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**Postural Orthostatic Tachycardia Syndrome (POTS):**

**State of the Science, Clinical Care, and Research**



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Francis S. Collins, M.D., Ph.D.  
Director, NIH

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## **Executive Summary**

Postural orthostatic tachycardia syndrome (POTS) is a disabling condition in which standing produces a rapid heart rate, along with symptoms such as light-headedness, palpitations, weakness, blurred vision, exercise intolerance, and fatigue. Problems with digestion, sleep, and concentration are also common, but vary from person to person. While the cause of POTS is unknown, low blood volume, dysregulation of the autonomic (involuntary) nervous system, and autoimmunity may all play a role, each perhaps leading to distinct subtypes of POTS. Treatment to manage symptoms helps some patients improve over time, but there is no cure. To address these issues, the National Institutes of Health (NIH) convened a workshop on “POTS: State of the Science, Clinical Care, and Research” in July 2019. This workshop generated several priorities for future research, including standardization of diagnostic criteria, tools, and outcome measures for POTS; studies on the natural history of POTS, its causal mechanisms, and risk factors; well-designed clinical trials and studies that make use of state-of-the-art cardiac and brain imaging; and enhanced multi-disciplinary collaboration.

## Introduction

In its report to accompany the fiscal year (FY) 2019 appropriations for the Department of Health and Human Services (HHS), the Senate Committee on Appropriations stated the following:

*“An estimated 1,000,000 to 3,000,000 Americans suffer from POTS, a debilitating neurological disorder that affects mostly adolescent and adult women. Recent research shows that POTS is associated with autoimmune antibodies that impact the neurologic and cardiovascular systems, but more research is needed to understand the role of these autoantibodies in POTS and identify treatments that may help patients with these antibodies. Due to the lack of effective treatments, many patients are unable to attend school or work, causing lost economic productivity and a financial strain on families. The Committee encourages NHLBI and NINDS to jointly host a symposium with participants from NIAID, NIDDK, NICHD, and leading external researchers and stakeholders to examine the current state of POTS research. The Committee directs NIH to provide a report to the House and Senate Committees on Appropriations 9 months after enactment of this act that reflects participants' findings on: (1) the current state of POTS research; (2) priority areas of focus for future POTS research through 2025; (3) a summary of ongoing or upcoming efforts by NIH to advance the scientific understanding of POTS; and (4) an estimate of the level of funding that would be needed annually to achieve objectives (2) and (3).” (Senate Report 115-289, page 92)<sup>1</sup>*

As directed by the Committee, the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Neurological Disorders and Stroke (NINDS), with participation from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Institutes within the National Institutes of Health (NIH), jointly convened a workshop on July 29, 2019, to discuss the state of the science and gaps in the current understanding of POTS. The workshop included presentations by leading experts in POTS research and care, officials from the three sponsoring Institutes, and patient advocates (see the Appendix). This report was prepared by NHLBI and NINDS based on workshop discussions and subsequent input and review by the workshop co-chairs in response to this request.

## Background

When a person moves from lying down to sitting upright or standing, nearly a half-liter of blood—about the same amount given in a typical blood donation—moves away from the chest to the lower extremities.<sup>2,3</sup> As a result, standing typically causes a temporary reduction in blood pressure and blood flow to the brain. Normally, these changes activate the autonomic (involuntary) nervous system, which leads to a temporary increase in heart rate and constriction

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<sup>1</sup> [www.congress.gov/115/crpt/srpt289/CRPT-115srpt289.pdf](http://www.congress.gov/115/crpt/srpt289/CRPT-115srpt289.pdf)

<sup>2</sup> [www.ncbi.nlm.nih.gov/pubmed/26271068](http://www.ncbi.nlm.nih.gov/pubmed/26271068)

<sup>3</sup> [www.ncbi.nlm.nih.gov/pubmed/30871704](http://www.ncbi.nlm.nih.gov/pubmed/30871704)

of the body's blood vessels so that blood pressure and blood flow return to normal within several heartbeats. This physiological response to standing is called orthostasis.<sup>4</sup>

POTS is a disabling condition characterized by an excessive increase in heart rate upon standing. Although the precise clinical definition of POTS is evolving with continued study, the 2011 American Autonomic Society Consensus Statement<sup>5</sup> and the 2015 Heart Rhythm Society Expert Consensus Statement<sup>6</sup> identify the following as working diagnostic criteria for POTS:

- An increase in heart rate (tachycardia) within 10 minutes of standing or upward head-tilt
  - of 30 beats per minute (bpm) or more in adults,
  - or of 40 bpm or more in adolescents aged 12-19;
- Absence of orthostatic hypotension, which is a decrease in blood pressure ( $\geq 20$ mm Hg systolic or  $\geq 10$ mm Hg diastolic) within three minutes of standing;
- Symptoms that develop or worsen on upright posture, including light-headedness, palpitations, weakness, blurred vision, exercise intolerance, and fatigue.

The World Health Organization (WHO) International Classification of Diseases (ICD-11) adds that symptoms of POTS typically persist for three months or longer.<sup>7,8</sup> Prevalence estimates for POTS range from 0.2 to 1.0 percent of the United States population, with adolescent and adult women making up 87-94 percent of those diagnosed.<sup>9,10</sup>

The underlying cause of POTS is unknown. Patient-reported data suggest that it often follows a precipitating event such as viral infection, concussion, surgery, pregnancy, or puberty.<sup>11</sup> Antecedent infections or trauma are common in people with autoimmune diseases, in which the immune system attacks the body's own tissues. So, it is possible that such events might trigger autoimmune mechanisms in POTS. In support of this theory, autoimmune diseases frequently co-occur with POTS, and unique self-directed antibodies (autoantibodies) have been detected in some individuals with POTS.<sup>3,10,11,12</sup>

POTS can be a debilitating condition that affects routine activities such as working or attending school.<sup>13,14</sup> Compared to healthy controls, individuals with POTS report significant pain, impaired physical abilities (e.g., climbing stairs), and consequent limitations in daily activity.<sup>13</sup> In addition to its common symptoms, many individuals with POTS report other symptoms such as sleep disturbance, gastrointestinal problems (e.g., constipation, nausea, abdominal pain,

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<sup>4</sup> [www.ncbi.nlm.nih.gov/pubmed/15860687](http://www.ncbi.nlm.nih.gov/pubmed/15860687)

<sup>5</sup> [www.ncbi.nlm.nih.gov/pubmed/21431947](http://www.ncbi.nlm.nih.gov/pubmed/21431947)

<sup>6</sup> [www.ncbi.nlm.nih.gov/pubmed/25980576](http://www.ncbi.nlm.nih.gov/pubmed/25980576)

<sup>7</sup> <https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/1533647472>

<sup>8</sup> Note added in proof: In March 2020, the Canadian Cardiovascular Society published a *Position Statement on Postural Orthostatic Tachycardia Syndrome (POTS) and Related Disorders of Chronic Orthostatic Intolerance*. It recommends diagnostic criteria consistent with those listed here. See [www.ncbi.nlm.nih.gov/pubmed/32145864](http://www.ncbi.nlm.nih.gov/pubmed/32145864).

