Received: 27 February 2022 | Accepted: 5 March 2022

DOI: 10.1111/ene.15320

european journal of neurology
the official journal of the european academy of neurology

POSITION PAPER

How to approach a neurogenetics diagnosis in different European countries: The European Academy of Neurology Neurogenetics Panel survey

Michelangelo Mancuso[1] | Henry Houlden[2] | Maria Judit Molnar[3] | Alessandro Filla[4] | Marianthi Breza[2] | Holm Graessner[5] | Claudio L. A. Bassetti[6] | Sylvia Boesch[7]

[1]Department of Clinical and Experimental Medicine, Neurological Institute, University of Pisa, Pisa, Italy

[2]Department of Neuromuscular Disease, UCL Queen Square Institute of Neurology, The National Hospital for Neurology and Neurosurgery, London, UK

[3]Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary

[4]Department of Neurosciences, Reproductive and Odontostomatological Sciences, Federico II University, Naples, Italy

[5]Institute for Medical Genetics and Applied Genomics, Centre for Rare Diseases, University of Tübingen, Tübingen, Germany

[6]Department of Neurology, Inselspital, University Hospital, Bern, Switzerland

[7]Department of Neurology, Center for Rare Movement Disorders Innsbruck, Medical University Innsbruck, Innsbruck, Austria

Correspondence
Michelangelo Mancuso, Department of Clinical and Experimental Medicine, Neurological Institute, University of Pisa, Pisa, Italy.
Email: michelangelo.mancuso@unipi.it

Abstract

Background and purpose: Seven thousand rare diseases have been identified; most of them are of genetic origin. The diagnosis of a neurogenetic disease is difficult, and management and training programs are not well defined through Europe. To capture and assess care needs, the Neurogenetics Panel of the European Academy of Neurology (EAN) has performed an explorative survey.

Methods: The survey covering multiple topics of neurogenetics was sent to all neurologists and neuropediatricians affiliated with the EAN practicing in Europe.

Results: We collected answers from 239 members based in 40 European member states. Even though most of the responders were aware of neurogenetic diseases, when we came to amenability of carrying out a complete genetic diagnosis, almost one-third of the responders declared they were not happy with the current way of ordering genetic analyses in their countries. Furthermore, although single-gene analysis is diffusely present in Europe, whole exome and genome sequencing are not easily accessible, with considerable variabilities among countries. Almost 10% of the responders did not know if presymptomatic and prenatal diagnosis was available in their countries, and 47.3% were not aware of which newborn screening programs were available. Finally, 96.3% of responders declared that there is a need for education and training in neurogenetics.

Conclusions: We believe that this survey may be of importance for all European stakeholders in neurogenetics in identifying key priorities, targeting areas to encourage education/travel fellowships, and educational seminars in the future, because this area will only accelerate, and diagnostic requirements will expand.

KEYWORDS
disease diagnosis, Europe, neurogenetics, rare diseases, survey

INTRODUCTION

A rare disease (RD) is defined as one that affects fewer than five per 10,000 persons in the European Union (EU) or fewer than 200,000 persons in the United States. Despite their relative rarity, about 6000–8000 RDs have been identified worldwide, affecting approximately 6%–8% of the general population (almost 30 million people in the EU) [1,2].

Rare neurological diseases (RNDs) constitute a significant proportion of RDs. Almost 80% of the RDs are caused by genetic anomalies, and over half of the cases affect the central and/or peripheral nervous system, either isolated or in combination with other systems, and may start in childhood. This is one of the main reasons why neurologists and neuropediatricians must be aware of and prepared to manage these diseases. Therefore, there is growing worldwide attention in neurogenetics diseases (NGDs), with several areas of the neurosciences sharing this interest.

Due to the significant clinical and genetic heterogeneity, either for the many genes involved (genetic heterogeneity) or the great variety of mutation types in a single gene (allelic heterogeneity), NGDs are often challenging to diagnose. The diagnostic process may take years, require several specialists, and need many medical investigations. Genetic diagnosis is now recognized as mandatory for NGDs, because it allows proper counseling, family planning, and access to therapy and novel clinical trials. This is even more relevant given the availability of personalized treatment in a growing number of diseases.

