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Awareness and Care Practices for Rare Neurologic Diseases among Senior Neurologists: A Global Survey

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Abstract

Objective: Rare neurologic diseases (RNDs) are difficult to diagnose and treat due to their low prevalence and complex nature. This survey evaluated awareness and current care status of RNDs among esteemed neurologists affiliated with the World Federation of Neurology (WFN).

Methods: A 34-question survey was distributed to renowned neurologists, including delegates from national neurology societies in the WFN Assembly, various WFN committees, and members of the Rare Neurologic Diseases Specialist group. Responses were stratified by geographical regions, including Africa, the Americas, Asia/Oceania, and Europe, and into four income groups based on the World Bank Indicator. Descriptive statistics summarized responses, stratified by geographical regions or income groups, and significant differences were assessed by Fisher's exact test.

Results: Of 190 invited neurologists, 64 responded (34% response rate). Among respondents, 89% agreed that RND patients should receive timely and effective care on par with more common neurological conditions. Additionally, 77% of respondents overall thought most RNDs could be accurately diagnosed in their country. However, there were significant differences in the perceived ability of respondents' country of practice to diagnose RNDs by region, specifically in Africa (25%), and by income of country of practice, specifically in the lower-income group (17%).

Conclusions: This global survey highlights varying RND diagnosis and care by country socioeconomic status, suggesting potential disparities in resources and preparedness. To improve outcomes and quality-of-life for RND patients, efforts should focus on improving diagnostic capabilities, fostering collaboration among neurology centers, and promoting education on the unique challenges and treatment options of RNDs.

Conference abstract:

Findings from this survey were presented at World Congress of Neurology, abstract PV1556/#3146 (1).

Keywords

attitudes; awareness; diagnosis; care; knowledge; practice

1. Introduction

Rare neurologic diseases (RNDs) are illnesses with very low prevalence (2). In Europe, a low prevalence of rare diseases is defined as affecting fewer than 1 person per 2,000 individuals (3). There are over 6,000 rare diseases, of which more than 70% are of genetic etiology, approximately 70% are solely pediatric onset (4), and over half have neurologic or neuromuscular involvement (2). Although each rare disease has a relatively low prevalence individually, the cumulative point prevalence is substantial, at 3.5 to 5.9% globally, affecting approximately 260 to 450 million people (4).

Despite technological and therapeutic advances (5) and increased awareness (2), RNDs remain difficult to diagnose. First, since they are rare, a physician may consider more common illnesses of similar presentation before considering the RND, delaying a definitive diagnosis. For instance, the RND amyotrophic lateral sclerosis (ALS), that can present like several more common conditions, necessitates a lengthy differential diagnosis (6). Second, a general practitioner may misinterpret test results, misdiagnose, or fail to make a referral to a neurologist or neurologist specialist early enough in the diagnostic process (7), incurring additional delays. ALS can take between 10 to 16 months to diagnose due to such misdiagnoses and deferred referrals (8). Patients with other RNDs may wait 3 to 10 years before a diagnosis (7, 9). Lastly, although screening and diagnostic tests, such as genetic and genomic sequencing (10, 11), and specialist clinical care may facilitate diagnosis, availability may be limited due to high costs and lack of resources. Moreover, even when genetic or genomic testing are available, diagnostic yield is only 30 to 50% (12, 13), leading to undiagnosed RNDs.

Although once considered generally recalcitrant to treatment, an increasing number of disease-modifying therapies have become available for treating RNDs (14, 15). Moreover, some RND organizations have established guidelines for optimal multidisciplinary care of patients with RNDs (3, 16). Therefore, a timely diagnosis is crucial for earlier intervention. Nevertheless, many new disease-modifying therapies come with a hefty price tag, so treatment can be expensive (17), and, consequently, challenging if resources are limited, even when a diagnosis has been made.

We launched the current survey of neurologists to evaluate awareness and current diagnosis and care practices for RNDs. Specifically, we assessed neurologist attitudes and awareness towards RNDs, presence of RND specialty centers, and availability of diagnostic tests and treatments for RNDs in the home country of respondents. The survey was administered to senior neurologists involved in the different committees and boards of the World Federation of Neurology (WFN). We summarized survey responses stratified by practicing country by geographic region (Africa, Americas, Asia/Oceania, Europe), and income groups (higher, upper-middle, lower-middle, lower) as defined by the World Bank Classification.

2. Material and methods

2.1 Survey instrument and sampling design

The survey was sent by email to 190 neurologists affiliated with different WFN committees. The survey comprised 34 questions (Supplementary Table S1). For some questions, participants could select multiple responses, therefore, percentages were higher than 100% for some survey items.