<sup>9</sup> [www.ncbi.nlm.nih.gov/pubmed/17352367](http://www.ncbi.nlm.nih.gov/pubmed/17352367)

<sup>10</sup> [www.ncbi.nlm.nih.gov/pubmed/30861229](http://www.ncbi.nlm.nih.gov/pubmed/30861229)

<sup>11</sup> [www.ncbi.nlm.nih.gov/pubmed/30372565](http://www.ncbi.nlm.nih.gov/pubmed/30372565)

<sup>12</sup> [www.ncbi.nlm.nih.gov/pubmed/29909990](http://www.ncbi.nlm.nih.gov/pubmed/29909990)

<sup>13</sup> [www.ncbi.nlm.nih.gov/pubmed/12059122](http://www.ncbi.nlm.nih.gov/pubmed/12059122)

<sup>14</sup> <https://bjcardio.co.uk/2016/03/a-profile-of-patients-with-postural-tachycardia-syndrome-and-their-experience-of-healthcare-in-the-uk/>

vomiting, weight loss), headache, gynecological abnormalities (e.g., abnormal bleeding, endometriosis, ovarian cysts, and uterine fibroids), pelvic pain, anxiety, changes in temperature regulation, sweating, fainting, and poor concentration and confusion, which is sometimes called “brain fog.”<sup>15,16</sup> Individuals with POTS also tend to have one or more associated conditions, or comorbidities. Common comorbidities include migraine, irritable bowel syndrome, hypermobile Ehlers-Danlos syndrome—a rare disorder that causes weakness in the connective tissues supporting skin, bones, blood vessels, and many other organs and tissues—and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).<sup>9,10,17</sup> While relatively little is known about outcomes of POTS over the lifespan, and the disorder itself has no mortality,<sup>6</sup> the morbidity resulting from POTS may be profound due to loss of productivity and impaired quality of life.

About half of individuals newly diagnosed with POTS are children and adolescents. Like adults, children and teens with POTS have tachycardia upon standing, no orthostatic hypotension, and multiple disabling cardiovascular, neurologic, gastroenterological, and/or musculoskeletal symptoms. In young people with POTS, onset commonly occurs near puberty.<sup>18</sup>

Although clinical descriptions consistent with POTS date to the late 19<sup>th</sup> century, the term POTS was not coined until 1993.<sup>19</sup> In the ensuing decades, awareness and understanding of the syndrome have improved significantly. Despite growing recognition and scientific study of POTS, there remains a lack of awareness across medical specialties, and people with persistent symptoms of POTS report significant delays (of up to several years) from onset to diagnosis.<sup>9</sup>

There is no cure and no standardized treatment for POTS. Available treatments focus on relieving symptoms, for example, by increasing blood volume (see “Current State of POTS Research: Diagnosis and Treatment of POTS” on page 8).

## **Current State of POTS Research**

### ***Challenges in Defining POTS***

Although recent consensus statements from the American Autonomic Society<sup>5</sup> and the Heart Rhythm Society<sup>6</sup> provide working definitions of POTS, there is still disagreement within the scientific and clinical communities on what the definition of POTS should be, and whether POTS is one or many related conditions. There is a need for a more precise definition of POTS using more specific diagnostic criteria and more consistent nomenclature.<sup>20,21,22</sup> Due to the many

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<sup>15</sup> [www.ncbi.nlm.nih.gov/pubmed/22721633](http://www.ncbi.nlm.nih.gov/pubmed/22721633)

<sup>16</sup> [www.ncbi.nlm.nih.gov/pubmed/21509337](http://www.ncbi.nlm.nih.gov/pubmed/21509337)

<sup>17</sup> [www.ncbi.nlm.nih.gov/pubmed/24685354](http://www.ncbi.nlm.nih.gov/pubmed/24685354)

<sup>18</sup> [www.ncbi.nlm.nih.gov/pubmed/29222399](http://www.ncbi.nlm.nih.gov/pubmed/29222399)

<sup>19</sup> [www.ncbi.nlm.nih.gov/pubmed/22143364](http://www.ncbi.nlm.nih.gov/pubmed/22143364)

<sup>20</sup> [www.ncbi.nlm.nih.gov/pubmed/28351847](http://www.ncbi.nlm.nih.gov/pubmed/28351847)

<sup>21</sup> [www.ncbi.nlm.nih.gov/pubmed/29343965](http://www.ncbi.nlm.nih.gov/pubmed/29343965)

<sup>22</sup> Note added in proof: In March 2020, a group of POTS experts, including three participants in the July 2019 NIH workshop, published a review article “to clarify the origins of the definition of POTS, to highlight gaps in definition that have resulted in diagnostic confusion and affected clinical care, to develop a direction for patient assessment and management, and to consider areas of future research.” While the review proposes a diagnostic flowchart

symptoms and comorbidities associated with POTS, and their variability from person to person, it is unclear whether POTS is best defined as a single syndrome or as a syndrome with several subtypes. The decision to define POTS as one or multiple syndromes could affect how it is studied and treated in the future as well as the efficacy of those studies and treatments.

