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## **Clinical autonomic nervous system laboratories in Europe: a joint survey of the European Academy of Neurology and the European Federation of Autonomic Societies**

Habek, M.; Leys, F.; Skoric, M.K.; Carneiro, D.R.; Calandra-Buonaura, G.; Camaradou, J.; ...  
; European Network Clinical ANS Labs

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## ORIGINAL ARTICLE

# Clinical autonomic nervous system laboratories in Europe

## A joint survey of the European Academy of Neurology and the European Federation of Autonomic Societies

Mario Habek<sup>1,2</sup>  | Fabian Leys<sup>3</sup>  | Magdalena Krbot Skorić<sup>1,4</sup> | Diogo Reis Carneiro<sup>5,6</sup> |  
Giovanna Calandra-Buonaura<sup>7,8</sup> | Jennifer Camaradou<sup>9,10</sup>  | Giacomo Chiaro<sup>11,12</sup> |  
Pietro Cortelli<sup>7,8</sup>  | Cristian Falup-Pecurariu<sup>13</sup> | Roberta Granata<sup>3</sup> | Pietro Guaraldi<sup>7,8</sup> |  
Raimund Helbok<sup>3</sup> | Max J. Hilz<sup>14,15</sup>  | Valeria Iodice<sup>11,12</sup> | Jens Jordan<sup>16</sup> |  
Evert C. A. Kaal<sup>17</sup> | Anita Kamondi<sup>18</sup> | Anne Pavy Le Traon<sup>19</sup>  | Isabel Rocha<sup>20</sup> |  
Johann Sellner<sup>21,22</sup> | Jean Michel Senard<sup>23</sup> | Astrid Terkelsen<sup>24</sup> | Gregor K. Wenning<sup>3</sup> |  
Thomas Berger<sup>25</sup> | Roland D. Thijs<sup>26,27</sup>  | Walter Struhal<sup>28</sup>  | Alessandra Fanciulli<sup>3</sup>  |  
the Collaborators of the European Network of Clinical ANS laboratories

<sup>1</sup>Department of Neurology, University Hospital Centre Zagreb, Zagreb, Croatia

<sup>2</sup>Department of Neurology, University of Zagreb, School of Medicine, Zagreb, Croatia

<sup>3</sup>Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

<sup>4</sup>Faculty of Electrical Engineering and Computing, University of Zagreb, Zagreb, Croatia

<sup>5</sup>Neurology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

<sup>6</sup>Faculty of Medicine, University of Coimbra, Coimbra, Portugal

<sup>7</sup>IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

<sup>8</sup>Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

<sup>9</sup>Patient Partner of the EAN Scientific Panel for Autonomic Nervous System Disorders, London, UK

<sup>10</sup>UCL Social Research Institute, University College London, London, UK

<sup>11</sup>Autonomic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

<sup>12</sup>UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK

<sup>13</sup>Department of Neurology, Faculty of Medicine, Transilvania University, Brasov, Romania

<sup>14</sup>Icahn School of Medicine at Mount Sinai, New York, New York, USA

<sup>15</sup>Department of Neurology, University Erlangen-Nuremberg, Erlangen-Nuremberg, Germany

<sup>16</sup>Institute of Aerospace Medicine, German Aerospace Center (DLR) and Medical Faculty, University of Cologne, Cologne, Germany

<sup>17</sup>Department of Neurology, Maasstad Ziekenhuis, Rotterdam, The Netherlands

<sup>18</sup>Department of Neurology, National Institute of Mental Health, Neurology and Neurosurgery, Budapest, Hungary

<sup>19</sup>Department of Neurology, Centre Hospitalier Universitaire de Toulouse and INSERM U 1297, Toulouse, France

<sup>20</sup>Institute of Physiology, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

<sup>21</sup>Department of Neurology, Landeskrankenhaus Mistelbach-Gänserndorf, Mistelbach, Austria

<sup>22</sup>Department of Neurology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

<sup>23</sup>Department of Cardiology, Toulouse University Hospital, Institute des Maladies Métaboliques et Cardiovasculaires, INSERM U 1297, Toulouse, France

<sup>24</sup>Department of Neurology, Aarhus University Hospital and Danish Pain Research Center, Aarhus University, Aarhus, Denmark

<sup>25</sup>Department of Neurology, Medical University of Vienna, Vienna, Austria

<sup>26</sup>Department of Neurology, Leiden University Medical Centre, Leiden, The Netherlands

European Network of Clinical ANS Laboratory (members are listed in Acknowledgments section).

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<sup>27</sup>Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, The Netherlands

<sup>28</sup>Department of Neurology, University Hospital Tulln, Karl Landsteiner University of Health Sciences, Tulln, Austria

### Correspondence

Alessandra Fanciulli, MD, PhD,  
Department of Neurology, Medical  
University of Innsbruck, Anichstraße 35,  
A-6020 Innsbruck, Austria.  
Email: [alessandra.fanciulli@i-med.ac.at](mailto:alessandra.fanciulli@i-med.ac.at)

### Abstract

**Background and purpose:** Disorders of the autonomic nervous system (ANS) are common conditions, but it is unclear whether access to ANS healthcare provision is homogeneous across European countries. The aim of this study was to identify neurology-driven or interdisciplinary clinical ANS laboratories in Europe, describe their characteristics and explore regional differences.

**Methods:** We contacted the European national ANS and neurological societies, as well as members of our professional network, to identify clinical ANS laboratories in each country and invite them to answer a web-based survey.

**Results:** We identified 84 laboratories in 22 countries and 46 (55%) answered the survey. All laboratories perform cardiovascular autonomic function tests, and 83% also perform sweat tests. Testing for catecholamines and autoantibodies are performed in 63% and 56% of laboratories, and epidermal nerve fiber density analysis in 63%. Each laboratory is staffed by a median of two consultants, one resident, one technician and one nurse. The median (interquartile range [IQR]) number of head-up tilt tests/laboratory/year is 105 (49–251). Reflex syncope and neurogenic orthostatic hypotension are the most frequently diagnosed cardiovascular ANS disorders. Thirty-five centers (76%) have an ANS outpatient clinic, with a median (IQR) of 200 (100–360) outpatient visits/year; 42 centers (91%) also offer inpatient care (median 20 [IQR 4–110] inpatient stays/year). Forty-one laboratories (89%) are involved in research activities. We observed a significant difference in the geographical distribution of ANS services among European regions: 11 out of 12 countries from North/West Europe have at least one ANS laboratory versus 11 out of 21 from South/East/Greater Europe ( $p = 0.021$ ).

**Conclusions:** This survey highlights disparities in the availability of healthcare services for people with ANS disorders across European countries, stressing the need for improved access to specialized care in South, East and Greater Europe.