2.2 Region and income status

The country respondents practiced in were classified based on region (Africa, Americas, Asia/Oceania, Europe), which were defined based on the definition “countrycode” in R-package (Supplementary Table S2) (18). The country respondents practiced in were

classified by income status (higher, upper-middle, lower-middle, and lower), as defined by the 2022 World Bank Classification.

2.3 Statistical analysis

Descriptive statistics summarized survey responses for all participants and stratified by region and income group of participants' practicing country. Fisher's exact tests assessed differences in survey responses between geographic region and income groups, separately. Statistical testing was performed between responses of "yes", "no", and "I don't know"; if there were no responses of "I don't know", testing was between responses of "yes" and "no". Adjusted p-values using the Bonferroni correction method accounted for multiple comparisons. Available case analysis was used to handle missing responses when comparing across geographic region and income groups. Statistical significance used an adjusted p-value < 0.05, i.e., q-value < 0.05 threshold. All analyses were performed in R version 4.3.2.

2.4 Ethics approval and participant consent

The WFN Board approved the work of the Subspecialist Group on RNDs, which conducted this study. The survey included a question about data protection, which stated: "This survey is by invitation only. We will not share or make public information that can link you to individual responses presented in our final report. You can request a copy of WFN's Data Protection and Privacy Policy Documents by emailing DPO@wfneurology.org. "Do you agree to the above?" All respondents agreed with the study's data protection clause.

3. Results

3.1 Demographic information of survey respondents by region and income groups

Response rate to the 34-question survey was 34% (64 of 190 neurologists). Respondents predominantly practiced in Europe (n=33, 52%), followed by Asia/Oceania (n=11, 17%), and equally in Africa and the Americas (n=10 and 16% each, Table 1). Respondents mostly practiced in higher-income countries (n=43, 67%), whereas the remainder practiced equally across upper-middle, lower-middle-, and lower-income countries (n=7 and 11% each). Most respondents practiced as adult neurologists (91%, versus pediatric, both, or other) and at a university hospital (84%, versus public non-academic, private, or research hospital or other).

3.2 Survey respondent attitudes and country practices on RNDs by region and income groups

Across region and income groups, most respondents (89%) agreed that patients with an RND should receive an accurate diagnosis, care, and therapy in as timely a manner as patients with more common neurological conditions (Table 2). When queried about whether their country was well organized to adequately diagnose and care for RND patients, generally, in most regions, approx. 35 to 55% responded "yes" while approx. 40 to 65% responded "no"; Africa stood out with 90% responding "no" versus 10% responding "yes", but not to a significant extent versus other regions. Breakdown by income group uncovered a trend of increasing proportion of "no", to the question regarding country preparedness to diagnose and treat RND patients, with decreasing income, although the trend lacked statistical significance. When asked about whether most RND cases could be diagnosed

in their country, the bulk of respondents answered “yes” in most regions, except Africa, where the majority responded “no”, a significant difference ($q=0.012$). This pattern was more pronounced and significant ($q<0.001$) by income group, where more respondents answered “no” in the ability of their country to accurately diagnose most RNDs with diminishing income. Respondents also differed significantly regarding the availability of a rare disease plan in their practicing country, with proportion replying “yes” increasing stepwise from Africa, Americas, Asia/Oceania, to Europe, i.e., by region ($q=0.005$), and by income ($q<0.001$). Interestingly, a large proportion of respondents from higher-income countries replied they did not know of a rare disease plan ($n=15$, 35%).

3.3 Knowledge of and presence of pediatric and adult RND centers by region and income groups

Upon querying whether their practicing country has centers mainly dedicated to pediatric RND, most respondents in most regions replied “yes”, except Africa, where most respondents answered “no” (Table 3). There were 9 (14%) respondents overall that did not know whether their country had a pediatric RND center. More respondents from lower-income countries reported their country did not have dedicated pediatric RND centers ($q=0.002$), with a similar percentage (14%) of respondents unaware of pediatric RND centers across income groups. A similar pattern emerged when respondents were asked about the presence of centers mostly dedicated to adult RND patients in their practicing countries.

Most survey respondents (82 to 90%) replied that newborn screening for some RNDs was available in their practicing country, except for Africa where only 11% replied “yes” ($q<0.001$). Most respondents practicing in higher- (90%) and upper-middle-income (71%) countries reported that newborn screening for some RNDs was available, compared to only 50% in lower-middle income countries and 14% in lower-income countries (14%). Availability of prenatal screening for the most common RNDs increased stepwise by region (order of Africa, Americas, Asia/Oceania, Europe; $q<0.001$) and by income ($q<0.001$). Overall, knowledge of availability of prenatal diagnosis in the practicing country was lower than for newborn screening (28% vs. 8.2%).

