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March 4, 2020

Francis Collins, MD, PhD
Director, National Institutes of Health
Building 1
9000 Rockville Pike
Bethesda, MD 20892

Re: NIH Report on Postural Orthostatic Tachycardia Syndrome (POTS)

Dear Dr. Collins,

The undersigned researchers and clinicians write to you to express concerns regarding the recent NIH report, "Postural Orthostatic Tachycardia Syndrome (POTS): State of the Science, Clinical Care, and Research" which you submitted to the House and Senate Appropriations Committees on January 31, 2020. We have concerns regarding the process NIH implemented to create the report. Additionally, there are several factual errors in the report, and the report fails to provide the information requested by Congress, which we consider essential to moving this field of research forward.

Concerns About The Process NIH Used to Create the Report

As you know, in the report accompanying the fiscal year (FY) 2019 appropriations for the Department of Health and Human Services, the Senate Committee on Appropriations stated, in pertinent part:

*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 the 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 Reports 115-289, page 92) (emphasis added)*

On July 29, 2019, 29 POTS experts from around the world gathered at the NIH offices in Bethesda, MD for the first-ever NIH research meeting on POTS. The group was eager to begin a conversation with NIH on the critical unmet needs in our field and exciting opportunities for new research that would allow us to deliver more effective treatments for millions of Americans living with POTS.

Unfortunately, the resulting NIH report does not reflect the findings of the meeting participants as directed by Congress. The report was written by NIH staff who, respectfully, have little to no expertise in POTS.

The meeting chairs, Satish Raj, MD, MSCI and Steven Vernino, MD, PhD, were the only meeting participants allowed to see a draft of the report prepared by NIH staff. A majority of the substantive edits provided by the meeting chairs were disregarded by NIH staff and not incorporated into the final report. No response was ever provided by NIH staff to the edits the meeting chairs requested, nor did the meeting chairs see a final copy of the report before it was submitted to Congress. The first time the meeting chairs saw the final report was February 11, 2020, eleven days after the final report was submitted to Congress.

None of the other POTS expert meeting participants were given an opportunity to review or comment on the draft report, despite the fact that their names appear on it. Other POTS expert meeting participants requested the opportunity to review and comment on the draft, but their requests were denied by NIH staff.

A fair and transparent process aimed at meeting the Congressional directive to provide a report that included the participants' findings would have allowed all of the POTS experts invited to the meeting adequate time to review and comment upon the report. If NIH staff disagreed with the POTS expert participants' findings, NIH staff could have noted this in the report or in an accompanying letter. Instead, the perspectives of the POTS experts who lent their time and talents to the NIH for the purposes of this meeting were largely ignored.

The Report Contains Several Factual Errors

The report contains several factual errors that should be corrected by the NIH in an amended report. The patient community, the academic community, and the media is likely to cite this report in the future; therefore, NIH has an obligation to ensure that the report is factually accurate.

First, the report asserts that NIH is funding over \$9.35M in POTS or related research. This is a grossly inflated number. Of the 14 studies included on the list prepared by NIH staff, only four of them are POTS or POTS related research studies, and one additional grant has a small portion of its funding related to POTS. In total, NIH is currently funding less than \$2M in grants related to POTS (see attached spreadsheet). NIH staff ignored edits on the draft report from both meeting chairs seeking to correct this misinformation. This is discussed further below.

Second, the report implies there is serious disagreement amongst experts on the POTS diagnostic criteria, relabeling internationally accepted consensus criteria as "key features" rather than diagnostic criteria. There is no serious disagreement amongst a majority of experts on the POTS diagnostic criteria. The NIH minimized the significance of internationally accepted consensus criteria and ignored edits on the draft report from the meeting chairs seeking to correct this misinformation.

Third, the report falsely claims that chronic fatigue syndrome is the most common co-morbidity in POTS. This was not presented by any expert during the NIH meeting, nor does this appear anywhere in the POTS literature. NIH provides two citations to support this claim. Citation 7 is a 2000 study from Mayo Clinic that does not make any assessment or assertion regarding the percentage of POTS patients who have co-morbid chronic fatigue syndrome. Citation 8 confirms that migraine, irritable bowel syndrome and Ehlers-Danlos syndrome are more common co-morbidities in POTS than chronic fatigue syndrome. Throughout the literature and in clinical practices that serve a large POTS population, it is clear that small fiber neuropathy, migraine, autoimmunity, neurocardiogenic syncope and Ehlers-Danlos syndrome are all equally or more common than chronic fatigue syndrome in the POTS population. NIH staff ignored comments from the meeting chairs regarding the NIH's over-emphasis of the relevance of chronic fatigue syndrome in the report.