### *Possible Causes of POTS*

The underlying cause or causes of POTS are currently unknown. Several case studies have described individuals with POTS who have reduced central blood volume, either constitutively or only upon standing.<sup>23,24,25,26</sup> A low blood volume (hypovolemia) during standing could lead to compensatory over-activation of the autonomic nerves that stimulate the heart, causing the heart to beat faster.<sup>3,11</sup> Because dehydration can cause hypovolemia and can even cause tachycardia without a drop in blood pressure—either at rest or in response to upright posture<sup>27</sup>—it is essential to rule out other potential causes of hypovolemia (including chronic dehydration) in the diagnosis of POTS.<sup>28,29</sup>

Another hypothesis suggests that POTS may be caused by damage or dysfunction in the autonomic nerves that regulate heart rate and other involuntary functions.<sup>3,11</sup> Within the autonomic nervous system, the sympathetic nerves stimulate the body’s “fight-or-flight” response, including increases in heart rate and blood pressure; the parasympathetic nerves stimulate the “rest-and-digest” response, including decreases in heart rate and blood pressure. Thus, too much sympathetic stimulation or too little parasympathetic stimulation could contribute to POTS. An NHLBI-supported study is examining how impaired autonomic regulation of blood flow to the brain could lead to the brain fog associated with POTS and is testing whether a two-drug combination (Digitalis and pyridostigmine, a parasympathetic stimulator) can reverse tilt-induced brain fog.<sup>30</sup> A related hypothesis holds that POTS is caused by a hyperadrenergic state, in which there are inappropriately high levels of the “fight-or-flight”

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consistent with current consensus statements on POTS, it also concludes that there is a need to more precisely define POTS, including:

- Duration of POTS. The authors note that signs and symptoms should persist for a minimum of three months, but preferably six.
- Time course of heart rate changes. While the authors agree that tachycardia in POTS should occur within 10 minutes of upright posture, they suggest that a more narrow window of 3-10 minutes might be desirable to exclude the normal temporary heart rate increase that occurs upon upright movement.
- Reproducible measurement of heart rate changes. The authors note that heart rate responses to postural change vary from person to person, and even vary for the same person across different timepoints and measures, including tilt table and standing tests. They advise using more than one type of test over time and at different times of day. They also call for better defining the normal range of heart rate changes that occur with upright posture, by age and sex. See [www.ncbi.nlm.nih.gov/pubmed/32222376](http://www.ncbi.nlm.nih.gov/pubmed/32222376).

<sup>23</sup> [www.ncbi.nlm.nih.gov/pubmed/9274896](http://www.ncbi.nlm.nih.gov/pubmed/9274896)

<sup>24</sup> [www.ncbi.nlm.nih.gov/pubmed/15781744](http://www.ncbi.nlm.nih.gov/pubmed/15781744)

<sup>25</sup> [www.ncbi.nlm.nih.gov/pubmed/24711524](http://www.ncbi.nlm.nih.gov/pubmed/24711524)

<sup>26</sup> [www.ncbi.nlm.nih.gov/pubmed/25059240](http://www.ncbi.nlm.nih.gov/pubmed/25059240)

<sup>27</sup> [www.ncbi.nlm.nih.gov/pubmed/31405195](http://www.ncbi.nlm.nih.gov/pubmed/31405195)

<sup>28</sup> [www.ncbi.nlm.nih.gov/pubmed/26198889](http://www.ncbi.nlm.nih.gov/pubmed/26198889)

<sup>29</sup> [www.ncbi.nlm.nih.gov/pubmed/23753844](http://www.ncbi.nlm.nih.gov/pubmed/23753844)

<sup>30</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9695261](https://projectreporter.nih.gov/project_info_description.cfm?aid=9695261)

signal norepinephrine (noradrenaline) in the blood.<sup>3,11</sup> Investigators at NINDS and Vanderbilt University have partnered to investigate this idea in a large cohort of individuals with POTS.<sup>31</sup>

There is evidence that immune or autoimmune problems also contribute to POTS, perhaps after a triggering event such as an infection or injury. Individuals with POTS frequently have a comorbid autoimmune disease, such as celiac disease; inflammatory bowel disease, including Crohn's disease and ulcerative colitis; Hashimoto's thyroiditis; multiple sclerosis; rheumatoid arthritis; or Sjögren syndrome.<sup>10,11,12</sup> Some individuals with POTS also harbor autoantibodies that react to targets in the neurologic or cardiovascular system.<sup>11,12</sup> This includes autoantibodies that target cellular receptors for norepinephrine,<sup>32</sup> and for the neurotransmitter acetylcholine.<sup>33</sup> NHLBI-funded researchers are working to define the prevalence and role of norepinephrine (adrenergic) receptor autoantibodies in POTS, and to develop drugs capable of neutralizing them.<sup>34</sup> Recently, these investigators found experimental evidence supporting the theory that these autoantibodies can cause POTS. In a small animal model, they found that injections of adrenergic receptor fragments triggered the production of receptor autoantibodies and the development of postural (tilt-induced) tachycardia.<sup>35</sup>

Genetic factors probably also affect susceptibility to POTS. Supporting evidence includes the frequent association of POTS with diseases and conditions that have a strong genetic component, such as Ehlers-Danlos syndrome and celiac disease. Some research on POTS has implicated genetic pathways that intersect with the theorized autonomic and immune causes of POTS. For example, an NIH-funded study found that identical twin sisters with POTS (but not asymptomatic family members) harbored a loss-of-function mutation in the gene encoding the norepinephrine transporter;<sup>36</sup> this transporter is needed to silence norepinephrine signaling, so its loss would be expected to cause the hyperadrenergic state theorized to cause at least some POTS cases. NIH investigators also have reported POTS in families who carry gene mutations that cause increased production of  $\alpha$ -tryptase, a protein involved in immune and inflammatory reactions.<sup>37</sup>

### ***Diagnosis and Treatment of POTS***

Diagnostic criteria and tools for POTS have not been standardized, and physician awareness of POTS remains low. A large self-report survey of individuals diagnosed with POTS (*The Big POTS Survey*) found that, on average, respondents saw seven physicians over a period of about five years to obtain their diagnoses.<sup>10</sup>

Nonetheless, there are basic components to an evaluation for POTS, including measurements of heart rate and blood pressure, as well as autonomic reflex testing. Many experts recommend a tilt table test, which measures heart rate and blood pressure while the patient lies on a bed and is

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<sup>31</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9787064](https://projectreporter.nih.gov/project_info_description.cfm?aid=9787064)