Genetic diagnostic services are already under considerable pressure to integrate the new discoveries and to ensure equal accessibility and fast responses to avoid treatment and management delays. However, does this statement apply for all European countries? Moreover, the quality of the awareness and training in neurogenetics among medical schools and residency programs is not completely known at the European level.

The aim of this work was to gather information on different aspects of neurogenetics, as understood by the European neurologists and neuropediatricians affiliated with the European Academy of Neurology (EAN). Topics of interest in this survey were: (i) provision of genetic services in Europe, current practices, and issues; (ii) genetic services in different European countries; (iii) genetic services throughout Europe; (iv) presymptomatic and new-born screening in neurogenetics; and (v) education on neurogenetics.

METHODS

The current project is a cross-sectional survey focused on members of the EAN, who deal with both adult and pediatric patients and whose clinical practice is performed in Europe. The Neurogenetics Panel management group of the EAN designed the questionnaire (see Appendix S1), taking into account the following elements at the national level: awareness of RNDs, national policies, access to different diagnostic tests (also covering presymptomatic and newborn screening), and education in neurogenetics. The survey was distributed by the EAN Scientific Department through the official society mailing list, which contained 1278 contacts, advertised through the official society channels, including social media reminders, and it was conducted online between 15 June 2021 and 15 October 2021. We invited, among the EAN members, only clinicians, including residents, practicing in the field of neurology and child neurology. Responses were collected through the Google forms platform and then anonymously analyzed.

RESULTS

A total of 239 neurologists (18% of the physicians listed in the EAN mailing list), of whom 6.7% were neuropediatricians, completed the survey (53% female; mean age, 47.7 years), representative of 40 European member states (affiliated with the EAN; Figure 1) and of all EAN scientific panels. Appendix S2 shows the obtained results.

Of these, 77% were employed in either academic or public hospitals, 7% were residents in neurology, and the remaining responders were either private neurologists or specialists affiliated with research centers. The full list of queries and the results are reported in Appendices S1 and S2, respectively.

General aspects

Almost all participants (99.2%) were aware of neurogenetic diseases and thought that neurogenetics has an important role in clinical neurology. Most of them (91.2%) follow patients with NGDs, mainly neuromuscular (51.9%), ataxia (54%), rare dementia (31.8%), movement disorders (53.1%), monogenic cerebral small vessels diseases (27.2%), mitochondrial diseases (43.5%), hereditary spastic paraplegia (43.9%), and epilepsy (24.3%). Although all of the responders agreed that family history is an important finding in the diagnostic flowchart, in almost 20% of cases the same is not usually collected, which could lead to wrong or delayed diagnosis.

Regarding the prescription of genetic tests, in most symptomatic patients they are prescribed by clinicians, including residents, whereas 20% of responders declared they are prescribed only by clinical geneticists. In cases of presymptomatic screening, neurologists with expertise in genetics are allowed to prescribe genetics for 60% of responders; however, the presymptomatic genetic test is preceded by a medical genetic counseling consultation in more than 90% of cases. Finally, in cases of prenatal diagnosis, almost all responders who are aware of the service declared that genetic testing is preceded by medical genetic counseling.

Genetics tests availability

Even though most of the responders were aware on NGDs, when we came to amenability of carrying out a complete genetic diagnosis,

FIGURE 1 European countries (in red) affiliated with the European Academy of Neurology where we have obtained responses to the survey. Numbers in brackets indicate the number of responders per country [Colour figure can be viewed at wileyonlinelibrary.com]

almost one-third of the responders declared they are not happy with the current way of ordering genetic diagnostic tests in their countries. As an example, polymerase chain reaction (PCR) fragment analysis and other techniques for repeat disorders are available in 40% of cases for limited common expansions diseases. Moreover, although single-gene analysis is diffusely present in European countries, whole-genome sequencing (WGS) is not easily accessible for more than 60% of responders. The European situation appears to vary from country to country with respect to access to next-generation sequencing (NGS) panels, whole exome sequencing (WES), and WGS, where most of the differences are between Western and Eastern Europe (see Figures 2, 3, and 4). Both the discrepancies and completeness of the acquired data among countries cannot be deeply evaluated in this survey due to the limited number of answers we have collected.