Fourth, the report states that half of individuals diagnosed with POTS are children and adolescents. This was not asserted by any expert during the meeting, nor is this supported by the published data on POTS. About half of POTS patients develop POTS symptoms in adolescence, and half develop POTS symptoms in adulthood.¹ A majority of adolescent onset patients have not fully recovered by the time they reach adulthood,² therefore a majority of individuals living with POTS are adults.

Fifth, the report claims “NIH investigators also have reported POTS in families who carry genetic mutations that cause increased production of alpha-tryptase.” NIH investigators did not report a genetic mutation. They reported on a few families who had duplicate copies of the alpha-tryptase gene, which is known to occur in about 5% of the general population.

Sixth, the report claims that “[p]hysicians also recommend that patients with POTS regularly check and track their blood pressure and pulse.” This was not stated by any of the experts during the meeting, and it is contrary to the advice that is given by most POTS experts to their patients. Regular monitoring of blood pressure and pulse is only recommended by clinicians to POTS patients in limited circumstances, such as when starting a new medication, or when beginning a new exercise regimen.

Seventh, the report states that structural studies of the autonomic nerves would be invasive and “unlikely to benefit patients.” The assertion that neuropathology studies are unlikely to benefit patients was never made during the expert meeting. In many autonomic labs, it is routine clinical practice to perform skin punch biopsies to screen for small fiber neuropathy in POTS patients. This benefits patients, because it can confirm the presence of small fiber neuropathy, providing validation for the patient, and leading to identification of a treatable underlying cause in some cases.

The Report Fails To Provide the Information Requested by Congress

Congress directed NIH to prepare a report that reflected the meeting participants’ findings on four objectives:

(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).

Objective 1

The report barely achieves objective 1. There has been 25 years of research progress in understanding POTS, but the report only includes a three-page summary. Outdated studies are cited throughout the report. A majority of the study findings POTS experts presented during the meeting were not mentioned or cited in the report.

Objective 2

The report broadly describes eight priority areas for future research. This is the one part of the report that seems to have met the objective.

¹ Shaw, BH, Stiles, LE, Bourne, K, Green, EA, Shibao, CA, Okamoto, LE, Garland, EM, Gamboa, A, Diedrich, A, Raj, V, Sheldon, RS, Biaggioni, I, Robertson, D, Raj, SR. The face of postural tachycardia syndrome – insights from a large cross-sectional online community-based survey. *J Intern Med* 2019; 286: 438– 448.

² Bhatia R, Kizilbash SJ, Ahrens SP, Killian KM, Kimmes SA, Knoebel EE, Muppa P, Weaver AL, Fischer PR. Outcomes of Adolescent-Onset Postural Orthostatic Tachycardia Syndrome. *J Pediatr.* 2016;173:149–153.

Objective 3

As noted above, the report grossly exaggerates NIH’s ongoing efforts to advance the scientific understanding of POTS by including millions of dollars in research funding that has nothing to do with POTS in the report.

NIH staff completely disregarded edits requested by the meeting chairs, who advised NIH staff that most of the funding on the list was not related to POTS whatsoever.

The items in **bold** in this table were presented in the NIH report as part of “Table 1 - Active NIH Funding for Projects on POTS and Related Research” (NIH POTS Report, page 15). The items in *red italics* are the actual numbers, as determined by the meeting chairs and other POTS experts who carefully reviewed each project NIH included in the report.

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

<u>NIH ICO</u>	Number of projects claimed to be POTS related by NIH	<i>Number of POTS related projects determined by POTS experts</i>	Active POTS Related Funding Claimed by NIH	<i>Active POTS Related Funding determined by POTS experts</i>
NHGRI	1	<i>1</i>	\$166,235	<i>\$166,235</i>
NHLBI	5	<i>3</i>	\$2,270,230	<i>\$1,588,514</i>
NIDCD	1	<i>NONE</i>	\$511,179	<i>NONE</i>
NICHD	1	<i>NONE</i>	\$400,541	<i>NONE</i>
NINDS	4	<i>NONE</i>	\$4,783,993	<i>NONE</i>
Office of the Director	2	<i>NONE</i>	\$1,226,406	<i>NONE</i>
Totals	14	<i>4</i>	\$9,358,584	<i>\$1,754,749</i>

Detailed comments on the relevance or non-relevance of each study listed by NIH can be found on the attached spreadsheet.