### KEYWORDS

Composite Autonomic Severity Score, cardiovascular autonomic function tests, (disorders of) autonomic nervous system, disorders of consciousness (other than epilepsy), neurological disorders, neurodisparity, orthostatic hypotension, Survey, syncope, sweat tests

## INTRODUCTION

Disorders of the autonomic nervous system (ANS) are common conditions estimated to affect 70 million people worldwide [1]. The cardiovascular ANS is the most frequently affected domain, with an incidence of a first-in-life syncope episode of 6.2 per 1000 person-years [2]. In contrast to other neurological disciplines, the evaluation of the ANS is associated with special caveats. Since on most occasions the ANS cannot be tested directly, its assessment relies on examining noninvasive physiological variables that express not only the activity of the autonomic reflex arch, but also the function of the effector organ and interaction of the body with external physical stimuli [3]. The evaluation is extensive and time consuming and test

batteries typically include the head-up tilt test, the Valsalva maneuver and deep breathing for the evaluation of sympathetic adrenergic and cardiovagal function, and the quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test, sympathetic skin response, and electrochemical skin conductance measurement for the evaluation of sudomotor function.

In 2005, the ANS panel of the European Federation of Neurological Societies conducted a survey on the distribution of ANS laboratories in Europe, asking for information on applied methods and equipment, existence of own normative data, commercial versus self-developed systems, and research and educational activities [4]. Although this survey included all types of ANS laboratories (i.e., cardiological, endocrinological, etc.) and not only neurologically

oriented ANS laboratories, it pinpointed a high heterogeneity in ANS services across Europe and, most importantly, large diversities in the techniques used to investigate ANS disorders, altogether highlighting an unmet need for ANS testing standards across European countries.

Recently, many efforts have been made to standardize clinical assessment of the ANS. Consensus definitions have been published to diagnose key aspects of cardiovascular autonomic failure, such as orthostatic hypotension and supine hypertension [5, 6]. The European Federation of Autonomic Societies (EFAS), endorsed by the American Autonomic Society (AAS) and the European Academy of Neurology (EAN), provided recommendations on the use of tilt table testing in the diagnosis of disorders that may cause transient loss of consciousness [7]. The AAS and the International Federation of Clinical Neurophysiology (IFCN) released definitions of autonomic disorders and methodological guidance for appropriate autonomic function testing [3]. The latter consensus statement emphasized the importance of evaluating the ANS with screening batteries encompassing tests of sympathetic adrenergic, cardiovagal and sudomotor function. In case of pathological findings, the severity of autonomic impairment in the different domains can be graded with a 10-point Composite Autonomic Severity Score (CASS) after normalizing each component for the confounding effects of age and gender [3, 8].

All the above international scientific efforts, together with the improvement of signal processing methodologies, increased availability of devices for autonomic function testing, and new treatment approaches have recently led to significant advances in the diagnosis and management of autonomic disorders. However, it is still unclear whether access to ANS healthcare facilities and the characteristics thereof are homogeneous across European regions.

In this joint effort between the Scientific Panel for ANS Disorders of the EAN and the EFAS, we aimed to identify neurology-driven or interdisciplinary (with at least one neurologist in the core team) clinical ANS laboratories in Europe, to understand the laboratory characteristics in terms of equipment, personnel, metrics, case mixture of the patients and research focus, and to investigate the differences in each of the studied variables among different European regions. Finally, we aimed to identify laboratories that have the necessary equipment for calculation of the CASS.

## METHODS

After a series of online preparatory meetings run in spring 2021, a panel of EAN and EFAS representatives, selected for their project-relevant expertise among the members of the EAN and EFAS professional network (the authors of this publication,  $n = 27$ ) prepared a web-based survey (Appendix S1). The study protocol and survey were drafted in English by A.F., M.H., D.R.C., W.S., R.H., and J.S., and reviewed and approved by all panel members, the EFAS Council and the EAN Scientific Committee on 28 May 2021.

Prior to launching the survey, the coordinating authors contacted eight autonomic and 29 neurological European national societies with an introductory letter about the nature and purposes of the survey. The representatives of each country were asked about

the number and localization of neurology-driven or interdisciplinary laboratories in the respective countries. Whenever possible, we asked to be in direct contact with the directors of the abovementioned laboratories. Otherwise, the respective national secretaries forwarded our communication to the members of their societies. In a following step, we used a snowball sampling technique, in which we asked the recruited survey participants to identify other directors of neurology-driven or interdisciplinary ANS laboratories in their country in order to invite them to participate in the survey as well [9]. Finally, each project team member was asked to identify any laboratory missed after the initial steps from his or her own professional network (see also Figure 1 and the Consensus-Based Checklist for Reporting of Survey Studies [CROSS] in Appendix S2).

On 16 September 2021 the survey was launched on a web-based platform (Survey Monkey Momentive Europe UC – Dublin, Ireland) and all identified laboratory directors were invited to complete it by 26 November 2021.

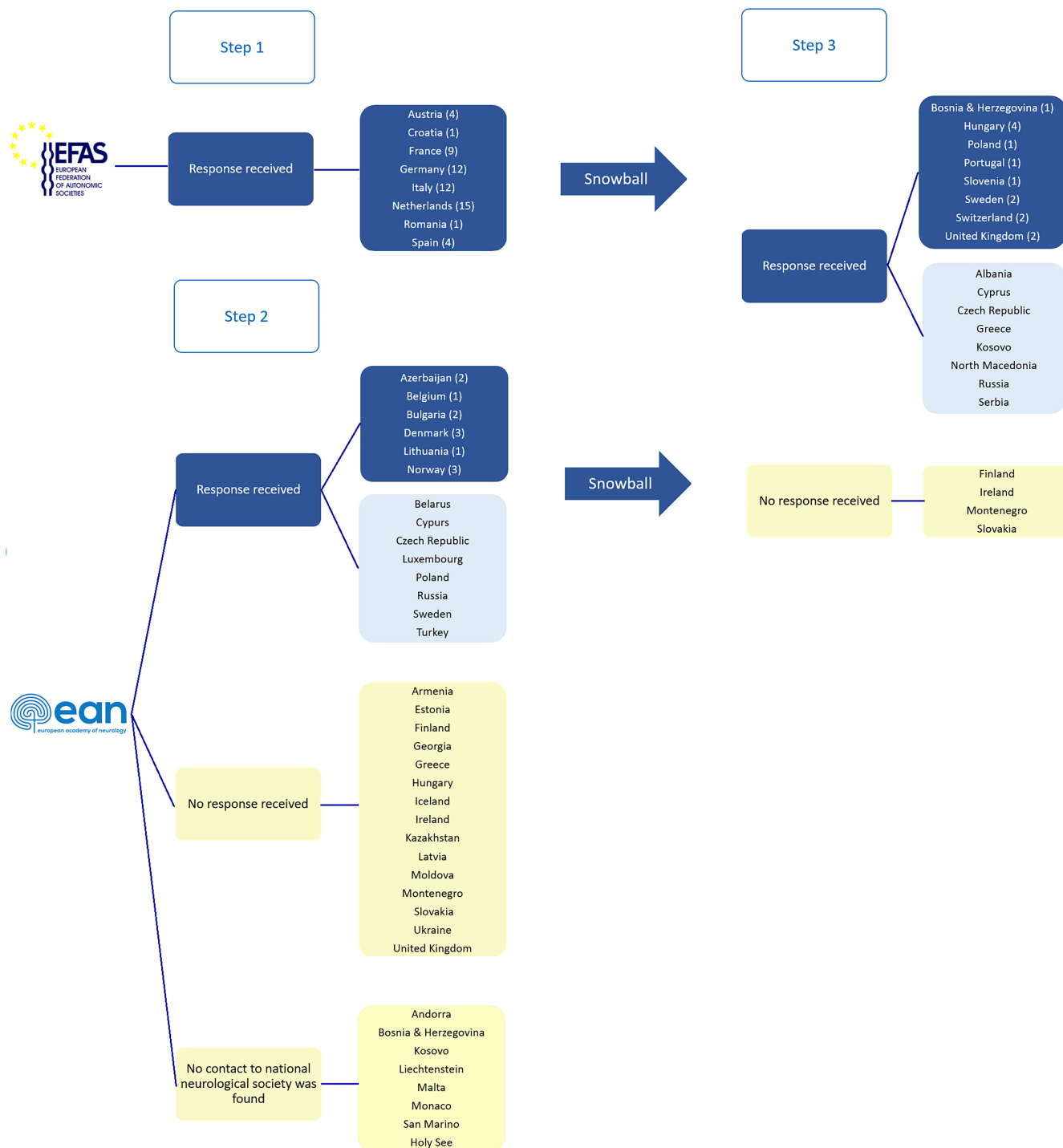
The survey censored the following information:

- Equipment: questions related to devices for blood pressure and heart rate monitoring, sudomotor testing, other autonomic function tests, blood examinations and histological analysis.
- Personnel: age, gender and years into practice of the head of the laboratory and number and rank of medical personnel and allied healthcare professionals.
- Metrics and case mixture of the patients: number of head-up tilt tests, inpatient and outpatient visits per year and case mix in the respective laboratories (including percentages of people with reflex syncope, cardiac syncope, postural orthostatic tachycardia syndrome, classic, initial and delayed orthostatic hypotension, psychogenic pseudosyncope and other causes of transient loss of consciousness).
- Research activities: whether the laboratory is actively involved in research activities and, if so, what is the focus of the research.

To analyze geographical differences, we applied the United Nations' geoscheme for Europe in the following way [10]:

1. Eastern Europe: Belarus, Bulgaria, Czech Republic, Hungary, Poland, Moldova, Romania, Russia, Slovakia, Ukraine;
2. Western Europe: Austria, Belgium, France, Germany, Liechtenstein, Luxembourg, Monaco, Netherlands, Switzerland;
3. Northern Europe: Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden, United Kingdom;
4. Southern Europe: Albania, Andorra, Bosnia and Herzegovina, Croatia, Greece, Holy See, Italy, Kosovo, Malta, Montenegro, North Macedonia, Portugal, San Marino, Serbia, Slovenia, Spain;
5. Greater Europe: Turkey, Cyprus, Armenia, Georgia, Kazakhstan, Azerbaijan.

We evaluated the differences in the studied variables between the North/West versus South/East/Greater European regions. The assignment of countries or areas to a specific group of the United Nations' geoscheme for Europe was chosen for statistical



**FIGURE 1** Methodological approach to identify the neurology-driven or interdisciplinary clinical autonomic nervous system (ANS) laboratories in Europe. In Step 1, we contacted all eight national ANS societies by e-mail (first e-mail in June 2021, up to three reminders until all information was collected) and asked for the number of neurology-driven or interdisciplinary clinical ANS laboratories in their countries. In this step we identified 58 laboratories. In Step 2, we consulted the European Academy of Neurology (EAN) Website in June 2021 for contact information of the European National Neurological Societies and, whenever possible, we compared this information with each National Neurology Society webpage. We found no National Neurology Society or no e-mail contact thereof in eight countries: Andorra, Bosnia & Herzegovina, Kosovo, Liechtenstein, Malta, Monaco, San Marino, Holy See. For 29 countries we sent an introductory mail to the institutional representatives listed on the EAN website in June 2021 explaining the nature and scope of the project and asking to be put in contact with neurology-driven or interdisciplinary clinical autonomic laboratories in the respective countries. Up to two reminders were sent to non-responders until the end of July 2021. Whenever survey participants were recruited, we asked them to identify other directors of neurology-driven or interdisciplinary laboratories in their country, in order to invite them to participate in the survey as well. This second step identified 12 more laboratories. In Step 3, the project team members reached out to colleagues of their professional network to gain (more detailed) information from those countries, for which no conclusive information was obtained in the former steps. This final step identified 14 more laboratories. Blue boxes indicate countries with at least one identified ANS laboratory, light blue boxes countries without identified ANS laboratories and yellow boxes countries from which no response was obtained. [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

convenience and does not imply any assumption regarding political or other affiliation of countries or territories.

Laboratories were deemed equipped for CASS testing if both QSART and invasive or noninvasive continuous blood pressure and heart rate monitoring devices were available.

