular, Coagulation & Microclotting
    - D-dimer, Fibrinogen, Fibrin Monomer, Thrombin–Antithrombin Complex (TAT) (93,95)
    - Immunofluorescent Fibrin Amyloid Qualitative and Quantitative Testing (70,71,96)
    - PT/INR, aPTT
    - Complete thrombophilia panel, especially in your cohort (PAI-1 genotype, MTHFR, Factor V Leiden, Prothrombin mutation)
    - VEGF-A (often elevated in microvascular pathology) (94,97)
    - sVCAM-1, sICAM-1 (endothelial activation markers)
    - von Willebrand Factor (vWF) antigen & activity, Factor VIII (93), ADAMTS13 activity

    - TGF-b, MMP-9, endothelin
  - Endocrine (98)
    - HgbA1C,Insulin, GAD65 (99)
    - Thyroid panel (TSH, FT3, FT4, TPO, TgAb) (100,101)
    - AM Cortisol, ACTH
  - General Autoimmune Work-up (102)
    - ANA with reflex, ENA panel: (Spike-induced autoimmunity is common)
    - Antiphospholipid Syndrome (APS) antibody panel (103)
- **Immune Panels:**
  - IgG, IgA, IgM, IgE, 23-valent pneumococcal titers, Tetanus/diphtheria titers, mannose binding lectin, and IgG subsets (titers are pre and post vaccine where applicable)
  - Viral reactivation:
    - EBV reactivation, particularly EBV early antigen-diffuse IgG and EBNA IgG
    - CMV IgG/IgM
    - HHV-6 IgG/IgM

  Cytokine panel and standard immunophenotyping
  - Mast Cell Activation / Immune Dysregulation (104,105)
  - MCAS Panel
    - Tryptase, Histamine, Chromogranin, Prostaglandin D2, Leukotrienes
    - 24-hour urine histamine and N-methylhistamine
    - IL-6, TNF-alpha
  - Immunoglobulins
    - IgG subclasses and Spike Specific as Above
    - Total IgG, IgA, IgM, IgE
  - Complement Activation
    - CH50
    - C3/C4
    - C1 Inh, quantitative and function
    - C1Q, serum quantitative and binding

  C4d in serum, may consider skin biopsy as well for C

- **Vascular and Microcirculatory Diagnostics:** endothelial dysfunction/microvascular hypoperfusion.
  - Advanced Diagnostics
    - ENDOPAT / EndoPAT-2000
      (Endothelial reactive hyperemia index—tracks endothelial dysfunction)
    - Laser Doppler Flowmetry or Laser Speckle Contrast Imaging
    - Microclot imaging with immunofluorescence as Above
  - Vascular Imaging
    - MRV Brain and Neck: CVST, Eagle Syndrome, Cerebrovenous Outflow Disorders

    - MRV of Abdomen and Pelvis
      To assess iliac vein compression (May-Thurner), pelvic venous congestion, renal vein compression.
    - Carotid and vertebral duplex
    - Lower extremity venous duplex with reflux study (106)
- **Autonomic Nervous System / Dysautonomia Testing (107,108)**
  - Standard ANS Battery
    - Tilt Table Test (with continuous beat-to-beat BP + $ETCO_2$ if possible)
    - QSART (Quantitative Sudomotor Axon Reflex Test)
    - Heart Rate Variability (HRV) analysis
    - Valsalva maneuver and Deep breathing test
  - Capnography: Based on Novak et al. (2024)
    - Resting capnography
    - End-tidal CO_2 monitoring during tilt
      Helps distinguish HYCH vs POTS via hypocapnia cerebral hypoperfusion patterns.
  - Autoantibodies to ANS Receptors