<sup>32</sup> [www.ncbi.nlm.nih.gov/pubmed/24572257](http://www.ncbi.nlm.nih.gov/pubmed/24572257)

<sup>33</sup> [www.ncbi.nlm.nih.gov/pubmed/10995864](http://www.ncbi.nlm.nih.gov/pubmed/10995864)

<sup>34</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9609479](https://projectreporter.nih.gov/project_info_description.cfm?aid=9609479)

<sup>35</sup> [www.ncbi.nlm.nih.gov/pubmed/31547749](http://www.ncbi.nlm.nih.gov/pubmed/31547749)

<sup>36</sup> [www.ncbi.nlm.nih.gov/pubmed/10684912](http://www.ncbi.nlm.nih.gov/pubmed/10684912)

<sup>37</sup> [www.ncbi.nlm.nih.gov/pubmed/27749843](http://www.ncbi.nlm.nih.gov/pubmed/27749843)

tilted upright to a 60 degree angle.<sup>19,38</sup> Similar measurements might be taken before, during, and after physical activity to look for exercise intolerance. Many experts perform laboratory tests to look for abnormal blood levels of adrenaline and related chemicals, and for signs of autoimmunity, either as a potential cause of POTS or as a diagnostic of a distinct autoimmune disease.<sup>19,38</sup>

A number of evidence-based questionnaires and symptom rating scales can be useful in the assessment of POTS, including the Winker Symptom Scale, which rates orthostatic intolerance symptoms; the Orthostatic Hypotension Questionnaire; the Composite Autonomic Symptom Score (COMPASS); and the Short Form 36 Health Survey, which asks patients about their physical, mental, and social health, and any role limitations. There is no questionnaire or scale specific to POTS.

Individuals with POTS may benefit from “volume loading,” or increasing their intake of water and salt (through a high-salt diet, salt tablets, or intravenous saline) to increase their blood volume.<sup>6,39</sup> Exercise training can be a successful strategy for alleviating some POTS symptoms. In a 2016 study, researchers enrolled 251 patients with POTS into a three-month exercise program that combined endurance and strength training with increased water and salt intake.<sup>40</sup> Patients began with rowing, swimming, or a recumbent bike. Their training increased in frequency and intensity over time, and they progressed to upright biking or jogging if able. Among patients who completed the three-month program, almost all reported improved quality of life and nearly three-quarters no longer met diagnostic criteria for POTS (heart rate increase of at least 30 bpm upon standing).

Unfortunately, not all individuals with POTS are able to complete an exercise training program due to exercise intolerance.<sup>13,14</sup> Indeed, in the 2016 study, nearly 60 percent of enrolled patients were not able to complete the three-month program.

In addition to volume loading and exercise, most patients benefit from drug treatments individualized to their unique symptoms and clinical findings. Commonly used options include blood volume expanders, beta-adrenergic blocking agents (“beta blockers”), drugs to constrict the blood vessels and increase blood pressure (vasoconstrictors), and drugs that blunt the sympathetic (fight-or-flight) response, called sympatholytics.<sup>41</sup> An NHLBI-funded randomized clinical trial is evaluating the sympatholytic drug moxonidine in individuals with a sympathetic subtype of POTS defined by nerve recordings.<sup>42</sup>

Physicians also recommend that patients with POTS improve their sleep hygiene and maintain a regular sleep schedule; eat small, frequent meals rather than fewer large ones; eat a balanced, nutritious diet; increase salt intake; and avoid processed foods and simple carbohydrates.<sup>3,19</sup>

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<sup>38</sup> [www.ncbi.nlm.nih.gov/pubmed/29705015](http://www.ncbi.nlm.nih.gov/pubmed/29705015)

<sup>39</sup> [www.ncbi.nlm.nih.gov/pubmed/9244228](http://www.ncbi.nlm.nih.gov/pubmed/9244228)

<sup>40</sup> [www.ncbi.nlm.nih.gov/pubmed/26690066](http://www.ncbi.nlm.nih.gov/pubmed/26690066)

<sup>41</sup> [www.ncbi.nlm.nih.gov/pubmed/29753556](http://www.ncbi.nlm.nih.gov/pubmed/29753556)

<sup>42</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9740250](https://projectreporter.nih.gov/project_info_description.cfm?aid=9740250)

With such treatments, POTS may resolve or improve with time. In a survey of 172 teens five years after they were diagnosed with POTS, 19 percent reported that their symptoms had resolved, and an additional 67 percent reported improved or only intermittent symptoms.<sup>43</sup> Many patients reported treatment with beta blockers, increased fluid and salt intake, and exercise. In a prospective study, 54 patients with “mild” POTS were counseled on hydration, salt intake, and exercise, and then followed for one year. Throughout the year-long study, about one-third to one-half of patients were taking beta blockers, and many patients were taking other drugs commonly used to treat POTS. At the end of the study, 37 percent of patients no longer met the study’s key diagnostic criterion for POTS (increased heart rate of 30 bpm or more during head tilt).<sup>44</sup>

## **Priorities for Future POTS Research**

### ***Standardized Assessment Criteria and Tools***

The wide range of symptoms, pathology, and comorbidities associated with POTS engender challenges in diagnosing individual patients, and in defining unique subtypes of POTS within the patient population. These challenges further impede research at many levels, including the design, interpretation, and comparison of clinical studies.

The ability to define subtypes of POTS could help guide therapeutic strategies for individual patients. Moreover, subtyping could accelerate clinical trials by matching patients to investigational treatments that have the best chances of working. However, caution should be taken not to over-emphasize subtyping at this early stage of research, as it could add to the challenge of diagnosis, causing POTS to be overlooked or inappropriately ruled out in some cases.

The current lack of standard assessment criteria for POTS has a negative impact on physician awareness and patient care, with substantial delays in diagnosis and treatment for many patients. Further research into the course of POTS and its mechanisms would inform the development of POTS-specific assessment tools, perhaps including a POTS-specific patient questionnaire. Such tools would, in turn, help improve timely diagnosis, as well as appropriate patient enrollment in clinical trials and evaluation of treatment outcomes.

### ***Natural History and Longitudinal Studies***

Much of the current knowledge regarding potential risk factors for POTS and its long-term course has come from patient surveys, the largest known being *The Big POTS Survey*.<sup>10</sup> Although these self-reported data are useful, they may not offer a complete picture of POTS. Prospective, long-term observational studies of POTS would provide a more robust evidence base regarding POTS risk factors and causes, patient outcomes, and potentially effective treatments.