Another important issue is the latency between the requested test and the obtained response. In more than 35% of cases, it takes more than 3 months for single-gene analysis and more than 68% for NGS gene panels; in more than 40% of cases analyzed by WES it takes more than 6 months.

Information about including the new-born screening for treatable RNDs and presymptomatic diagnosis is not diffusely provided to the general neurologists, but it is mainly provided to those not directly involved in the field. Almost 10% of the responders did not know if presymptomatic and prenatal diagnoses are available in their countries, and 47.3% were not aware of which newborn screening programs are available in their countries. We should be aware of the risks neurologists take by doing presymptomatic and, more rarely, prenatal genetic testing on their own (61% and 29% of the responders, respectively); however, in most cases (91% and 83%, respectively) the genetic testing is preceded by a medical genetic counseling consultation.

Education in neurogenetics

Of the responders, 96.3% declared that there is a need for education and training of neuroresidents in neurogenetic diseases. A neurogenetic program is known to be available in 34% of the medical school curriculums, in 24.6% of the neurological residency curriculums, and in 33% after the neurological residency program.

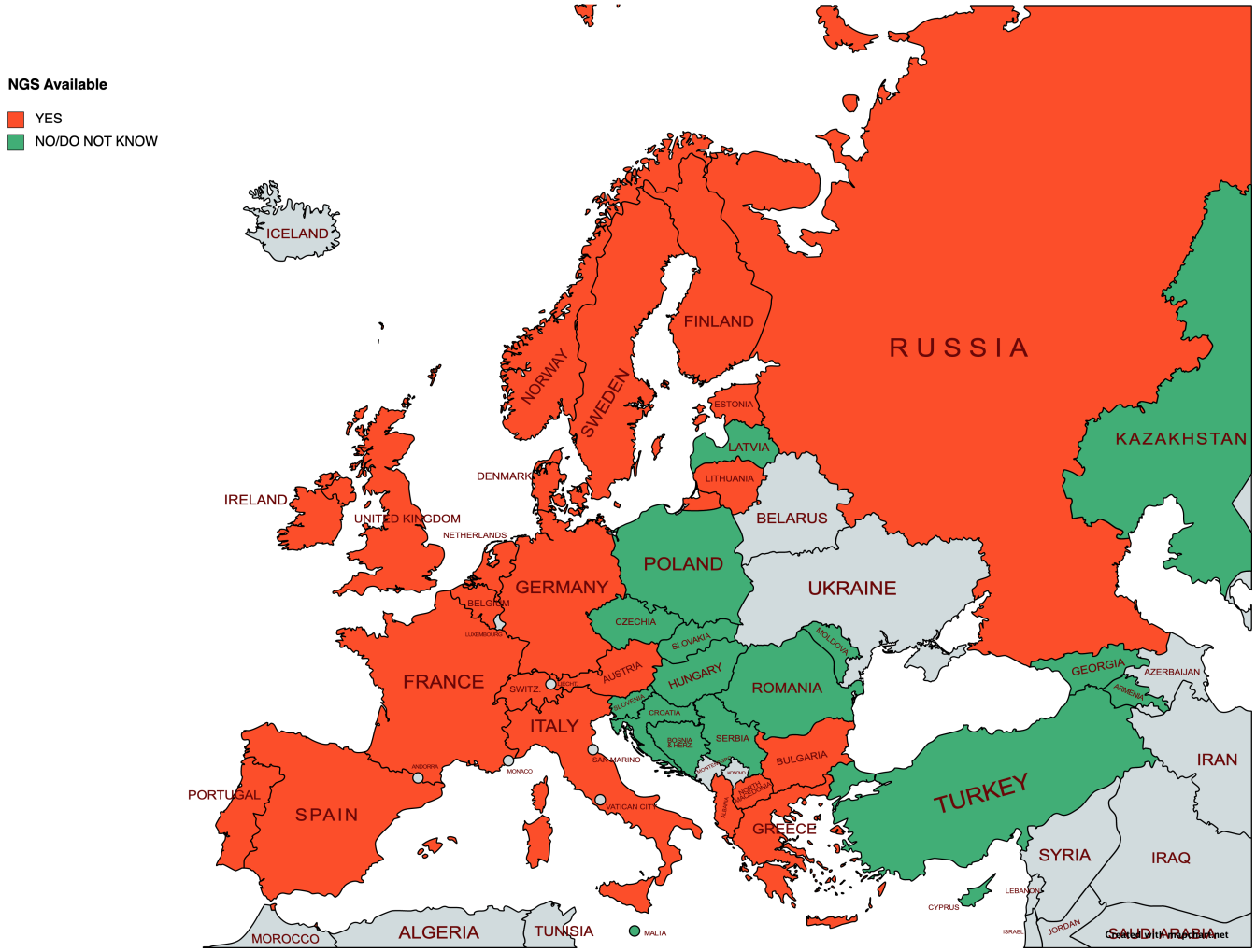

FIGURE 2 Next-generation sequencing (NGS) availability based on survey responders [Colour figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

The total number of RDs is estimated to be >7000, with a global prevalence of 3.5%–5.9%, and there are an estimated 263–446 million persons affected globally at any point in time [3].

In Europe, it is estimated that >500,000 persons are affected by RNDs, and globally, the management presents a significant challenge [4,5] to health policy makers, health care providers, patients, and society in general due to gaps in knowledge, lack of awareness, difficulties in gene testing, and treatment access due to the high costs.

With this work, we aim to provide evidence that a survey tool, used in the context of the EAN, is a useful means to collect information about the state-of-the-art of health-related activities for NGDs, which may help to improve and homogenize health care service to the RD community.