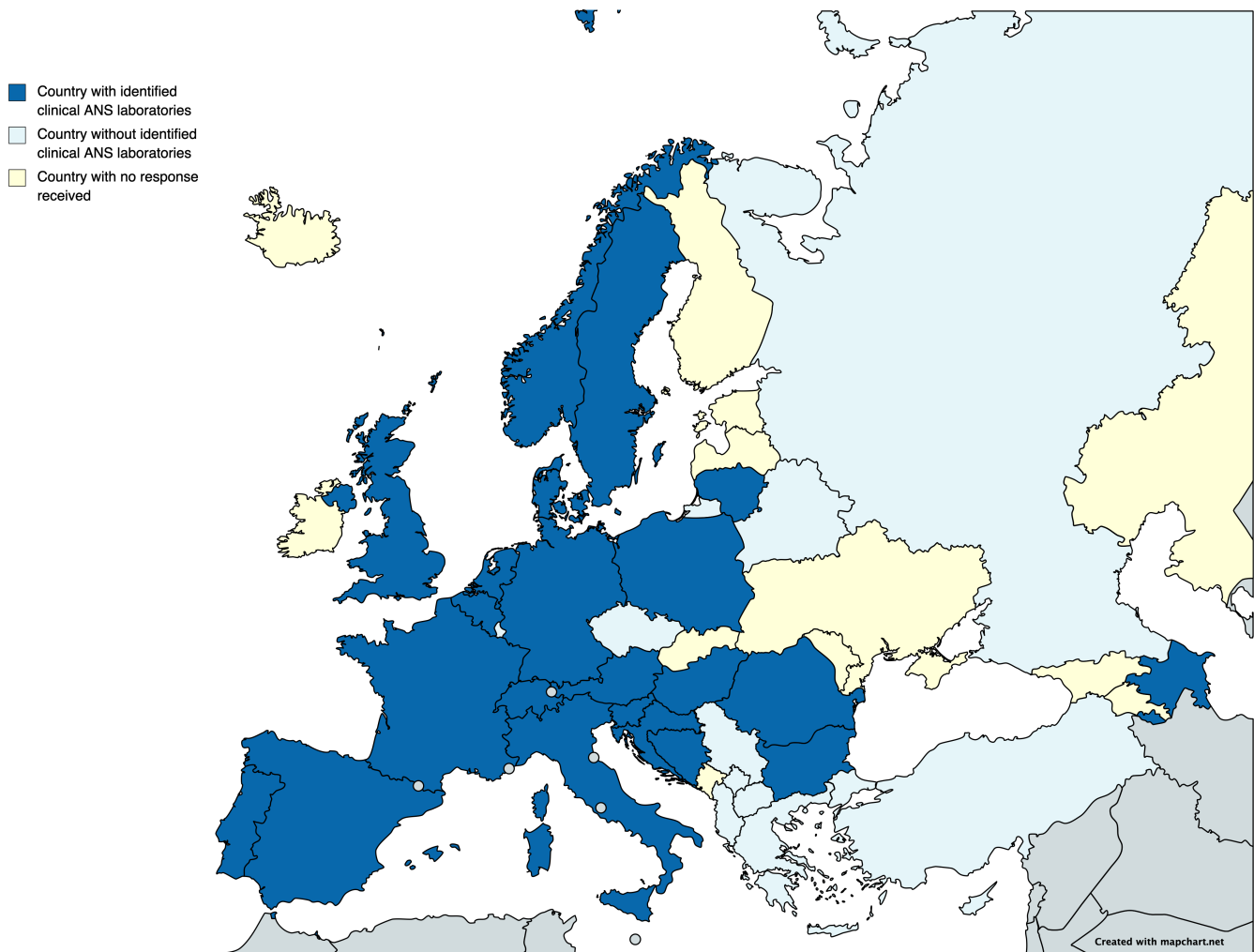
## Statistical analysis

Statistical analysis was performed with the IBM SPSS v25 software (IBM Corporation, United States). We tested the data distribution using the Kolmogorov–Smirnov test. Qualitative variables were summarized in numbers (percentage), and quantitative variables by median (interquartile range [IQR]) for non-normally or mean  $\pm$  standard deviation for normally distributed data. Outliers were assessed for all variables and analyzed in their national and geographical context. The differences in qualitative variables between two European regions

and according to gender distribution of the head of the laboratories were tested with the chi-squared test. Differences in quantitative variables were tested with the parametric independent samples *t*-test or non-parametric Mann–Whitney test, depending on the data distribution. Two-tailed *p* values  $<0.05$  were taken to indicate statistical significance. Due to the large number of comparisons, a Bonferroni correction was applied. We tested four hypotheses: whether there is a difference in (i) equipment, (ii) personnel, (iii) metrics and case mix, and (iv) research focus of the ANS laboratories between the two European regions. For each hypothesis, the denominator of the Bonferroni formula was adapted to the number of comparisons run.

## Ethical Standards

During the study purposing phase, the coordinating authors were counseled by the Innsbruck Ethical Committee and the Internal



**FIGURE 2** Distribution of clinical autonomic nervous system (ANS) laboratories across Europe. Blue indicates countries with at least one identified clinical ANS laboratory (four from Eastern Europe, six from Western Europe, five from Northern Europe, six from Southern Europe and one from Greater Europe). Light blue indicates countries without identified clinical ANS laboratories and yellow indicates countries from which no response was obtained. Created using <https://mapchart.net/europe.htmlwileyonlinelibrary.com>. This work is licensed under a Creative Commons Attribution-ShareAlike 4.0 International License. [Colour figure can be viewed at [wileyonlinelibrary.com](https://wileyonlinelibrary.com)]

Data Protection Coordinator of the Medical University of Innsbruck. Given the observational nature of this study, which did not include any direct patient-related data but was instead focused on collecting general information from the neurologists running the European laboratories, no ethics approval was needed by Austrian law. The participants gave electronic informed consent to participate in the survey and to have their name and affiliations listed among the collaborators of the study in the resulting publications. The study was performed in accordance with the Declaration of Helsinki and followed the current European regulations for data protection.

## RESULTS

### Participating societies

We collected information on the existence of neurology-driven and interdisciplinary ANS laboratories from 33 out of 51 European countries (65%). There was no statistically significant difference in the response rate between North/West European (12 of 19) versus South/East/Greater European countries (21 of 32;  $p = 0.859$ ). We identified 84 laboratories in 22 countries and 46 (55%) responded to the survey (Figure 2).

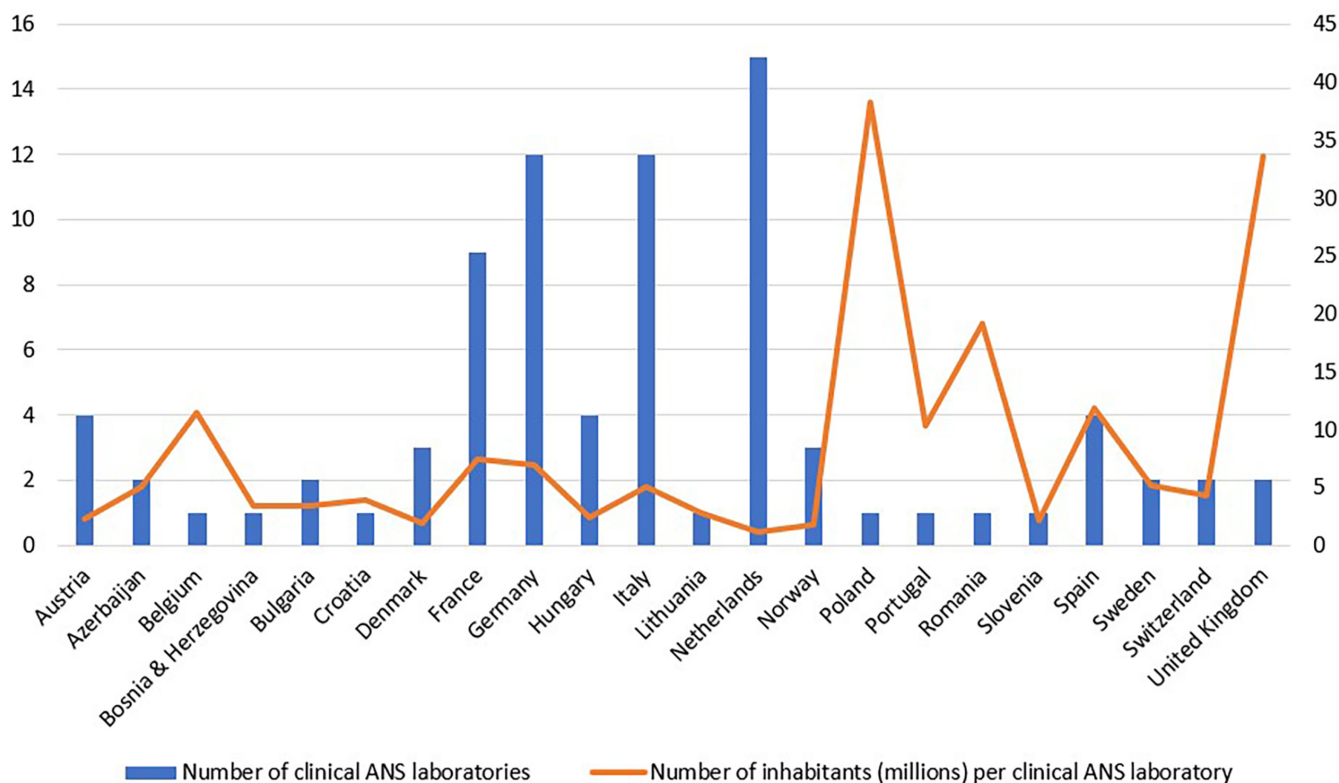
The numbers of identified neurology-driven ANS laboratories per country are shown in Figure 3. The number of inhabitants per laboratory ranged from 1,180,527 inhabitants/laboratory in Netherlands to 38,179,800 inhabitants/laboratory in Poland.