Larger longitudinal studies would be powerful but difficult to implement, given the lack of a

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<sup>43</sup> [www.ncbi.nlm.nih.gov/pubmed/26979650](http://www.ncbi.nlm.nih.gov/pubmed/26979650)

<sup>44</sup> [www.ncbi.nlm.nih.gov/pubmed/22795533](http://www.ncbi.nlm.nih.gov/pubmed/22795533)

consensus POTS definition, absence of standard diagnostic tools, and low physician awareness. The patient advocacy group Dysautonomia International used its website and Facebook page to promote its *Big POTS Survey*, which at the time of the workshop had reached more than 7,200 people diagnosed with POTS. This suggests a strong potential for future efforts to identify and recruit patients for large analyses. As an interim step toward large longitudinal studies, researchers could work with patient advocates to explore the establishment of a POTS registry. Other rare disease registries, such as the Ehlers-Danlos Society Global registry,<sup>45</sup> could be leveraged or serve as a model for a POTS registry. Additionally, NIH-funded cohort studies of cardiovascular or neurologic health could be leveraged to ascertain and monitor individuals with POTS.

### ***Immunological Studies***

Deeper, more thorough investigations of immune system involvement in POTS could be informative. Several case studies and small case series have tested for specific autoantibodies in individuals with POTS, and have found autoantibodies targeting adrenergic receptors and other receptor types that are involved in autonomic and cardiac function.<sup>11,33,34</sup> However, with rare exceptions,<sup>36</sup> most of the autoantibody types associated with POTS have not been shown to cause disease in model systems nor have they been correlated with symptom severity in patients. Further functional studies of these autoantibodies—including detailed analyses of how they affect target molecules, cells, and tissues—could help assess their potential to cause POTS. Clinical trials of targeted immune-modulating therapies could also determine whether autoantibodies play a primary causative role in POTS, or act more as secondary bystanders.<sup>46</sup> Finally, immunophenotyping—a method used to identify specific cell types in a mixed population (e.g., from a blood or tissue sample)—could help determine whether certain types of immune cells, including antibody-producing B cells, are altered in POTS. The gut microbiome and its interaction with the immune system may also be important in POTS given the gastrointestinal symptoms experienced by many individuals.

### ***Neurological Studies***

Description of findings related to autonomic nerve dysfunction (neuropathy) in POTS date to the first published use of the term “POTS” in 1993.<sup>47</sup> Many of the symptoms common in POTS, such as gastrointestinal problems, abnormal sweat response, and temperature dysregulation, are consistent with an autonomic neuropathy. Moreover, as discussed above, the detection of autoantibodies that target receptors of norepinephrine and acetylcholine also is consistent with impaired autonomic function.

Yet, current understanding of the nervous system’s involvement in POTS is limited. For example, several studies have found that POTS sometimes involves dysfunction in the autonomic (vagal and sympathetic) nerves that connect to the heart to control heart rate.<sup>48</sup> However, no studies have examined whether POTS also involves dysfunction in the vasomotor

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<sup>45</sup> [www.ehlers-danlos.com/eds-global-registry](http://www.ehlers-danlos.com/eds-global-registry)

<sup>46</sup> [www.ncbi.nlm.nih.gov/pubmed/2873869](http://www.ncbi.nlm.nih.gov/pubmed/2873869)

<sup>47</sup> [www.ncbi.nlm.nih.gov/pubmed/8423877](http://www.ncbi.nlm.nih.gov/pubmed/8423877)

<sup>48</sup> [www.ncbi.nlm.nih.gov/pubmed/30879357](http://www.ncbi.nlm.nih.gov/pubmed/30879357)

nerves, which control blood vessel dilation and restriction. Although one NIH-funded group developed a small-animal model for neuropathic POTS,<sup>49</sup> this model has not been widely adopted, and no others have been reported. Finally, structural and molecular studies of the autonomic nerves in patients could aid more robust investigation of the theory that autonomic neuropathy causes POTS or some types of POTS.

### ***Genetic and Sex-Specific Analyses***

As described above, case series have found gene mutations that segregate with POTS in affected families. However, most individuals with POTS do not appear to harbor the mutations identified thus far (e.g., the norepinephrine transporter mutation found in one family with POTS<sup>36</sup> was not found in a case series of men with orthostatic intolerance<sup>50</sup>). Larger scale efforts may help identify other genetic factors at play. For example, an ongoing NIH-supported study is investigating the possibility that in some cases, new mutations arising very early in development could contribute to POTS; the study is using whole exome sequencing to test for such mutations in individuals with POTS whose parents are unaffected.<sup>51</sup>

The female predominance of POTS is not understood; it could point to genetic or hormonal factors in POTS. In that regard, reports of POTS following menarche or pregnancy could be significant. Future studies could explore whether female sex hormones or significant hormonal changes affect susceptibility to POTS. Studies on the course of POTS in pregnant women could be enlightening, as well, since pregnancy has been shown to ameliorate or exacerbate the mother's autoimmune disease symptoms, depending on the disease.<sup>52</sup> If POTS has a strong autoimmune basis, pregnancy could dramatically improve or worsen its course.

### ***Imaging Studies***

Efforts to leverage new and emerging biological imaging technologies could also help shed light on POTS. For example, cardiovascular magnetic resonance imaging (MRI) is increasingly used as a non-invasive means to investigate heart structure and function in research and clinical settings,<sup>53</sup> and could enhance the current understanding of heart dysfunction in individuals with POTS. Brain imaging could be used to explore poor concentration and brain fog, which are reported by about 95 percent of people living with POTS,<sup>10,54</sup> and are likely to have a strong impact on quality of life. Research on cognitive impairment in POTS has been limited. Cognitive testing has found that deficits in attention, working memory, and executive function (i.e., planning and monitoring one's behavior) are common, but also that many individuals with perceived cognitive impairment score within normal ranges.<sup>55</sup> Cognitive deficits could arise from cardiovascular dysfunction or they could be secondary to other factors, such as sleep disturbance.<sup>16</sup> Non-invasive brain imaging, such as functional MRI (fMRI), could be used to explore and better understand these issues.