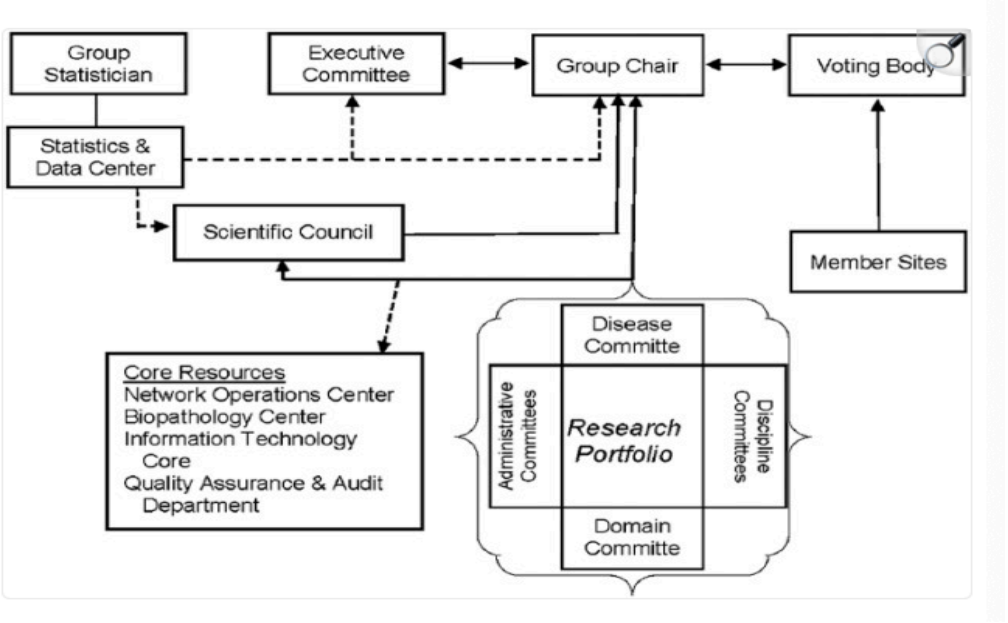
- **Mitochondrial, Metabolic & Fatigue Pathways (78,109)**
    - Spike protein disrupts mitochondrial function, redox balance, and energy metabolism.
    - Tests
      - Lactate (rest + post-exercise)
      - Pyruvate
      - Carnitine panel (free + total)
    - Organic acids test (OAT)
      - Amino acid profile
      - Homocysteine
      - Insulin, fasting, HbA1c, C-peptide
    - Lipid panel: (Spike-exposed patients often show post-viral dyslipidemia)

- **Neurologic/Cognitive Work-Up:** For brain fog, small fiber neuropathy, neuroinflammation.
  - Peripheral Neuropathy
    - Skin biopsy for nerve fiber density (IENFD)
    - QSART (autonomic small fiber involvement)
    - EMG/NCS
  - Neuroinflammation (110)
    - Neurofilament Light Chain (NfL) (111)
    - S100B
    - GFAP
    - Lumipulse p tau 217/amyloid 42
    - p Tau 181

    - APO E genotype
  - Procedures:
    - Lumbar Puncture
  - Neurovascular Imaging
    - MRI brain with perfusion
    - MR angiography/venography of brain
    - EEG
    - Polysomnography (112–114)
- **Cardiopulmonary Work-Up**
  - Cardiac Assessment
    - Echocardiogram, Strain imaging (GLS)
    - Cardiac MRI if myocarditis suspected
    - Holter monitor or Zio patch (arrhythmia/POTS overlap) (115)
  - Pulmonary
    - PFTs including DLCO (116)
    - 6-minute walk test with pulse oximetry
    - CPET (if tolerated)
    - Lung Perfusion Scan including SPECT Scan and V/Q Scans
- **Gastrointestinal Dysfunction:**
  - Stool testing (microbiome/microbiota shifts)
  - Zonulin (gut permeability)
  - Fecal calprotectin
  - SIBO
  - Celiac panel
- **Spike Protein–Specific & Viral Persistence Testing:**
  - Antibody Directed towards Variants and Vaccine
    - Attomarker Spectrum Abs (117)
  - Direct Spike Protein / Viral Protein Assa Sys (26)
    - Cell-free spike protein assay (59)
    - Circulating S1 subunit protein
    - Spike-specific immune complexes (IgG–S1, IgM–S1, IgG–S2)
  - Innate Immune Exhaustion
    - Monocyte subset panel (classical/intermediate/nonclassical): Bruce Patterson
    - CD14, CD16 expression
    - CD56, Caspase-1 (Amerimmune Labs—their standard immunophenotyping covers much of the needed subsets)
    - HLA-DR expression on monocytes (low = chronic immune fatigue.
  - Lymphocyte Subsets
    - CD4/CD8 ratio
    - NK cell number and function
    - B-cell panel (CD19+, naïve vs. memory)