### Equipment and personnel

Table 1 provides an overview of the equipment and personnel characteristics of the laboratories. All laboratories perform cardiovascular autonomic function testing, while 83% also perform sweat testing. Sixty-three percent of the laboratories perform epidermal nerve fiber density and other histological analyses. We identified 13 laboratories (29%) that have the required equipment for performing the CASS assessment. The majority of the directors of the laboratories are male (61%), are aged between 40 and 49 years, and have 10–19 years of clinical experience. There was no statistically significant difference in characteristics of the laboratories based on the gender of the head of the laboratory, except that female directors reported a higher number of inpatient admissions per year [90 (IQR 13–148) vs. 8 (IQR 1–36);  $p = 0.007$ ]. The laboratories are staffed by a median (IQR) of two consultants (1–3), one resident (0–2), one technician (1–2), and one nurse (0–2).

### Metrics and case mixture of the patients

The metrics and case mixture of the patients referred to the laboratories are shown in Table 2. The median (IQR) number of head-up tilt tests/laboratory/year is 105 (49–251), with two laboratories performing more than 1000 examinations per year. An ANS outpatient clinic is available in 35 centers (76%) with a median of 200 (IQR 100–360) outpatient visits/year. Nine centers report more than 300 outpatient visits/year. Inpatient admissions are available in 42



**FIGURE 3** Number of clinical autonomic nervous system (ANS) laboratories in each European country from which information on the availability of clinical ANS laboratories was obtained. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 1** Equipment and personnel of the European clinical autonomic nervous system laboratories

Equipment (N = 46)	
Blood pressure monitoring, n (%)	46 (100)
Riva-Rocci	19 (41.3)
Invasive continuous	4 (8.7)
Noninvasive continuous	41 (89.1)
Volume clamp	27 (58.7)
Pulse wave	19 (41.3)
Other (Photoplethysmography)	1 (2.2)
Heart rate monitoring, n (%)	46 (100)
Other <sup>a</sup>	8 (17.4)
Sweat testing, n (%)	38 (82.6)
Sympathetic skin response	29 (63)
Quantitative sudomotor axon reflex test	14 (30.4)
Electrochemical skin conductance	10 (21.7)
Thermoregulatory sweat test	6 (13)
Other <sup>b</sup>	3 (6.5)
Blood tests, n (%)	
Catecholamines	29 (63)
Antibodies	26 (56.5)
Others <sup>c</sup>	4 (8.9)
Histology, n (%)	
Dermal nerve fiber density	29 (63)
Others <sup>d</sup>	5 (10.9)
Personnel	
Head of the laboratory, n (%)	
Female	18 (39.1)
Age group, n (%)	
30–39 years	8 (17.4)
40–49 years	21 (45.7)
50–59 years	14 (30.4)
60–69 years	3 (6.5)
Years into practice, n (%)	
Resident	2 (4.3)
Junior consultant (0–4 years)	1 (2.2)
Consultant (5–9 years)	4 (8.7)
Senior consultant (10–19 years)	16 (34.8)
>20 years	23 (50)
Consultants, median (IQR)	2 (1–3)
Residents, median (IQR)	1 (0–2)
PhD students, median (IQR)	1 (0–2)
Postdoctoral fellows, median (IQR)	0 (0–0)
Medical students, median (IQR)	1 (0–2)
Technicians, median (IQR)	1 (1–2)
Nurses, median (IQR)	1 (0–2)
Biomedical engineer, median (IQR)	0 (0–1)

(Continues)

**TABLE 1** (Continued)

<sup>a</sup>24-h electrocardiogram (ECG), 24-h ambulatory blood pressure monitoring, ergometry, implantable loop recorder; variability studies; photoplethysmography, long-term noninvasive ECG monitoring.

<sup>b</sup>Two laboratories use dynamic sweat test, and one has thermal sensory testing.

<sup>c</sup>Copeptin, synacthen test, cryoglobulin.

<sup>d</sup>Abdominal fat biopsy for amyloidosis, skin biopsy with a-syn staining for research purposes, skin biopsy with assessment of sweat glands, hairs and vessels innervation; three laboratories referred their patients elsewhere for biopsies.

**TABLE 2** Metrics and case mix of patients referred to European clinical autonomic nervous system laboratories

Laboratory metrics	
Number of tilt table tests per year	105 (48.5–251)
Number of outpatient visits per year	200 (100–360)
Number inpatient visits per year	20 (4.25–110)
Case mixture in the respective laboratories	
Reflex syncope, %	20.5 ± 18.6
Neurogenic orthostatic hypotension, %	20.3 ± 18.2
Non-neurogenic orthostatic hypotension, %	6.7 ± 7.0
Postural orthostatic tachycardia syndrome, %	5 (2–15)
Initial orthostatic hypotension, %	5 (0.75–10)
Delayed orthostatic hypotension, %	3.7 ± 3.9
Psychogenic pseudosyncope, %	3 (1–7.75)
Cardiac syncope, %	1 (0–4)
Other transient loss of consciousness, %	1 (0–5)

Note: Data are presented as mean ± standard deviation or median (interquartile range).

centers (91%) with a median (IQR) of 20 (4–110) inpatient stays/year. Eleven centers care for more than 100 patients with autonomic disturbances per year in inpatient settings.