3.4 RND diagnostic tool accessibility by region and income groups

Our survey next asked respondents about availability of tools to diagnose RNDs, which spanned routine blood and urine examination, non-routine biochemical tests, tissue biopsy, neurophysiology, neuroimaging, PCR fragment analysis, and molecular genetic tests modalities (Supplementary Table S3; Figure 1 by region, Figure 2 by income groups).

Routine blood and urine examination was generally available across all regions and income groups; however, non-routine biochemical tests for mitochondrial, lysosomal, lipid storage, and amino-acidopathy RNDs were least available in Africa followed by Asia/Oceania and in the lower-income group. Tissue biopsy tests were also widely accessible for muscle, skin, and brain diagnostics, except for some significant differences by country income group for brain tissue analysis, which were relatively less available for all save the higher-income group.

Neurophysiology tests were broadly offered across regions and income groups (above 75% across regions), aside from evoked potentials, which were not as readily available in Africa (60%) or low-income (43%) countries. On the other hand, except for computed tomography and magnetic resonance imaging, most other neuroimaging platforms, including magnetic resonance spectroscopy, positron emission tomography, and brain ultrasound, differed in availability by region and income group.

PCR fragment analysis and molecular genetic tests, encompassing single-gene, targeted panel, next generation sequencing, and whole genome and exome sequencing, universally differed significantly in availability by region and income groups, generally being lower in Africa and Asia/Oceania to a lesser extent, and in lower-middle- and lower-income countries.

3.5 RND treatment accessibility by region and income groups

Over half of all respondents (53%) replied that gene therapy was available in their country; however, access varied significantly by region and income group, with lower access in Africa (10%) and lower-income countries (0%) ($q < 0.001$). This was recapitulated in the availability of enzyme replacement therapy for RNDs, with just over 60% of respondents overall declaring access in their country, with region- and income group-dependent availability, again lowest in Africa (10%) and the lower-income group (0%) ($q < 0.001$). A similar number of respondents overall did not know whether gene therapy (17%) or enzyme replacement (16%) were available in their country; interestingly, most belonged to higher- or upper-middle income countries. Concerning RND-specific drugs, this was the most accessible, at 73% of overall respondents, and did not vary significantly by country ($q = 0.3$); nevertheless, access to RND-specific drugs significantly dropped step-wise with decreasing practice country income.

Lastly, we inquired about coverage for RND treatments, and whether costs were borne by a national health service; 34% and 27% of respondents replied that coverage was complete and partial, respectively, in their country. By region, respondents that said coverage was complete practiced mostly in Europe (61%), whereas those stating it was partial primarily practiced in Asia/Oceania (64%). Respondents answering “no” to coverage by a national health service practiced mostly in Africa (90%). By income group, complete coverage was highest in higher-income countries (47%), while partial coverage was almost equal across higher- (30%), upper-middle (29%), and lower-middle- (29%) income countries.

4. Discussion

In this study, we surveyed attitudes towards RNDs and diagnostic and care availability in the country of practice of eminent neurologists across the world. This was the first survey, to our knowledge, to assess the state of RND awareness and care practice among neurologists globally. We found that 89% of respondents agreed that RND patients deserved the same level of attention and care as patients with more common neurological conditions. Yet, 56% of respondents did not believe their country is well organized for diagnosis and care for patients with RNDs. Importantly, 35% of respondents from higher-income countries replied they did not know of a rare disease plan and there were also significant knowledge gaps

regarding the availability of dedicated pediatric or adult RND centers, prenatal diagnosis, and treatment, across regions and income groups. Notably, there were significant differences by region and income groups, indicating there may be substantial disparities in terms of accessibility to RND diagnostic tools and treatments by geographic regions and income levels. Specifically, access to diagnostic tests and treatments were lower in respondents from Africa and access dropped as respondent's country income level decreased.

Few surveys have been conducted of awareness of RNDs among neurologists or physicians more broadly. A 2021 survey of 239 members of the European Academy of Neurology (EAN) spanning 40 European countries found high levels of recognition of RNDs (19). On the other hand, a 2019 survey of Italian neurologists (n=104) found good awareness among members of the Italian Society of Neurology, Neurogenetics and Rare Neurologic Diseases Scientific Group, but relatively irregular awareness at the national and regional levels (20), underscoring knowledge gaps among neurologists despite national initiatives. In addition, surveys of awareness of rare diseases among medical (21, 22), nursing, and physiotherapy (22) students in Poland found knowledge gaps regarding RND prevalence, proportion ascribed to genetic etiology, and more frequent onset in pediatric patients. We also observed a significant knowledge gap relating to RND resources in the respondent's countries. Taken together, these findings highlight the need for improved RND education to ensure patients with RND receive appropriate and timely care (19–22).