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<sup>49</sup> [www.ncbi.nlm.nih.gov/pubmed/11408377](http://www.ncbi.nlm.nih.gov/pubmed/11408377)

<sup>50</sup> [www.ncbi.nlm.nih.gov/pubmed/12589229](http://www.ncbi.nlm.nih.gov/pubmed/12589229)

<sup>51</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9625792](https://projectreporter.nih.gov/project_info_description.cfm?aid=9625792)

<sup>52</sup> [www.ncbi.nlm.nih.gov/pubmed/18716941](http://www.ncbi.nlm.nih.gov/pubmed/18716941)

<sup>53</sup> [www.ncbi.nlm.nih.gov/pubmed/29386064](http://www.ncbi.nlm.nih.gov/pubmed/29386064)

<sup>54</sup> [www.ncbi.nlm.nih.gov/pubmed/23999934](http://www.ncbi.nlm.nih.gov/pubmed/23999934)

<sup>55</sup> [www.ncbi.nlm.nih.gov/pubmed/29628432](http://www.ncbi.nlm.nih.gov/pubmed/29628432)

## ***Clinical Trials***

There have been few clinical trials to evaluate treatments for POTS. A 2018 systematic review of intervention studies in POTS identified 25 case series and only three randomized clinical trials that evaluated various treatments given for at least four weeks.<sup>56</sup> The review found significant variability in study participant characteristics, including age, symptom severity, and treatment status. There was also significant variability of outcome measures used, especially quality of life measures, which included a wide range of questionnaires, many of which were unique to one or two studies. This lack of standardization makes it difficult to compare results across studies. Intent-to-treat trials, which analyze all randomized participants, have been rare. Instead, most clinical trials in POTS have excluded data from participants who did not complete the trial intervention (e.g., because of adverse effects or difficulty with adherence), which can inflate the appearance of efficacy. The following achievements and standards could support and strengthen future clinical trials in POTS:

- An evidence-based consensus definition for POTS;
- Reducing variability among trial participants through:
  - Better understanding and identification of POTS subtypes, using biomarkers if possible;
  - Better understanding and identification of POTS comorbidities;
  - Characterization of treatment status (e.g., treatment-naïve vs. refractory);
- Development and use of standardized clinical outcome measures;
- Standardized monitoring of salt and fluid intake, and exercise;
- Trial duration of at least six months.

## ***Collaborative Research Efforts***

As summarized here, POTS has diverse clinical manifestations and potentially diverse underlying mechanisms. This heterogeneity, combined with current gaps in the understanding of POTS, points to a need for expertise and tools spanning multiple fields, including but not limited to cardiology, neurology, internal medicine, pediatrics, epidemiology, immunology, genetics, and biological imaging. Enhanced collaboration across disciplines could help accelerate POTS research, including progress in fundamental issues such as defining POTS and its subtypes and development of standard outcome measures for clinical trials.

## **Additional Ongoing and Upcoming NIH Efforts**

NIH recognizes the complexity of this debilitating disorder, and NHLBI, NINDS, and other Institutes support and conduct basic, translational, and clinical research relevant to POTS. Most of this research is conducted through investigator-initiated projects at academic and medical institutions, and focuses on finding better ways to identify, prevent, treat, and ultimately cure POTS and related diseases and conditions.

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<sup>56</sup> [www.ncbi.nlm.nih.gov/pubmed/29937049](http://www.ncbi.nlm.nih.gov/pubmed/29937049)

Ongoing NIH-funded studies to advance understanding, diagnosis, and treatment of POTS have been highlighted throughout this report. NIH supports several other basic and clinical studies relevant to POTS including, but not limited to, the following:

- The temporarily increased heart rate and blood vessel constriction that normally occur upon standing are triggered in part by an autonomic nervous system pathway called the baroreflex. However, there is a less understood pathway called the vestibulo-sympathetic reflex (VSR) that also helps maintain steady blood flow to the brain with standing and other postural changes. A project supported by the National Institute on Deafness and Other Communication Disorders (NIDCD) is developing a functional map of VSR nerve cells and their connections.<sup>57</sup>
- An NIH-funded study will assess the prevalence of orthostatic intolerance in a diverse cohort of young people with ME/CFS and controls, and will examine its relationship with cognitive fatigue and dizziness. This grant is funded by the NIH Office of the Director and managed by NICHD.<sup>58</sup>
- NIH released new trans-NIH program announcements ([PAR-20-165](#) and [PAR-20-168](#)) to stimulate research on ME/CFS, which may include studies to better understand the underlying causes and mechanisms of POTS in individuals with ME/CFS.<sup>59</sup>

## NIH Funding for POTS and Related Research

The publicly available NIH Research Portfolio Online Reporting - Expenditures and Results Tool (RePORTER)<sup>60</sup> was used to identify NIH-supported research projects related to POTS that are active in fiscal year 2020 (FY 2020), and to estimate total NIH funding for this research. To capture relevant projects in both clinical and basic research, RePORTER was searched for active project descriptions containing the terms “postural orthostatic tachycardia” or “orthostatic intolerance.”<sup>61</sup>

The analysis revealed that at the time of this report, five NIH Institutes are supporting almost \$6 million in basic, translational, and clinical research relevant to POTS (see Table 1 for total NIH funding by Institute, and Table 2 in the Appendix for a full list of projects). NIH is committed to advancing research to better understand, prevent, and treat POTS. Although NIH

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<sup>57</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9679488](https://projectreporter.nih.gov/project_info_description.cfm?aid=9679488)

<sup>58</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9315183](https://projectreporter.nih.gov/project_info_description.cfm?aid=9315183)

<sup>59</sup> In April 2020, NIH released two funding opportunity announcements related to this program. One announcement invites standard R01 research project grant proposals ([PAR-20-165](#)). The other announcement invites exploratory/developmental research grant proposals, which are capped at two years and \$275,000 in total direct costs ([PAR-20-168](#)).