## Research activities

Forty-one laboratories (89.1%) are currently involved in research activities. [Table 3](#) summarizes the censored research focuses. The five most frequent research areas are orthostatic hypotension, movement disorders, postural orthostatic tachycardia syndrome, reflex syncope and rare diseases.

## Differences among European regions

We observed a significant difference in the availability of ANS healthcare services among different European regions (11/21 countries from South/East/Greater Europe vs. 11/12 countries from North/West Europe;  $p = 0.021$ ). However, there was no statistically significant difference in the number of inhabitants per laboratory



**TABLE 3** Research focus of the European clinical autonomic nervous system laboratories

Involved in research activities, N (%)	41 (89.1)
Research focus, n (%)	
Orthostatic hypotension	29 (63)
Movement disorders	23 (50)
Postural orthostatic tachycardia syndrome	17 (37)
Reflex syncope	15 (32.6)
Rare diseases	15 (32.6)
Stroke	13 (28.3)
Other	12 (26.1)
Sweating disorders	11 (23.9)
Multiple sclerosis	10 (21.7)
Epilepsy	9 (19.6)
Autoimmune autonomic ganglionopathy	9 (19.6)
Sleep disorders	9 (19.6)
Cardiac syncope	7 (15.2)
Other transient loss of consciousness	6 (13)
Urinary/bowel dysfunction	6 (13)
Headache	6 (13)
Psychogenic pseudosyncope	4 (8.7)

between the North/West Europe and South/East/Greater Europe (7,174,395 [1,180,527–33,540,500] vs. 9,547,146 [2,108,708–38,179,800];  $p = 0.587$ ). There was also no difference between the two European regions in terms of equipment, personnel, metrics, case mixture of the patients, and research activities of the laboratories (Tables 4 and 5).

## DISCUSSION

The EAN and the EFAS play a key role in defining the standards of care and research for European people with autonomic disorders through guidelines, consensus statements and interactions with health policy makers [11]. In order to make applicable and realistic recommendations, these need to be tailored to the available resources across European countries and take regional differences into account. Both aspects were not well known to date. The main goal of the present EAN-EFAS joint effort was to fill this gap in knowledge by collecting information on ANS laboratories, ultimately facilitating benchmarking of autonomic healthcare provision across European countries.

The survey provides several important insights. First, the 2005 survey of the EFNS Scientist Panel on Autonomic Nervous System Disorders [4] identified 48 neurology-driven or interdisciplinary ANS laboratories, and the current survey 84. Even though a direct comparison between the two surveys is not entirely possible due to design differences, both surveys focused on European countries, adopted comparable laboratory identification strategies, and clearly distinguished between neurology and

non-neurology-driven ANS laboratories. It is therefore conceivable that the 75% increase in the number of censored neurology-driven or interdisciplinary ANS laboratories reflects an incremental trend in the availability of specialized healthcare services for people with ANS disorders in Europe. This is particularly relevant in light of the results of the Global Burden of Disease 2015 Neurological Disorders Collaborator Group, which showed that neurological disorders are the leading global cause of disability-adjusted life years and the second cause of death after cardiovascular disease [12]. In line with this, the Intersectoral Global Action Plan on Epilepsy and Other Neurological Disorders (GAP), which addresses the worldwide and European challenges and gaps in providing care and services for people with neurological disorders, has recently identified a unique window of opportunity to provide an integrated and cross-sectorial response to improve neurological health in the general population [13].

The second objective of our survey was to understand the equipment and personnel composition of each ANS laboratory. Cardiovascular autonomic function testing represents the cornerstone of every identified laboratory. More than 80% of laboratories also have at least one test for sudomotor function. This again represents a significant improvement compared to the 2005 survey, in which only 43% of the identified laboratories performed sweat testing [6]. A substantial number of laboratories also has access to additional tests. This is of particular importance since combining ANS tests often enables a more accurate assessment of the severity degree and neuroanatomical localization of autonomic dysfunction, in turn, facilitating an earlier diagnosis and personalized interventions [14].

The recent AAS/IFCN consensus statement emphasized the CASS as an important tool for the evaluation and follow-up of people with ANS disorders. We found that 28% of all censored laboratories have the necessary equipment for completing the CASS battery. This represents good potential for running future multicenter clinical studies, both observational (i.e., natural history studies and registries for rare autonomic disorders) and interventional. Using the CASS has the advantage of standardizing findings, thus facilitating comparisons among laboratories for both routine and research purposes. Its applicability is, however, limited to centers with a QSART facility, while not considering other, equally adequate, sudomotor function tests.

In the personnel part of the survey, we found that most of the laboratories have at least one consultant, resident, technician and nurse. We also found that the head of the laboratories was females in 18 (39%) centers only, emphasizing gender gaps in leadership positions. Gender disparities also affect autonomic research; it has been reported that the percentage of publications in autonomic medicine by a female first author is consistently below 50% over the last 30 years [15]. The percentage of publications with at least one female author, however, increased from 49% in 1994 to 69% in 2019, indicating a positive trend.

The availability of postdoctoral fellows and biomedical engineers is limited. The discipline of biomedical engineering has

**TABLE 4** Differences in equipment, personnel, metrics, case mix of the patients referred to the clinical autonomic nervous system laboratories between macro-European regions

	South/East/Greater Europe (16 laboratories)	North/West Europe (30 laboratories)	<i>p</i> value
<b>Equipment</b>			
Blood pressure monitoring, <i>n</i> (%)			
Riva-Rocci	5 (31.3)	14 (46.7)	0.362
Invasive continuous	0 (0)	4 (13.3)	0.282
Noninvasive continuous	13 (81.3)	28 (93.3)	0.325
Volume clamp	7 (43.8)	20 (66.7)	0.209
Pulse wave	8 (50)	11 (36.7)	0.531
Other (photoplethysmography)	1 (6.3)	0 (0)	0.348
Heart rate monitoring, <i>n</i> (%)			
ECG	16 (100)	30 (100)	-
Other	4 (25)	4 (13.3)	0.421
Sweat testing, <i>n</i> (%)			
Sympathetic skin response	12 (75)	17 (56.7)	0.338
Quantitative sudomotor axon reflex test	4 (25)	10 (33.3)	0.739
Electrochemical skin conductance	3 (18.8)	7 (23.3)	1.000
Thermoregulatory sweat test	2 (12.5)	4 (13.3)	1.000
Other	2 (12.5)	1 (3.3)	0.542
Blood testing, <i>n</i> (%)			
Catecholamines	9 (56.3)	20 (66.7)	0.534
Antibodies	8 (50)	18 (60)	0.548
Other	0 (0)	4 (13.3)	0.282
Histology, <i>n</i> (%)			
Dermal fiber density	8 (50)	21 (70)	0.213
Other	1 (6.3)	4 (13.3)	0.645
CASS <sup>a</sup>	3 (18.8)	10 (33.3)	0.333
<b>Personnel*, <i>n</i> (%)</b>			
Head of the laboratory			
Female	9 (56.3)	9 (30)	0.116
Age group			
30–39 years	2 (12.5)	6 (20)	0.742
40–49 years	7 (43.8)	14 (46.7)	
50–59 years	5 (31.3)	9 (30)	
60–69 years	2 (12.5)	1 (3.3)	
Years into practice, <i>n</i> (%)			
Resident	0	2 (6.7)	0.530
Junior consultant (0–4 years)	0	1 (3.3)	
Consultant (5–9 years)	2 (12.5)	2 (6.7)	
Senior consultant (10–19 years)	4 (25)	12 (40)	
>20 years	10 (62.5)	13 (43.3)	
Number of consultants, median (IQR)	2 (1–2.75)	2 (1–4)	0.649
Number of residents, mean ± SD	0.75 ± 0.775	1.97 ± 2.189	0.009
Number of PhD students, median (IQR)	1 (0–1.75)	0.5 (0–2)	0.911
Number of postdoctoral fellows, median (IQR)	0 (0–0)	0 (0–0)	0.937
Number of medical students, median (IQR)	1 (0–1.75)	1 (0–2)	0.807
Number of technicians, median (IQR)	1 (1–2)	1 (0–2.25)	0.772