Appendix II: COG Structure

The organizational structure of the COG is shown in Figure 1 (118).



COG's leadership structure encompasses three branches, which include the Group Chair, the Executive Committee, and the Voting Body. The Constitution and Bylaws, which guide the governance of the organization, were enacted in 2000 and are reassessed at least every 5 years. The Group Chair is an elected individual who serves as the organization's chief executive officer for a term of 5 years, renewable once. The Group Chair has responsibility for the overall administrative, fiscal, and scientific leadership of COG. This includes serving as principal investigator of the National Clinical Trials Network Group Operations Grant and other appropriate grants, leading the Executive Committee, appointing individuals to scientific leadership positions, overseeing the Network Operations Center, and representing COG at the NCI. The Group Statistician is appointed by the Group Chair (with approval of the Executive Committee) to oversee the Statistics and Date Center (SDC), to serve as PI for the SDC grant, and to provide statistical direction to the Scientific Council. The Executive Committee is composed of the Group Chair and 18 additional voting members, including the vice chair, the Group Statistician, and representatives of the member institutions and the scientific and administrative committees. The Executive Committee is responsible for strategic planning of the organization and oversees fiscal, administrative, and legal issues. The Voting Body comprises PIs from each member institution and cofunctions with the Group Chair and the Executive Committee to provide guidance for ensuring execution of COG's mission. The Voting Body is also responsible for electing the Group Chair, approving new member institutions, and ratifying amendments to the organizational constitution. The Scientific Council, whose members are appointed by the Group Chair, provides guidance regarding the scientific direction of COG research,

reviews scientific concepts, prioritizes research efforts, and assures conduct of research is to the highest scientific standards.

Research proposals that support the overall COG mission arise from Disease, Discipline, and Domain Committees. These Committees serve to develop and vet research concepts and priorities, which are then submitted to the Scientific Council for consideration of further development. Table 1 details the array of the COG committees.

Table 1.

COG Committees.

Administrative Committees	Discipline Committees	Disease Committees	Domain Committees
• Bioethics	• Adolescent-Young Adult	• Acute Lymphoblastic Leukemia	• Cancer Control/Supportive Care
• Data and Safety Monitoring	• Behavioral Science	• Acute Myeloid Leukemia	• Cellular Therapy
• Diversity and Health Disparities	• Clinical Research Associates	• Bone Tumors	• Developmental Therapeutics
• Executive	• Cytogenetics	• Central Nervous System Tumors	• Epidemiology
• Industry Relations Advisory	• Diagnostic Imaging	• Hodgkin Disease	• Outcomes-Survivorship
• Institutional Performance Monitoring	• Hematology/Oncology	• Neuroblastoma	
• International Affairs	• Integrated Translational Science (Hematologic Malignancies)	• Non-Hodgkin Lymphoma	
• Membership	• Integrated Translational Science (Solid Tumors)	• Rare Tumors	
• NCORP	• Laboratory Science	• Renal Tumors	
• Nominating	• Neuroscience	• Soft Tissue Sarcomas	
• Patient Advocacy	• Nursing		
• Return of Results	• Pathology		
• Scientific Chairs	• Pharmacy		
• Scientific Council	• Radiation Oncology		
• Voting Body	• Statistics		
• Young Investigators	• Surgery		