For example, NIH claimed an NINDS intramural study, Biomarkers of Catecholaminergic Degeneration, is a POTS related study. However, the study is about neurodegenerative disorders like Parkinson’s and multiple system atrophy, diseases that occur in the elderly that have nothing to do with POTS. The meeting chairs pointed out this error to NIH staff, but their requested edits were ignored.

In addition to exaggerating the amount of funds NIH is spending on POTS or POTS related research, the report offers no information on upcoming efforts by NIH to advance the scientific understanding of POTS between 2020 and 2025. In fact, all of the POTS related grants cited by NIH expire by 2023.

Objective 4

The report completely fails to address objective 4. No estimate of the level of funding needed to achieve objectives 2 and 3 is provided.

While the report was supposed to reflect the participants’ findings on the amount of funding needed to achieve the research objectives, NIH staff told the POTS expert speakers prior to the meeting that they were not allowed to recommend or even mention dollar amounts needed to fund the research priorities identified. There was no time on the agenda developed by NIH staff allocated to discussing what POTS research NIH was already funding, or the funding needed to achieve the priority areas identified by the meeting participants.

The report states “NIH is committed to sustained funding in order to advance research on POTS.” Again, this is not what Congress asked the NIH to report on. Congress asked NIH to report **the participants’ findings** regarding the top research priorities until 2025, and how much it would cost to fund those priorities. Moreover, sustained funding of \$2M per year is insufficient to properly study even one of the eight priority areas mentioned in the report.

Conclusion

We urge the NIH to prepare a revised report with input from the meeting chairs and other POTS experts that offers Congress more accurate information on POTS, an accurate assessment of NIH’s active POTS research funding, specific priority areas for future research, and the funding necessary to achieve those objectives by 2025.

Sincerely,

Satish Raj, MD, MSCI, FACC

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cc: Hon. Senator Roy Blunt
Hon. Senator Patty Murray
Hon. Representative Rosa DeLauro
Hon. Representative Tom Cole
Members of the Senate Appropriations Committee, Subcommittee on Labor, Health and Human Services, Education and Related Agencies
Members of the House Appropriations Committee, Subcommittee on Labor, Health and Human Services, Education and Related Agencies

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NIH Claimed POTS Funding vs Actual POTS Funding