(Continues)

TABLE 4 (Continued)

	South/East/Greater Europe (16 laboratories)	North/West Europe (30 laboratories)	p value
Number of nurses, median (IQR)	1 (0–1)	1 (0–2.25)	0.530
Number of biomedical engineers, median (IQR)s	0 (0–1)	0 (0–1)	0.802
Laboratory metrics**, median (IQR)			
Number of tilt table tests per year	130 (41–250)	100 (50–265.5)	0.917
Number of outpatient visits per year	175 (105–380)	212 (100–350)	1.000
Number of inpatient visits per year	75 (32.5–129.75)	10 (2.75–25)	0.036
Case mix in the respective laboratories***			
Reflex syncope, %, mean $\pm$ SD	22.0 $\pm$ 19.0	19.8 $\pm$ 18.6	0.702
Neurogenic orthostatic hypotension, %, mean $\pm$ SD	21 $\pm$ 15	20 $\pm$ 19.9	0.857
Postural orthostatic tachycardia syndrome, %, mean $\pm$ SD	6.6 $\pm$ 9.9	13.8 $\pm$ 16.9	0.125
Initial orthostatic hypotension, %, mean $\pm$ SD	7.6 $\pm$ 9.6	4.8 $\pm$ 4.7	0.188
Non-neurogenic orthostatic hypotension, %, mean $\pm$ SD	7.2 $\pm$ 7.7	6.5 $\pm$ 6.8	0.757
Delayed orthostatic hypotension, %, mean $\pm$ SD	4 $\pm$ 4.7	3.6 $\pm$ 3.6	0.727
Psychogenic pseudosyncope, %, mean $\pm$ SD	3.3 $\pm$ 3.0	4.9 $\pm$ 4.2	0.186
Cardiac syncope, %, median (IQR)	1 (0–10)	0 (0–3.5)	0.571
Other transient loss of consciousness, %, median (IQR)	2 (0–8.75)	0 (0–5)	0.152

Note: Due to corrections for multiple comparisons, every section has corrected *p* value for statistical significance, calculated according to number of comparisons. Abbreviations: CASS, Composite Autonomic Severity Score; ECG, electrocardiogram; IQR, interquartile range; SD, standard deviation.

<sup>a</sup>Quantitative sudomotor axon reflex test and (invasive or noninvasive continuous blood pressure) and heart rate monitoring devices.

\**p* < 0.006; \*\**p* < 0.017; \*\*\**p* < 0.006.

emerged as a *connection element* between medicine and engineering [16]. The results of our survey indicate that efforts should be made in the future to further implement bioengineer positions in clinical autonomic practice and research. Despite a presumably similar spectrum of patients, there is also substantial variation among European countries in the duration of residency training programs, and especially in the choice of obligatory rotations to external medical disciplines [17]. It is important for the laboratories to train an adequate number of residents, clinical fellows and postdoctorate students in clinical autonomic practice and research to secure enough personnel resources in the future, particularly in view of the aging population and increasing demand resulting from neurological disease burden [14].

In the third part of the survey, we evaluated the metrics and case mixture of the patients referred to the laboratories. We observed high variability in the numbers of head-up tilt examinations, and inpatient and outpatient visits per laboratory. The fact that reflex syncope and neurogenic orthostatic hypotension represented the most frequently diagnosed cardiovascular autonomic disorders is in line with the respective prevalence of such autonomic disorders in the general population [1].

Another positive aspect highlighted by the survey is that most of the interviewed laboratories are involved in research activities at a similar rate to that found in the 2005 survey [6]. The observation that orthostatic hypotension is the most frequent area of research of neurology-driven and interdisciplinary ANS laboratories may be based on the fact that it develops in several common neurological

conditions such as Parkinson's disease, neuropathies and lesions to the central ANS system of diverse etiologies, thus introducing a referral bias in comparison to cardiology-driven laboratories, which may, in turn, be more biased towards other causes of syncope.

Health disparities, defined as differences in health and health-care among different groups of people, can affect people with any disease, including neurological disorders [18]. The term neurodisparity has been used to highlight this inequity, which has existed across a range of neurological conditions for decades, both in the United States and Europe [18–20]. In order to minimize neurodisparities, neurology stakeholders first need to recognize differences in the availability of neurological care and then act accordingly [20]. Maybe one of the best examples of neurodisparity in Europe is seen in access to treatment and physical rehabilitation among people with multiple sclerosis, where geographical location determines access to and the type of treatment provided [21, 22]. Similarly, our survey identified neurodisparity in the availability of ANS services across Europe. Laboratories were more frequent in North/West Europe compared to South/East/Greater Europe. This indicates that geographical factors are particularly relevant in producing neurodisparity in Europe. However, additional factors have to be taken into account when looking at a wider European context, such as the differences in population density among European regions, the reimbursement policies for ANS services in each country, and the historical autonomic background of some countries. We also observed interesting organizational differences among countries. Some, such as the United Kingdom or Croatia, have a centralized

**TABLE 5** Comparison of the research focus of the clinical autonomic nervous system laboratories between macro-European regions