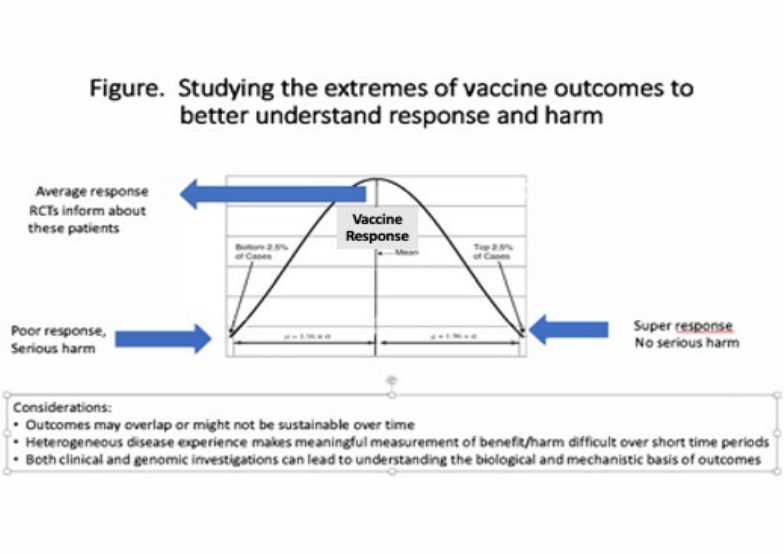
Note. COG = Children's Oncology Group; NCORP = National Cancer Institute Community Oncology Research Program.

Appendix III: Studies that could be done in proposed PACVS & Long-COVID network

Studying Extreme Phenotypes

"Extreme phenotypes" are referred to as phenotypes in individuals that experience safety outcomes of interest and greater than expected benefits. Studies should focus on obtaining both clinical and genomic data from individuals with "extreme phenotypes." These groups of patients who are at the extremes of the vaccine response paradigm (see Figure below) could be particularly useful to understanding the clinical and biological basis of these phenotypes, especially when compared with opposite phenotypes. For example, non- or poor responders compared to individuals with greater than expected efficacy or effectiveness, and those without specific serious vaccine-induced adverse effects or Long-COVID compared to individuals with safety outcomes of interest. Although the numbers tested would likely be small, the pay-off in understanding what might explain their vaccine response, and potentially that of others, could be large and have public health significance.

Figure. Studying the extremes of vaccine outcomes to better understand response and harm



Reported vaccine injuries that have been reported and could be treated and studied in Centers

Common Symptoms

Long-COVID and PACVS are a complex multisystem disease where multiple symptoms have been identified and, in some cases, end organ damage (e.g., heart, kidney, brain, lungs, eyes, vasculature, liver, etc.) (119–122).

With end organ damage, there is a risk of a rise of disease states now and in years to come.

Fatigue, brain fog and post-exertional malaise (PEM) are commonly reported symptoms, but more than 200 Long-COVID symptoms have been identified (123).

React 19 data showed the most common PCVS symptoms reported were: 25% neuropathy, 22% tinnitus, 20% dysautonomia/POTS, 19% autoimmune disorder, 14% small fiber neuropathy, 4.7% myocarditis, 4% new cancer diagnosis (46).

Long-COVID and PCVS are highly heterogeneous and there are no limits to the diversity of these cases.

Virtually any organ system in the body may be affected. Below are some of the most systems most reported:

Neurological conditions

A study by Liotta E et al in *Annals of Clinical and Translational Neurology* found that 30% to 40% of people have neurological aftereffects of COVID-19. In a review published in the journal Nature Review Neurology researchers explored the links between vaccination and neurological diseases (124).

A study by Xu E et al provides evidence of increased risk of long-term neurologic disorders in people who had COVID-19 (125).

Data from React 19 show over 80 % of COVID vaccine injured patients have neurological issues (46) and a study by Krumholtz et al finds this connection as well (27).

The most important and common neurological complications include cerebrovascular disorders, including cerebral venous sinus thrombosis, transient ischemic attack, intracerebral hemorrhage, ischemic stroke, demyelinating disorders including transverse myelitis, first manifestation of MS, and neuromyelitis optica, altered sense of taste or smell, cognitive impairment and brain fog, POTS and dysautonomia, headache, weakness, neuropathic pain, numbness, tremor and other movement disorders, seizures, visual impairment, and neurodegenerative disease.