<sup>60</sup> <https://projectreporter.nih.gov/reporter.cfm>

<sup>61</sup> On the RePORTER website, under *Fiscal Year*, the check boxes were used to select “Active Projects.” The search terms were entered into the *Text Search* box exactly as follows: “postural orthostatic tachycardia” or “orthostatic intolerance”

*Text Search Logic* was set to “Advanced” and *Limit Project search* was set to “Project Title,” “Project Terms,” and “Project Abstract.” These settings were used to narrow the results to projects with a substantive focus on the search terms, rather than an incidental reference. The search results were then manually curated to identify any projects without clear relevance to POTS, and these were excluded. Funding of additional POTS-related projects is possible during the remainder of FY 2020.

generally does not set aside funding for research on specific diseases, NIH encourages investigators to apply for funding to support POTS research, including research that addresses the scientific gaps and opportunities summarized in this report, and will fund meritorious applications after peer review.

Per a directive from Congress in FY 2020 appropriations (H.R.1865/P.L. 116-94; p. 115)<sup>62</sup> and in the interest of making it easier for the public to identify and track NIH funding for POTS-related research, NIH is currently developing a POTS-specific category under its Research, Condition, and Disease Categorization (RCDC) system.<sup>63</sup> This new RCDC category will enable NIH to analyze, track, and publicly report its annual investments in POTS-related research projects.

**Table 1. Active NIH Funding for Projects on POTS and Related Research**

NIH Institute	Number of Projects	Active Funding
NHGRI*	1	\$166,235
NHLBI	3	\$1,588,514
NIDCD	1	\$511,179
NICHD**	1	\$400,541
NINDS	2	\$3,099,849
<b>Total</b>	<b>8</b>	<b>\$5,766,318</b>

\* National Human Genome Research Institute.

\*\*This grant is funded by the NIH Office of the Director and managed by NICHD.<sup>58</sup>

## Conclusion

Despite growing recognition of POTS by clinicians and scientists, persistent challenges remain in patient care and research. These include heterogeneity of symptoms and comorbidities in the patient population, an evolving clinical definition of POTS, and gaps in understanding its causes and mechanisms.

Priorities for future POTS research could include:

- Development of standard assessment criteria, tools, and outcome measures;
- Collaborative efforts to collect and analyze objective natural history data;
- Further research on the mechanisms of POTS, including studies of:
  - Immune system involvement, especially focused on autoimmunity and microbiome interactions; and
  - Nervous system involvement;
- Further analysis of known or putative risk factors, including genetics and female sex;
- Enhanced use of state-of-the-art cardiac and brain imaging;
- Design and execution of randomized, controlled, intent-to-treat clinical trials of appropriate duration, using standardized patient criteria and outcome measures; and

<sup>62</sup> [www.govinfo.gov/content/pkg/CPRT-116HPRT38679/pdf/CPRT-116HPRT38679.pdf](http://www.govinfo.gov/content/pkg/CPRT-116HPRT38679/pdf/CPRT-116HPRT38679.pdf)

<sup>63</sup> [https://report.nih.gov/categorical\\_spending.aspx](https://report.nih.gov/categorical_spending.aspx)

- Enhanced multi-disciplinary collaboration.

NIH is committed to supporting research to advance the understanding of POTS and to support timely, effective diagnosis and treatment for patients. The current NIH research portfolio relevant to POTS spans basic research on the autonomic control of blood flow to clinical research on drug therapies for POTS. With a program that was announced in FY 2020 and the first grants expected to be funded in FY 2021, NIH hopes to stimulate additional research on the underlying causes and mechanisms of POTS in individuals with ME/CFS. In addition, NIH encourages investigators with an interest in the challenges and priorities outlined in this report to submit appropriate project applications, and to seek guidance from NIH program officials where needed.

## Appendix

### NIH Workshop Agenda: Postural Orthostatic Tachycardia Syndrome (POTS) State of the Science, Clinical Care, and Research

Monday, July 29, 2019  
8:00am-4:30pm  
Bethesda, MD 20817

- 8:30 a.m. – 8:35 a.m. Welcome from NIH IC/Division Directors
- 8:35 a.m. – 8:45 a.m. Introductions: Co-Chairs and Participants  
Objectives of this Workshop-NIH Program Officers  
Format of the Workshop
- 8:45 a.m. – 9:00 am **Brief Overview of POTS**  
Clinical presentation, evaluation techniques, what is known about the epidemiology of POTS, and current clinical care options  
Definition of POTS  
Presenters (Co-Chairs): Satish Raj and Steven Vernino
- 9:00 a.m. - 12:30 p.m. **State of Knowledge by Body System Sessions**  
*Current understanding of the etiology, pathogenesis, clinical evaluation, and management of POTS; review of unanswered questions; and discussion of research needs*
- 9:00 a.m. – 9:30 a.m. Clinical Presentation, Epidemiology and Natural History -Face of POTS from the Big POTS Survey  
Presenter: Lauren Stiles  
Facilitator: Blair Grubb
- 9:30 a.m. - 10:00 a.m. Etiology: Genetics, Co-Morbid Conditions and Clinical Associations (e.g., EDS, Sjogren’s, Mast Cell Activation Syndrome, ME/CFS)  
Presenter: Artur Fedorowski  
Facilitator: Taylor Doherty
- 10:00 a.m. – 10:15 a.m. Break
- 10:15 a.m. - 10:45 a.m. Pathophysiology: Cardiovascular, Pulmonary, Renin-Angiotensin, and Sympathetic Nervous Systems  
Presenter: David Systrom  
Facilitator: Italo Biaggioni
- 10:45 a.m. - 11:15 a.m. Pathophysiology: Immunology of POTS  
Presenter: Jonas Axelsson

Facilitator: Steve Vernino

- 11:15 a.m. – 11:45 a.m.      Autonomic Testing, Symptom/Severity Scoring  
Presenter: Glen Cook  
Facilitator: Andre Diedrich
- 11:45 a.m. – 12:15 p.m.      Gastrointestinal Systems  
Presenter: Laura Pace  
Facilitator: Cyndya Shibao
- 12:15 p.m. – 12:45 p.m.      Break
- 12:45 p.m. – 1:05 p.m.      Sleep and Fatigue Issues  
Presenter: Mitch Miglis  
Facilitator: Peter Rowe
- 1:05 p.m. – 1:25 p.m.      Cognitive and Neuropsychological Issues  
Presenter: Amy Arnold  
Facilitator: Tae Chung
- 1:25 p.m. – 1:45 p.m.      Headache and other Neurological Abnormalities  
Presenter: Melissa Cortez  
Facilitator: Roy Freeman
- 1:45 p.m. – 2:05 p.m.      Pediatric Considerations  
Presenter: Jeffrey Boris  
Facilitator: Jeffrey Moak
- 2:05 p.m.– 2:35 p.m.      Therapy Update  
Presenter: Brent Goodman  
Facilitator: Robert Sheldon
- 2:35 p.m. – 2:45 p.m.      Break
- 2:45 p.m. – 3:30 p.m.      **Subgroup Discussions**  
Break into Subgroups to Identify Research Needs and Priorities.
1. Clinical Presentation, Symptoms and Comorbidities  
(e.g., fatigue, GI symptoms, cognitive changes, headache)
  2. Pathophysiology: Cardiopulmonary, Renin Angiotensin,  
Sympathetic Nervous Systems, Small Fibers
  3. Pathophysiology: Immunology of POTS