We found that while 89% of neurologists believed patients with RNDs should receive timely access to care and treatment, only 44% believed their country was well-situated to do so. Global initiatives are needed to improve the ability to care for RNDs for neurologists in these countries. There are several organizations that promote RND awareness and/or advocate for patient representation, such as the European ORPHANET (4) and EAN (23) and the European Reference Networks, including the one for Rare Neurological Diseases (ERN-RND), EpiCare, EURO-NMD (24, 25). National organizations have also been established, such as the Italian National Network of Accredited Centres (20, 26). Registries are also an important step forward towards increasing RND visibility, and several such efforts have been launched, such as the Italian National Registry of Rare Diseases (26) and the US-led Global Rare Diseases Patient Registry Data Repository (27). Although these organizations' efforts have borne fruit in raising awareness, nonetheless, knowledge gaps remain and access to RND diagnostic tools and care remains suboptimal, particularly in lower-income countries.

Neurologists practicing in Africa and in lower-middle- and lower-income countries reported their countries had the lowest preparedness and ability to diagnose and treat RND patients. This problem is not unique to Africa and lower-income countries; a survey of European EAN members found that almost one third of responders were dissatisfied with the protocol for ordering genetic tests in their country (19), which would hinder diagnostic capacity. In Italy, survey neurologists stated an RND diagnosis was possible in 75% of cases, but that it varied by specific RND (20). Therefore, diagnostic gaps remain for patients with RND, even in more resource rich settings. We also found that countries in Africa and of lower income lacked a national rare disease plan, and, we identified substantial knowledge gaps regarding availability of a national rare disease plan, even among respondents from higher-income

countries. Our findings are aligned the Italian survey of neurologists that noted around 20% were unaware that coordinated care was available for RND patients through dedicated national centers (20). Thus, even knowledge of resources for RNDs is suboptimal.

Most RNDs, around 70%, have a pediatric onset (4), which makes the distinction between RND centers dedicated to children and adults important. However, our survey highlighted a lack of RND centers dedicated to pediatric patients in lower-income countries. Critically, a sizable number of respondents practicing in countries across all income groups were unaware whether RND centers dedicated to pediatric patients were available, indicating knowledge gaps more broadly. Findings were similar when we queried about adult RND centers, albeit the knowledge gap was less significant. A small survey of 20 ERN-RND members emphasized the challenges of transitioning pediatric RND patients to the care of an adult neurologist (28). Consequently, around half of pediatric health care providers continued to care for their RND patients well into adulthood. Although small, the study may suggest a disconnect in care between pediatric and adult RNDs, possibly the result of an on-going knowledge gap.

We also found suboptimal access to newborn screening and prenatal testing in countries in Africa and of lower-middle- to lower-income. However, this lack was by no means limited to these regions and socioeconomic groups, since availability was not 100% in higher- or upper-middle income countries for newborn screening and reached only 58% (higher-income) and 29% (upper-middle income) for prenatal screening. Moreover, 35% of neurologists practicing in higher- and 29% in upper-middle income countries replied they were unaware about availability of prenatal screening, a considerable knowledge gap. Our findings are similar to an EAN survey, which found that almost 10% of neurologists queried were unfamiliar with availability of prenatal diagnosis, while nearly 50% were uncertain about newborn screening programs (19). In an Italian survey, 40% of surveyed neurologists were unaware of newborn testing (20). Therefore, this issue is a global one, not limited only to some regions and income groups.

RND diagnoses are challenging because of their rare and complex nature. Several diagnostic tools are available to facilitate diagnosis, but they range greatly in cost, and, therefore, accessibility. Indeed, we observed that RND diagnostic tool availability differed by region and country income. Nevertheless, we identified a few diagnostic modalities that were widely adopted across all regions and income groups, which included routine blood and urine examination, tissue biopsy (brain biopsy to a lesser extent), neurophysiology (evoked potentials to a lesser extent), and some imaging methods. However, several more advanced imaging platforms as well as non-routine biochemical tests and molecular PCR and sequencing methods were generally less available in Africa and Asia/Oceania and lower-middle- and lower-income countries. Despite better availability in higher-income countries, the process may remain cumbersome; the EAN survey underscored the challenges of ordering genetic testing in Europe (19). In Italy, almost 30% of neurologists referred their patient to a center outside their region of practice and reported variability in diagnostic tool availability (12 to 99%) based on the RND center expertise (20). Therefore, lack in access to diagnostic tools remains broadly across the world, although some regions experience greater shortages.

It may be possible to tackle the lack of availability in diagnostic tools, for instance of molecular tests. A recent genetic testing study of adult RND patients (n=377) found that diagnostic yield was 32% overall, but varied by approach, and was actually highest by directed testing (50%), a less costly approach, than exome testing, which had only a 25% diagnostic yield (12). The outperformance of more targeted sequencing strategies, such as gene panels may be condition-dependent, e.g., muscle diseases, and could offer a cost-effective first-line solution for well-defined phenotypes (12, 13). However, next generation sequencing may be better geared for more phenotypically heterogeneous RNDs (13). By identifying what RND a patient may have can help prioritize targeted versus next generation sequencing, helping physicians allocate resources more effectively. Moreover, as next generation sequencing costs continue to drop, it will render the technology more accessible, even in lower resource settings.