Diabetes

Studies indicate a significantly increased risk of new-onset type 2 diabetes following a COVID-19 diagnosis or the COVID vaccine (18,126).

Immune system

SARS-CoV-2 can cause lasting dysfunction of the immune system (127).

Multiple doses of the mRNA COVID-19 vaccines may result in higher levels of IgG4 antibodies, and impaired activation of CD4 + and CD8 + T cells (19,54). Additionally, **complement activation and inflammatory responses** occur with mRNA-LNP vaccines. The lipid nanoparticle components induce complement activation primarily via the alternative pathway and stimulate proinflammatory cytokine release (IL-1β, TNF-α, IL-6, IL-8), although complement inhibitors like Soliris did not suppress cytokine production in vitro, suggesting complex inflammatory pathways (128).

Autoantibody production has been observed in a subset of vaccinated individuals. Approximately 10% of healthy individuals receiving mRNA vaccines (but not viral vector vaccines) developed neutralizing anti-type I interferon autoantibodies, with some showing functional neutralizing activity against IFN-α-induced immune responses (129). However, a larger study found that autoantibody dynamics remain remarkably stable after mRNA vaccination, contrasting with COVID-19 infection, which increases new autoantibody reactivities (130).

Hyperinflammatory syndromes have been reported in patients with preexisting immune dysregulation, including hemophagocytic lymphohistiocytosis following mRNA vaccination (131). Case reports describe multiple concurrent autoimmune conditions (acute disseminated encephalomyelitis, myasthenia gravis, thyroiditis) developing post-vaccination (132).

Kidney disease

People with long-COVID experienced a substantial decline in eGFR within 1 year from the infection date. The prevalence of proteinuria appeared to be high (133). Cases of new-onset or relapsed kidney diseases have been reported after COVID-19 vaccination as well (134).

Close monitoring of kidney function is prudent among patients with persistent COVID-19 symptoms and in those injured by the COVID vaccines.

Cardiovascular complications

The presence of Long-COVID symptoms after infection with SARS-CoV-2 is strongly associated with the development of cardiovascular disease (135–137).

However, mRNA Covid-19 vaccines are also linked to an increased risk of myocarditis and pericarditis (20,138–141).

Other complications that have reported include Takotsubo cardiomyopathy, postural orthostatic tachycardia syndrome (POTS), arrhythmias, sudden cardiac death, and cardiac tamponade (142).

A study reported by Bruno R et a demonstrated SARS COV 2 impact on accelerated arterial aging, especially in women (143).

Pulmonary

PASC and PACVS can have various lung issues, including pneumonia, acute respiratory distress syndrome (ARDS), and pulmonary fibrosis (scarring). Symptoms include difficulty breathing, chest pain, and extreme fatigue (142,144).

Blood clots

COVID-19 vaccination and COVID-19 infection increase the risk of blood clots. The deep vein thrombosis – clots that form in large veins – was nearly double in people who had had COVID-19 compared to those who had not (72,145). Clots after mRNA COVID-19 vaccines have also been reported (146–151). Numerous studies have shown fibrinolytic-resistant microclots in PASC. These microclots entrap various inflammatory molecules, including proteins that prevent clot breakdown (72).

A study published by Yasmin S et al sheds further light on the risk of developing a rare blood-clotting condition known as thrombosis with thrombocytopenia syndrome (TTS) after a covid vaccination (17). A new study published in the *Journal of Medical Virology* suggests the long lasting effects of Long-COVID such as fatigue and brain fog may lie in tiny blood clots called microclots and a sticky molecular web spun by immune cells known as neutrophil extracellular traps, or NETs. Their results showed that Long-COVID blood had nearly 20 times more microclots than the control population (152).