We are aware that our survey tool has some limitations. First, the survey did not collect enough responses from neuropediatricians, with only 6.7% of responders being involved in the care of children. Second, although a large proportion of countries in Europe were included in the study, for some of them we have obtained a very low number of responders, and this might have biased the results for some countries. Third, the results were based on a single subject response per country. This might also have biased the results of care needs in some European countries. However, all respondents were affiliated with the EAN and members of different EAN panels, and we assume they were likely to be well informed about the NGDs in their respective countries. It would be important in the future to both replicate and expand our data to have more insights in the field of neurogenetics; collaboration with other entities, including additional scientific associations, could be a way to go.

Even though absolute conclusions cannot be reached, several messages arise from this survey.

(i) Information about the country organization for molecular diagnosis of NGDs is not diffusely provided to the clinicians working in the neurological field, but mainly to those not directly involved in the RD world.
(ii) The awareness of the neurologist about new-born screenings for inherited treatable diseases is relatively low.

FIGURE 3 Diagnostic whole exome sequencing (WES) availability based on survey responders [Colour figure can be viewed at wileyonlinelibrary.com]

(iii) This survey reveals that, in spite of the many initiatives undertaken to facilitate the diagnosis and management of RNDs in Europe, there is still much to be done to support these patients, including an easy approach to specific diagnostic gene testing, presymptomatic diagnosis, and carrier and newborn screening. A deeper collaboration between all stakeholders in the arena (academia, physicians, researchers, EU politicians, patients' advocacy groups, and industries) is a crucial need.

(iv) Despite the strong epidemiological impact of neurogenetics diseases and the high costs related to them, education in clinical genetics and neurogenetics is still inadequate in most countries. Neurogenetics programs in both medical schools and residency curriculums and in continuing medical education are strongly encouraged.