Our last set of survey questions concerned RND treatment accessibility, which again showed variation by region and income groups, especially for newer therapies such as gene therapy and enzyme replacement therapy. Few surveys have been conducted of disease-modifying therapy for RNDs; a recent survey of Italian centers queried treatment for spinal muscular atrophy, noting higher disease prevalence possibly as a result of adoption of disease-modifying therapies, including gene replacement and antisense oligonucleotides (29). On the other hand, we found RND-specific drugs did not vary by region, although access significantly dropped step-wise with lower practice country income. Coverage of RND treatment cost was also variable, and less covered outside of Europe and within lower-income countries. Nevertheless, coverage was not universal in higher-income countries. Increasing access to disease-modifying therapies, even in higher-income countries, is a primary concern for patients because they significantly improve patient outcomes (30, 31). In a survey of patient representatives (n=95), almost half stated that developing therapies and preventive strategies was their main priority, given the direct impact of RNDs on their well-being, while professionals (n=61) favored investigation of disease mechanisms and models, with the ultimate goal of developing treatments (24). We highlight, herein, remaining work to be done to enhance access to disease-modifying therapies for RND patients.

Our study has some limitations. First, this was a scoping survey that was not validated. Moreover, respondents may have differed in their definitions, e.g., a “specific drug for RNDs”. Second, the study was relatively small overall, and even smaller by some regions and income groups. Consequently, responses by regions with few respondents may not be representative of the continent, which may be more heterogeneous and not reflected in this survey. Likewise, replies from the few respondents practicing in upper-middle-, middle-, and lower-income countries may not be characteristic of those income groups. This relatively small respondent sample size also precluded analysis of replies by country, but many respondents from one country within a region may have biased findings for that region. In addition, given our sample size, we were unable to account for differences between specific countries within a region. Furthermore, the response rate was low (34%), and regional disparities in participation were evident. Neurologists practicing in Europe were overrepresented among survey participants, constituting 51.6% of respondents compared to their estimated WFN membership proportion of 33.3%. However, participants from Asia-Oceania constituted 17.2% of respondents versus 23.5% of membership while participants

from the Americas constituted 15.6% of respondents versus 27.5% of membership, and were, therefore, underrepresented in the survey. Participants from Africa constituted 15.6% of respondents and participated in proportion to their 15.7% of membership. Nevertheless, disparities in participation across Europe, Asia-Oceania, and the Americas may have biased results, and respondents more interested in sharing their knowledge and perspectives may have been more likely to participate in the survey.

5. Conclusions

Our study has some strengths and was a unique opportunity to query attitudes about care for RND patients and treatment and diagnostic availability in the country of practice of a cohort of esteemed neurologists. Our study highlighted some disparities in resource access, but also some strengths, for instance, in some diagnostic modalities, such as tissue biopsy and neurophysiology, even in lower resource settings. This suggests a potential approach for RND diagnosis in that context. Interestingly, our study also revealed some substantial knowledge gaps in RND care and diagnosis, even in higher- and upper-middle-income countries, signifying that, even among established neurologists, knowledge of RNDs and the infrastructure to care for patients remains suboptimal. Awareness campaigns may be warranted. Therefore, further research and initiatives are crucial to advance the diagnosis and care of RND worldwide, even in higher income countries (23, 25). Efforts should focus on improving diagnostic capabilities, fostering collaboration among neurology centers, and promoting education on the unique challenges and treatment options to improve outcomes and quality-of-life for RND patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

Data will be made available to qualified investigators upon request.

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Highlights

- Rare neurologic diseases (RNDs) are difficult to diagnose and treat.
- We surveyed neurologists worldwide on RND diagnostic and care availability.
- Most respondents agreed that RND patients should receive timely and effective care.
- There were differences across respondents' country of practice to diagnose RNDs.
- This global survey highlights potential disparities in resources and preparedness for RNDs.