Postural orthostatic tachycardia syndrome (POTS)

One global online survey found that 66% of 2,314 adults with post-acute sequelae of SARS-CoV-2 (PASC) had a COMPASS-31 score > 20, suggestive of moderate to severe autonomic dysfunction. A follow-up study from the same research group, published in 2025, found that 71.9% of 526 participants with long COVID had COMPASS-31 scores ≥20, indicating moderate-to-severe autonomic dysfunction, with a median symptom duration of 36 months (153,154). Another study found that (79%) of those with Post-acute sequelae of Long-COVID met the internationally established criteria for POTS (155). A study published in *Nature Cardiovascular Research*, showed increased incidence in POTS for people who are vaccinated or who have had COVID-19 (156–159).

Most PASC/PACVS patients have severe fatigue, post-exertional malaise, inappropriate tachycardia, gastrointestinal symptoms (constipation, difficulty swallowing, nausea etc.) and brain fog. Some patients can have bowel and bladder incontinence, temperature dysregulation, and extreme fluctuations in their blood pressure (160,161).

Sleep issues

Research suggests that about 40% of people with Long-COVID and PCVS report sleep issues. Problems can include insomnia, daytime sleepiness, waking up several times a night, or not feeling refreshed in the morning (162).

Gastrointestinal issues

Some patients report bloating, constipation, diarrhea, vomiting, GERD, peptic ulcer disease and other signs of stomach distress. A study in Nature Communications reported that people who had COVID experienced significantly more gastrointestinal symptoms a year after their infection than people who had not had the virus (125). Massad et al. found similar long term gastrointestinal issues after the COVID vaccines (21).

Other reported injuries

An analysis of a Japanese database of 18 million people showed that people who received COVID-19 vaccines had a significantly higher risk of death in the first year after vaccination compared to the unvaccinated, and the risk increased with each additional dose (163).

A peer-reviewed study published in EXCLI Journal was the first to uncover statistically significant evidence of increased cancer following COVID-19 vaccination in Italy (164).

A case of metastatic breast carcinoma to the skin expressing SARS-CoV-2 spike protein, consistent with mRNA-vaccine–derived spike was described in a recent case report. Immunohistochemistry showed spike-positive, nucleocapsid-negative tumor cells compatible with mRNA-derived spike rather than viral infection (22).

Several studies have shown a link between recovering from SARS COV 2 infection and or receiving a covid vaccine and new onset or worsening autoimmune disease (6,165,166).

There are now data from multiple studies that showed that even mild COVID increased the risk of development of new-onset dementia in people older than 50 (167,168). Roh J et al found an increased risk of Alzheimer's disease post COVID vaccine (169).

Appendix IV: Individual Opinions

Henry (Hank) Bernstein, DO, MHCM, FAAP:

Dr. Bernstein appreciates and respects the safety concerns raised by some experts on the COVID-19 Workgroup. However, Dr. Bernstein feels the process and timeline proposed to advance their initiative's conceptual model would benefit from refinement. Therefore, he is NOT in support of the proposed 3 recommendations in this Post COVID Vaccination Chronic Injuries — Proposed Action document for the following reasons:

It is challenging to make specific recommendations based upon the imbalanced presentation and discussion of the data without the input and interpretations of the FDA and 2 manufacturers with the WG.

It would be helpful to more clearly distinguish the diagnostic, evaluation, and management criteria for Post-Acute COVID Vaccination Syndrome (PACVS) versus Post-Acute COVID Syndrome (PACS or Long COVID).

Emphasize a more collaborative effort in further exploring notable concerns so the right people are doing the right job at the right time for the right population so as not to reinvent the wheel.

Consider helpful lessons learned from historical examples such as paralysis associated with oral polio vaccine (VAPP) or intussusception associated with rotavirus vaccine.

Adequately tap into previously established scientific processes intended to thoroughly and appropriately examine hypotheses. It should include:

The IOM's Committee on Immunization Safety Review. "Since its founding in 1970 as the Institute of Medicine, the National Academy of Medicine has helped to achieve better outcomes for people in the United States and around the world — from launching the patient safety movement to securing compensation for veterans wounded by chemical exposures. [Its] capacity for impact is rooted in [its] independence, objectivity, and unwavering commitment to evidence as the foundation for effective action."