We believe that this work may be of importance for all European stakeholders in RNDs and NGDs in identifying key priorities that should be accomplished to do better in the near future:

Key Priority 1: Ensuring European patients get the right diagnosis faster wherever they live, including prenatal diagnosis and newborn screening for the treatable NGDs.

All experts in the field know that the diagnostic journey of a patient with an NGD is frequently an odyssey, which is complex and burdensome [6]. It features multiple consultations and tests, and often conflicting diagnoses. These reflect disease variety, diagnostic uncertainty, and clinician unfamiliarity, and may lead to incorrect family planning and treatment delay.

Key Priority 2: Keep increasing awareness of rare conditions among health care professionals.

Although this survey is encouraging, we still have work to do in this scenario, as different national realities revealed that the neurological community is not always well aware of RNDs [7,8].

Key Priority 3: Developing a neurogenetics curriculum during medical school, and neurological and child neurology training and continuous medical education programs.

Key Priority 4: Translation of pediatric issues to adulthood. Given the amount of early-onset genetic disorders and the possibility for early diagnosis and treatment, efforts to harmonize transition of patients with neurogenetic disorders from pediatric neurology to adult neurology is highly warranted across Europe.

Key Priority 5: Technical red flag issue/transparency. How do you know what you get? As gene panels for each diagnostic area

FIGURE 4 Diagnostic whole-genome sequencing (WGS) availability based on survey responders [Colour figure can be viewed at wileyonlinelibrary.com]

expand, such as in charcot-marie-tooth disease (CMT) or dystonia, it will be important to harmonize the genes and flanking introns being tested across European and the rest of the world's diagnostic laboratories. This is a technical issue of extracting standard data from the exome or genome that each panel is taking on through a collaborative PanelApp [9].

Key Priority 6: To speed up the diagnosis of cases not diagnosed within their own countries, cross-border collaboration can be offered through the European Reference Network for Rare Neurological Disorders (ERN-RND), Neuromuscular Disorders (ERN EuroNMD), and Epilepsies (ERN EpiCare) using the Clinical Patient Managements System developed by the EU.

Key Priority 7: Unsolved cases and cases where the detection of variants of uncertain significance (VUS) may seriously hamper the diagnosis of inherited NGDs should be directed to collaborative research programs.

Key priorities 1, 2, 3, 4, and 6 are currently be taken up by the ERN-RND, ERN EuroNMD, and ERN EpiCare. Notably, and in collaboration with the EAN, an RND postgraduate curriculum is being developed, and cross-ERN working groups have been established on transition and NGS diagnostics.

ACKNOWLEDGMENTS

MM, SB, HG and AF of this publication are members of the European Reference Network for Rare Neurological Diseases - Project ID No 739510. MM and MJM are also members of the European Reference Network for Rare Neuromuscular Diseases. Open Access Funding provided by Universita degli Studi di Pisa within the CRUI-CARE Agreement.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Michelangelo Mancuso: Conceptualization (equal), data curation (equal), formal analysis (equal), methodology (equal), writing–original draft (lead). **Henry Houlden:** Conceptualization (equal), methodology (equal), writing–review & editing (equal). **Maria Judit**

Molnar: Conceptualization (equal), methodology (equal), writing–review & editing (equal). **Alessandro Filla:** Conceptualization (equal), writing–review & editing (equal). **Marianthi Breza:** Data curation (equal), investigation (equal), writing–review & editing (equal). **Holm Graessner:** Investigation (equal), writing–review & editing (equal). **Claudio L. A. Bassetti:** Methodology (equal), writing–review & editing (equal). **Sylvia Boesch:** Conceptualization (equal), data curation (equal), methodology (equal), writing–review & editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Michelangelo Mancuso https://orcid.org/0000-0003-2738-8562
Claudio L. A. Bassetti https://orcid.org/0000-0002-4535-0245

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Mancuso M, Houlden H, Molnar MJ, et al. How to approach a neurogenetics diagnosis in different European countries: The European Academy of Neurology Neurogenetics Panel survey. *Eur J Neurol*. 2022;29:1885–1891. doi:10.1111/ene.15320