4. Autonomic Testing, Symptom/Severity Scoring, Common Research Data Elements

3:30 p.m. – 4:30 p.m.

**Concluding Discussion**

Moderators: Satish Raj and Steven Vernino

Participants: All

4:30 p.m.

Adjourn

**Workshop Participants**

**NIH Contacts**

Cheryl L. McDonald, MD; Division of Cardiovascular Sciences, NHLBI

Codrin Lungu, MD; Division of Clinical Research, NINDS

Karen C. Lee, MD, MPH; Director, Behavioral Pediatrics and Health Promotion Program, NICHD

**Workshop Co-Chairs**

Satish R. Raj, MD, MSci; University of Calgary

Steven A. Vernino, MD, PhD; UT Southwestern Medical Center

**Invited Experts**

Hasan Abdallah, MD; Children's Heart Institute

Amy C. Arnold, PhD; Penn State College of Medicine

Jonas Axelsson, MD, PhD; Karolinska University Hospital

Jeffrey R. Boris, MD; Pediatric Cardiologist, Media, Pennsylvania

Italo Biaggioni, MD; Vanderbilt University Medical Center

Kamal R. Chémali, MD; Eastern Virginia Medical School

Tae Chung, MD; Johns Hopkins University

Glen A. Cook, MD, LCDR; Uniformed Services University

Melissa Cortez, DO; University of Utah

Anil Darbari, MD, MBA; Washington School of Medical Health Sciences

André Diedrich, MD, PhD; Vanderbilt University Medical Center

Taylor Doherty, MD; University of California, San Diego

Artur Fedorowski, MD; Skåne University Hospital

Roy Freeman, MD; Harvard Medical School

David S. Goldstein, MD, PhD; Autonomic Medicine Section, NINDS

Brent P. Goodman, MD; Mayo Clinic Arizona

Blair P. Grubb, MD; The University of Toledo Medical Center

Mitchell Miglis, MD; Stanford University

Amanda J. Miller, PhD; Penn State College of Medicine

Jeffrey Moak, MD; Children's National Health System

Laura A. Pace, MD, PhD; University of Utah

Peter C. Rowe, MD; Johns Hopkins University School of Medicine

Robert S. Sheldon, MD, PhD; University of Calgary  
Cyndya A. Shibao, MD, MSci; Vanderbilt University Medical Center  
Julian M. Stewart, MD, PhD; New York Medical College  
Lauren Stiles, JD; Stony Brook University School of Medicine; Dysautonomia International  
David M. System, MD; Harvard Medical School

**Government and Organizational Participants**

Joanna Derksen Bare; Office of Management, NHLBI  
Jean Bérubé, JD; Office of Science Policy, Engagement, Education, and Communications, NHLBI  
Andrew Breeden, PhD; Division of Neuroscience, NINDS  
Marc Charette, PhD; Division of Cardiovascular Sciences, NHLBI  
Shara Grant, PhD; Postdoctoral Fellow, NCCIH  
Jacqueline Rutter Gully; Dysautonomia International  
Christy Jagdfeld, CPA; Dysautonomia International  
Walter Koroshetz, MD; Director, NINDS  
Barbara McMakin; Office of Communications and Public Liaison, NINDS  
Gail D. Pearson, MD, ScD; Associate Director, Division of Cardiovascular Sciences, Director, Office of Clinical Research, NHLBI  
Allison Ramiller, Solve ME/CFS Initiative  
Daniel Stimson, PhD, JD; Office of Science Policy, Engagement, Education, and Communications, NHLBI  
Christine Torborg, PhD; Office of Science Policy and Planning, NINDS  
Elizabeth R. Unger, MD, PhD; Centers for Disease Control and Prevention  
Vicky Whittemore, PhD; Channels, Synapses, and Circuits Cluster, NINDS

**Table 2. Active NIH Projects on POTS and Related Research – Details**

<b>Institute/OD</b>	<b>Project No.</b>	<b>Project Title</b>	<b>Active Funding</b>
NHGRI	K08 HG008986-03	Individual Genomic Analyses to Discover the Molecular Basis and Mechanisms Contributing to Adult-Onset Disease <sup>51</sup>	\$166,235
NHLBI	R01 HL128393-03	Autoimmune Basis for Postural Tachycardia Syndrome <sup>34</sup>	\$587,364
NHLBI	R56 HL142583-01	Autonomic Determinants of Postural Tachycardia Syndrome <sup>42</sup>	\$390,661
NHLBI	R01 HL134674-03	Cardiovagal Baroreflex Deficits Impair Neurovascular Coupling and Cognition in Postural Tachycardia Syndrome <sup>30</sup>	\$610,489
NICHD/OD	R01 HD072208-05	Pediatric CFS in a Community-Based Sample <sup>58</sup>	\$400,541
NIDCD	R01 DC008846-11	Chemical Anatomy and Synaptology of Vestibulo-Sympathetic Pathways <sup>57</sup>	\$511,179
NINDS	U54 NS065736-10	Autonomic Rare Diseases Clinical Research Consortium <sup>64</sup>	\$1,250,001
NINDS	U54 NS105541-03	Cornell ME/CFS Collaborative Research Center <sup>65</sup>	\$1,849,848

<sup>64</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9564196](https://projectreporter.nih.gov/project_info_description.cfm?aid=9564196)

<sup>65</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9774340](https://projectreporter.nih.gov/project_info_description.cfm?aid=9774340)