The CDC's active surveillance systems (i.e., VAERS; VSD; CISA; V-Safe) work together to rapidly detect and assess potential safety concerns to help inform public health actions.

Vaccine Adverse Event Reporting System (VAERS) - our country's early warning system for vaccine safety. Anyone can submit a vaccine experience to VAERS, but it does NOT identify causality. Instead, it is valuable in finding potential signals to be thoroughly explored.

The Vaccine Safety Datalink (VSD) has multiple participating integrated healthcare organizations that links EHR data on over 12 million persons. In addition, VSD Rapid Cycle Analyses can monitor a limited set of pre-specified outcomes.

Clinical Immunization Safety Assessment (CISA) project is a network of vaccine safety experts from CDC, eight research centers and other partners. CISA provides consultations for U.S. healthcare providers with complex vaccine safety questions about individual patients residing in the US. CISA conducts vaccine safety research and contributes to emergency response activities.

V-safe is a safety monitoring system initially created to monitor the safety of COVID-19 vaccines. It allows participants to share their health experiences after vaccination through brief check-ins conducted via text message or email.

(6) Incorporate lessons learned from the National Vaccine Injury Compensation Program (VICP) which is designed to compensate people injured by vaccines in the childhood and adolescent immunization schedule. All vaccines included in the child and adolescent vaccine schedule are covered by VICP except dengue, PPSV23, Mpox, RSV, and COVID-19 vaccines. Consideration could be made that COVID-19 vaccines, approved or authorized by the FDA, now be covered by the VICP rather than the Countermeasures Injury Compensation Program (CICP).

(7) Include the various communication strategies the CDC has used for years to effectively engage with the public and accurately convey health information.

(8) It is not clear whether the CDC/ACIP is the right federal agency to spearhead such an initiative, given that PACVS happens to <1% of the population who receives COVID vaccination.

(9) Consider John Kotter's 8 Steps for Leading Change and Why Transformation Efforts Fail in wanting to move this conceptual model forward.

Mitchell Miglis, MD, Clinical Associate Professor, Department of Neurology and Neurological Sciences, Secondary in Department of Psychiatry and Behavioral Sciences, Stanford University:

Dr. Miglis agrees with goal of creating ICD-10 diagnostic codes to better capture post-acute COVID vaccination syndrome (PACVS) for clinical and research purposes, just as ICD-10 codes were created for Long-COVID (LC). He agrees with the allocation of resources to better treat and better study both PACVS and LC, acknowledging that both the acute and chronic complications of SARS-CoV-2 infection are likely significantly more common than similar complications from COVID vaccination. He agrees that more robust epidemiological studies are needed to more accurately understand the true prevalence, scope and severity of PACVS. He does not agree with the utilization of some of the assays mentioned in the Appendices IA and IB that are currently not validated for clinical use or supported by consensus expert opinion.

Comments on "**Post COVID Vaccination Chronic Injuries – Recommendations for Action" to be added to Appendix**

Stanley Perlman, M.D., Ph.D.:

Dr. Perlman agrees that better definitions of post-acute COVID vaccination syndrome (PACVS) and ICD-10 diagnostic codes for PACVS are important. He appreciates all the work performed by the Working Group to develop this document. However, he has not signed the document because he thinks that PACVS needs to be better defined before ICD-10 Diagnostic Codes should be formulated. Said in another way, he does not agree with the concept that ICD-10 diagnostic codes can be used to facilitate definition of PACVS. Efforts should be made to gather as much data as possible for this purpose. He also does not believe that the CDC has sufficient expertise and is sufficiently well situated to define PACVS and to develop these codes. Rather other entities are more experienced and more appropriate for these purposes. He also disagrees with the approach of combining PASC (Post Acute Sequelae of COVID-19) and PACVS until more is known about the latter entity. Combining the two may be useful in terms of clinical care but will make it difficult to distinguish differences in manifestations, in underlying factors and in therapeutic options.

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