	South/East/Greater Europe (16 laboratories) n (%)	North/West Europe (30 laboratories) n (%)	p value
Research			
Research activity	16 (100)	25 (83.3)	0.147
Research focus			
Orthostatic hypotension	12 (75)	17 (56.7)	0.338
Movement disorders	11 (68.8)	12 (40)	0.120
Postural orthostatic tachycardia syndrome	7 (43.8)	10 (33.3)	0.534
Reflex syncope	5 (31.3)	10 (33.3)	1.000
Rare diseases	6 (37.5)	9 (30)	0.744
Stroke	5 (31.3)	8 (26.7)	1.000
Other	5 (31.3)	7 (23.3)	0.726
Sweating disorders	4 (25)	7 (23.3)	1.000
Multiple sclerosis	5 (31.3)	5 (16.7)	0.283
Epilepsy	4 (25)	5 (16.7)	0.698
Autoimmune autonomic ganglionopathy	5 (31.3)	4 (13.3)	0.241
Sleep disorders	6 (37.5)	3 (10)	0.047
Cardiac syncope	2 (12.5)	5 (16.7)	1.000
Other transient loss of consciousness	4 (25)	2 (6.7)	0.163
Urinary/bowel dysfunction	3 (18.8)	3 (10)	0.649
Headache	1 (6.3)	5 (16.7)	0.406
Psychogenic pseudosyncope	1 (6.3)	3 (10)	1.000

Note: Due to corrections for multiple comparisons, p value is statistically significant at  $p < 0.003$ .

model with one or two high-volume centers per country; others, such as the Netherlands, Italy, Austria, France and Germany have a higher number of centers across the country, but these are medium sized. Reimbursement policies and an "all-in-one test battery" versus a "stepwise examination approach" may contribute to determining such organizational structures, and both pros and cons for a centralized versus decentralized ANS care provision can be postulated. The all-in-one test battery likely leads to better opportunities to build adequately sized case series to study rare autonomic disorders and educate a higher number of healthcare professionals, while a stepwise approach may warrant better access to ANS healthcare services for people living in remote areas or with reduced mobility due to age or disease-related causes.

Some limitations should be taken into account when interpreting the results reported in this study. First, we had a responder rate of 55%, which is relatively low. The multiple networking approaches described in the methods were developed on purpose to counteract this anticipated difficulty of the chosen study design. Moreover, the results of the survey are based on the personal opinion and view of responders, who, however, proved to be physicians with 10 to 19 years' professional experience, and thus were likely well informed in clinical autonomic practice and research matters. Finally, our approach might have missed smaller laboratories in some countries, especially those with no national autonomic society, emphasizing an important need for more capillary professional networking

activities to reach out to ANS experts practicing outside of larger academic centers.

In conclusion, our data provide a good basis for understanding the challenges of clinical autonomic practice in Europe and for planning concerted actions for better disease management and collaborative research. It also highlights significant differences in the availability of healthcare services for people with ANS disorders across European countries, stressing the need for improved access to diagnostic and treatment facilities across Europe, and thereby investment in health service improvement and spending by national governments. Both the EFAS and the EAN are called to intensify their educational and health policy activities to increase the expertise in ANS disturbances in the neurological community and to promote the establishment of new ANS laboratories in underserved countries.

#### AUTHOR CONTRIBUTIONS

Study conception: Alessandra Fanciulli, Mario Habek, Jennifer Camaradou, Pietro Cortelli, Cristian Falup-Pecurariu, Pietro Guaraldi, Raimund Helbok, Max J. Hilz, Valeria Iodice, Jens Jordan, Anne Pavy Le Traon, Isabel Rocha, Johann Sellner, Jean Michel Senard, Astrid Terkelsen, Gregor K. Wenning, Thomas Berger, Roland Thijs, Walter Struhal. Study design: Alessandra Fanciulli, Mario Habek, Diogo Reis Carneiro, Raimund Helbok, Anne Pavy Le Traon, Johann Sellner, Thomas Berger, Roland Thijs, Walter Struhal. Study coordination: Alessandra Fanciulli, Mario Habek. Data collection: Alessandra

Fanciulli, Mario Habek, Fabian Leys, Giovanna Calandra-Buonaura, Giacomo Chiaro, Cristian Falup-Pecurariu, Roberta Granata, Pietro Guaraldi, Valeria Iodice, Evert C. A. Kaal, Anita Kamondi, Anne Pavy Le Traon, Astrid Terkelsen, Gregor K. Wenning, Roland Thijs, Walter Struhal. Data analysis: Mario Habek, Magdalena Krbot Skorić, Alessandra Fanciulli, Fabian Leys. Writing of the first draft: Mario Habek. Writing – review and editing: Alessandra Fanciulli, Diogo Reis Carneiro, Fabian Leys, Giovanna Calandra-Buonaura, Jennifer Camaradou, Giacomo Chiaro, Pietro Cortelli, Cristian Falup-Pecurariu, Roberta Granata, Pietro Guaraldi, Raimund Helbok, Max J. Hilz, Valeria Iodice, Jens Jordan, Evert C. A. Kaal, Anita Kamondi, Anne Pavy Le Traon, Isabel Rocha, Johann Sellner, Jean Michel Senard, Astrid Terkelsen, Gregor K. Wenning, Magdalena Krbot Skorić, Thomas Berger, Roland Thijs, Walter Struhal.

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Mario Habek: participated as a clinical investigator and/or received consultation and/or speaker fees from Biogen, Sanofi Genzyme, Merck, Bayer, Novartis, Pliva/Teva, Roche, Alvogen, Actelion, Alexion Pharmaceuticals and TG Pharmaceuticals, outside of the present work. Fabian Leys: none. Dr Leys is supported by grants from the US MSA Coalition and Dr Johannes and Herta Tuba Foundation. Magdalena Krbot Skorić: received consultation and/or speaker fees from Sanofi Genzyme and Roche, outside of the present work. Diogo Reis Carneiro: received speaker fees from Almirall, outside of the present work. Giovanna Calandra-Buonaura: received honoraria for speaking engagements or consulting activities from Abbvie, Bial and Zambon, outside the present work. Jennifer Camaradou: participated as a costed PPI Patient Public Involvement lead in a study at University College London funded by the UK National Institute for Health Research (NIHR)132914 and UK NIHR20334 at Bristol UWE, received consultation fees from Roche Canada, Roche Global, Medable Inc, GSK Glaxco Smith Klein, outside of the present work, and received small honoraria as a lay

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## DATA AVAILABILITY STATEMENT

The first and the last authors take full responsibility for the integrity of data and agree to share any data not published within this article in a de-identified form upon reasonable request from any qualified investigator.

## ORCID

Mario Habek  <https://orcid.org/0000-0002-3360-1748>

Fabian Leys  <https://orcid.org/0000-0003-1714-5305>

Jennifer Camaradou  <https://orcid.org/0000-0002-5742-2840>

Pietro Cortelli  <https://orcid.org/0000-0002-3633-8818>

Max J. Hilz  <https://orcid.org/0000-0002-6802-1751>

Anne Pavy Le Traon  <https://orcid.org/0000-0002-9375-1553>

Roland D. Thijs  <https://orcid.org/0000-0003-1435-8970>

Walter Struhal  <https://orcid.org/0000-0001-7360-7784>

Alessandra Fanciulli  <https://orcid.org/0000-0002-2854-4179>

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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