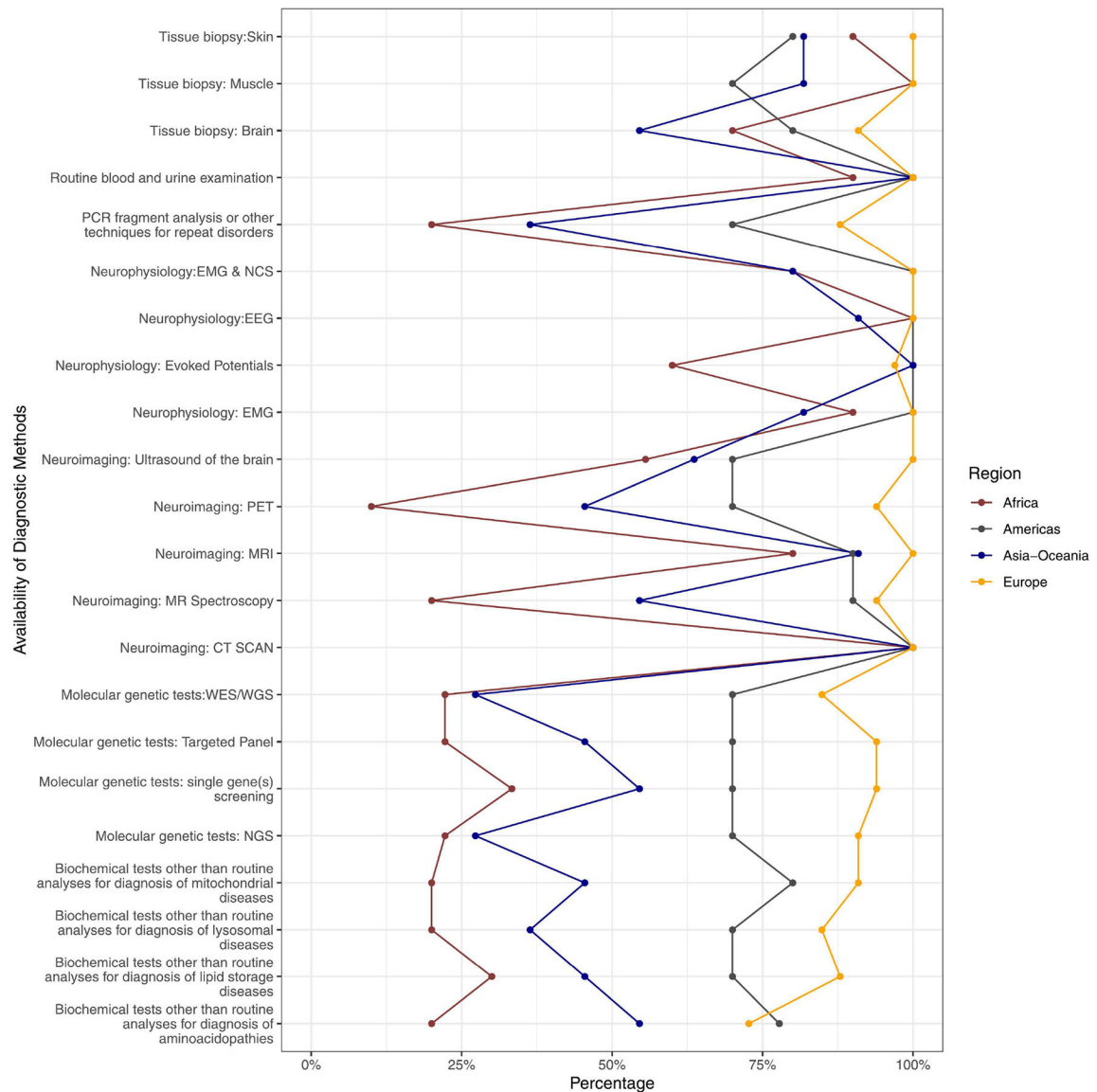


Figure 1. Availability of diagnostic methods for RNDs by regions.

Availability of diagnostic methods in survey respondents' countries, i.e., answered "yes", stratified by regions. Asia and Oceania are grouped together. Percentage represents the percentage of respondents from the region who answered that the diagnostic method is available in their country.