March 4, 2020

Institute	Grant Number	Study Title and Citation in NIH Report	NIH Reporter Database Link	NIH Claimed POTS Related Research Funding	Actual NIH POTS Related Research Funding	POTS Expert Determination: Is this a POTS or POTS Related Study?	POTS Expert Notes
NHGRI	K08 HG008986-03	Individual Genomic Analyses to Discover the Molecular Basis and Mechanisms Contributing to Adult-Onset Disease 49	https://projectreporter.nih.gov/project_info_description.cfm?aid=9625792&icde=0	\$166,235	\$166,235	POTS Related	POTS Expert Notes This study is primarily focused on Ehlers-Danlos syndrome. Project ends Jan 2022.
NHLBI	R01 HL128393-03	Autoimmune Basis for Postural Tachycardia Syndrome 34	https://projectreporter.nih.gov/project_info_description.cfm?aid=9699979&icde=48577742	\$587,364	\$587,364	POTS	This is a POTS study. Project ends Dec 2020.
NHLBI	R00 HL122507-05	Autonomic: Angiotensin-(1-7) Interactions in Hypertension 55	https://projectreporter.nih.gov/project_info_description.cfm?aid=9482723	\$244,491		NOT POTS	Principal Investigator Dr. Amy Arnold confirms that this study is not related to POTS research. Study population is autonomic failure and rats with metabolic syndrome.
NHLBI	R56 HL42583-01	Autonomic Determinants of Postural Tachycardia Syndrome 42	https://projectreporter.nih.gov/project_info_description.cfm?aid=9740250&icde=48577789&ddparam=8&ddvalue=8&ddsub=8&cr=1&cs=AS&cb=AS&cballe=AS&cballe	\$390,661	\$390,661	POTS	This is a POTS study. Project ends Aug 2023
NHLBI	R01 HL134674-03	Cardiovascular Baroreflex Deficits Impair Neurovascular Coupling and Cognition in Postural Tachycardia Syndrome 30	https://projectreporter.nih.gov/project_info_description.cfm?aid=9695261&icde=48577797&ddparam=8&ddvalue=8&ddsub=8&cr=1&cs=AS&cb=AS&cballe=AS&cballe	\$610,489	\$610,489	POTS	This is a POTS study. Project ends May 2021
NHLBI	R15 HL147286-01	Identification of Central Neural Pathways Responsible for FG21-induced Changes in Sympathetic Metabolic and Cardiovascular Activity 61	https://projectreporter.nih.gov/project_info_description.cfm?aid=9731974	\$437,225		NOT POTS	This is about exploring mechanisms of metabolic syndrome that regulate blood pressure, and it has nothing to do with POTS.
NICH/D	R01 HD072208-05	Pediatric CFS in a Community-Based Sample 58	https://projectreporter.nih.gov/project_info_description.cfm?aid=9315183	\$400,541		NOT POTS	This study is screening a pediatric population for chronic fatigue syndrome, and then screening CFS patients for orthostatic intolerance. There is no mention of the POTS criteria being applied. The PI has never published on POTS before.
NIDCD	R01 DC008846-11	Chemical Anatomy and Synaptology of Vestibulo-Sympathetic Pathways 56	https://projectreporter.nih.gov/project_info_description.cfm?aid=9679288	\$511,179		NOT POTS	This study is exploring vestibular pathways that regulate blood pressure, claimed relevance to "neurogenic orthostatic hypotension and intolerance." There is no evidence linking POTS to vestibular BP regulation problems. PI has never published on POTS.
NINDS	US4 NS065736-10	Autonomic Rare Diseases Clinical Research Consortium 62	https://projectreporter.nih.gov/project_info_description.cfm?aid=9564196	\$1,250,001		Most of this is NOT POTS	This is the Autonomic Disorders Consortium grant for research on rare autonomic disorders like MSA, PAF and AAG. POTS is not a rare autonomic disorder. A small amount of the total may have been spent to support Dr. Diedrich's vagus nerve stimulation study in POTS. Grant expires June 2020 and the Autonomic Disorders Consortium was not renewed by NIH.
NINDS	ZIA NS003034-12	Biomarkers of Catecholaminergic Neurodegeneration 31	https://projectreporter.nih.gov/project_info_description.cfm?aid=10018406&icde=48577672&ddparam=8&ddvalue=8&ddsub=8&cr=2&cs=AS&cb=AS&cballe=AS&cballe	\$1,495,263		NOT POTS	This is an intramural grant to study Parkinsons/MSA. PI confirmed that this study has nothing to do with POTS.
NINDS	US4 NS105541-03	Cornell ME/CFS Collaborative Research Center 63	https://projectreporter.nih.gov/project_info_description.cfm?aid=9774340	\$1,849,848		NOT POTS	This is an ME/CFS study that has no mention of POTS in the study description on the Reporter database. PI has never published on POTS. Cornell doesn't even see POTS patients. They refer to Columbia.
NINDS	K23 NS109274-01A1	Mechanisms and Clinical Impact of Myocardial Injury Following Traumatic Brain Injury 64	https://projectreporter.nih.gov/project_info_description.cfm?aid=9816144	\$188,881		NOT POTS	This is a study about hypotension and cardiac injury in severe TBI. Severe TBI is not associated with POTS. Hypotension and myocardial injury are not associated with POTS. PI has never published on POTS.
OD	OT2 OD026580-01S1	Development of the Predictive NeuroCardiovascular Simulator 57	https://projectreporter.nih.gov/project_info_description.cfm?aid=10092300&icde=4859554&ddparam=8&ddvalue=8&ddsub=8&cr=1&cs=AS&cb=AS&cballe=AS&cballe	\$691,875		NOT POTS	This is a study about mapping pathways of autonomic cardiovascular control with the goal of treating arrhythmias. POTS is not an arrhythmia. POTS is not mentioned in the NIH Reporter abstract. The PI has never published on POTS.
OD	OT2 OD023867-01S4	Mapping the Linkage between Auricular Vagus Nerve Receptors and Cardiovascular Modulation 65	https://projectreporter.nih.gov/project_info_description.cfm?aid=9981061	\$534,531		NOT POTS	This is mapping of the auricular branch of the vagus branch, which has nothing to do with POTS. PI has never published on POTS.

\$9,358,584 NIH Claimed POTS Related Research Funding	\$1,754,749 Actual NIH POTS Related Research Funding
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