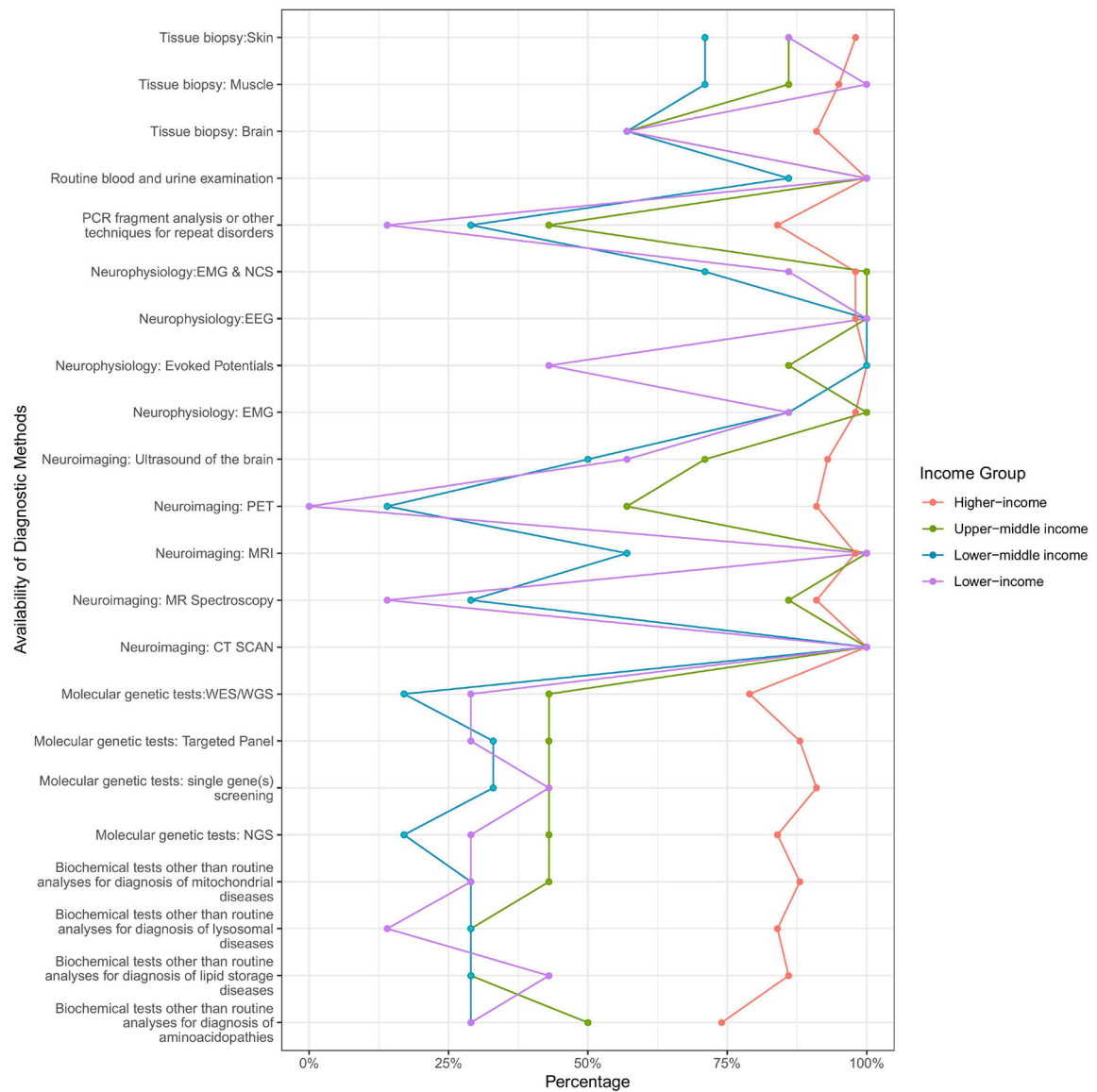


Figure 2. Availability of diagnostic methods for RNDs by income groups.

Availability of diagnostic methods in respondents' countries, i.e., answered "yes", stratified by income groups based on the World Bank Indicator. Asia and Oceania are grouped together. Percentage represents the percentage of respondents from the region who answered that the diagnostic method is available in their country.

Table 1.

Demographic information of survey respondents by region and income groups

Response	Regions					Income Groups			
	Overall N=64 [†]	Africa N=10 [†]	Americas N=10 [†]	Asia/Oceania N=11 [†]	Europe N=33 [†]	Higher-income N=43 [†]	Upper-middle income N=7 [†]	Lower-middle income N=7 [†]	Lower-income N=7 [†]
What is the institution you are working for?									
University Hospital	54 (84%)	10 (100%)	8 (80%)	8 (73%)	28 (85%)	35 (81%)	7 (100%)	5 (71%)	7 (100%)
Public Non-Academic Hospital	5 (7.8%)	0 (0%)	0 (0%)	0 (0%)	5 (15%)	5 (12%)	0 (0%)	0 (0%)	0 (0%)
Private Hospital	10 (16%)	1 (10%)	4 (40%)	2 (18%)	3 (9.1%)	6 (14%)	2 (29%)	1 (14%)	1 (14%)
Research Hospital	5 (7.8%)	0 (0%)	0 (0%)	2 (18%)	3 (9.1%)	3 (7.0%)	1 (14%)	1 (14%)	0 (0%)
Other	4 (6.3%)	0 (0%)	2 (20%)	0 (0%)	2 (6.1%)	4 (9.3%)	0 (0%)	0 (0%)	0 (0%)
Which is your specialty?									
Adult Neurologist	58 (91%)	6 (60%)	9 (90%)	11 (100%)	32 (97%)	41 (95%)	7 (100%)	6 (86%)	4 (57%)
Pediatric Neurologist	2 (3.1%)	1 (10%)	0 (0%)	0 (0%)	1 (3.0%)	1 (2.3%)	0 (0%)	0 (0%)	1 (14%)
Both	5 (7.8%)	3 (30%)	1 (10%)	0 (0%)	1 (3.0%)	2 (4.7%)	0 (0%)	1 (14%)	2 (29%)
Other	7 (11%)	2 (20%)	2 (20%)	1 (9.1%)	2 (6.1%)	2 (4.7%)	3 (43%)	2 (29%)	0 (0%)
<i>I_n</i> (%)									

Table 2.

Survey respondent attitudes and country practices on RNDs by region and income groups

Response	Regions					Income Groups			
	Overall N=64 ¹	Africa N=10 ¹	Americas N=10 ¹	Asia/Oceania N=11 ¹	Europe N=33 ¹	Higher- income N=43 ¹	Upper- middle income N=7 ¹	Lower- middle income N=7 ¹	Lower- income N=7 ¹
Do you think that patients with RNDs should receive an accurate diagnosis, effective care, and available therapy as timely as the patients with more common neurological conditions ?									
No	7 (11%)	2 (20%)	2 (20%)	1 (9.1%)	2 (6.1%)	3 (7.0%)	0 (0%)	1 (14%)	3 (43%)
Yes	57 (89%)	8 (80%)	8 (80%)	10 (91%)	31 (94%)	40 (93%)	7 (100%)	6 (86%)	4 (57%)
Do you think that your Country is already well organized to provide adequate diagnosis and care for RNDs patients?									
I do not know	1 (1.6%)	0 (0%)	0 (0%)	0 (0%)	1 (3.0%)	1 (2.3%)	0 (0%)	0 (0%)	0 (0%)
No	36 (56%)	9 (90%)	6 (60%)	7 (64%)	14 (42%)	19 (44%)	4 (57%)	6 (86%)	7 (100%)
Yes	27 (42%)	1 (10%)	4 (40%)	4 (36%)	18 (55%)	23 (53%)	3 (43%)	1 (14%)	0 (0%)
Do you think that the majority of RNDs could be accurately diagnosed in your own Country?									
No	14 (23%)	6 (75%)	3 (30%)	3 (27%)	2 (6.5%)	2 (4.9%)	4 (57%)	3 (50%)	5 (83%)
Yes	46 (77%)	2 (25%)	7 (70%)	8 (73%)	29 (94%)	39 (95%)	3 (43%)	3 (50%)	1 (17%)
No response / Unknown	4	2	0	0	2	2	0	1	1
Does your Country have a Rare Disease Plan?									
I do not know	17 (27%)	2 (20%)	4 (40%)	0 (0%)	11 (33%)	15 (35%)	0 (0%)	1 (14%)	1 (14%)
No	20 (31%)	7 (70%)	3 (30%)	7 (64%)	3 (9.1%)	5 (12%)	4 (57%)	5 (71%)	6 (86%)
Yes	27 (42%)	1 (10%)	3 (30%)	4 (36%)	19 (58%)	23 (53%)	3 (43%)	1 (14%)	0 (0%)

¹ n (%);

² Fisher's exact test;

³ Bonferroni correction for multiple testing

Table 3.
Knowledge of and presence of pediatric and adult RND centers by region and income groups

Response	Regions					Income Groups			
	Overall N=64 ¹	Africa N=10 ¹	Americas N=10 ¹	Asia/Oceania N=11 ¹	Europe N=33 ¹	Higher- income N=43 ¹	Upper- middle income N=7 ¹	Lower- middle income N=7 ¹	Lower- income N=7 ¹
Are there any centers mainly involved in the most frequent Pediatric RNDs, in your country?									
I do not know	9 (14%)	1 (10%)	1 (10%)	1 (9.1%)	6 (18%)	6 (14%)	1 (14%)	1 (14%)	1 (14%)
No	13 (20%)	7 (70%)	1 (10%)	2 (18%)	3 (9.1%)	3 (7.0%)	1 (14%)	3 (43%)	6 (86%)
Yes	42 (66%)	2 (20%)	8 (80%)	8 (73%)	24 (73%)	34 (79%)	5 (71%)	3 (43%)	0 (0%)
Are there centers mainly involved in the most frequent Adulthood RNDs in your country?									
I do not know	4 (6.3%)	0 (0%)	0 (0%)	1 (9.1%)	3 (9.1%)	3 (7.0%)	0 (0%)	1 (14%)	0 (0%)
No	16 (25%)	9 (90%)	2 (20%)	3 (27%)	2 (6.1%)	4 (9.3%)	2 (29%)	3 (43%)	7 (100%)
Yes	44 (69%)	1 (10%)	8 (80%)	7 (64%)	28 (85%)	36 (84%)	5 (71%)	3 (43%)	0 (0%)
Is there newborn screening for some RNDs present in your country?									
I do not know	5 (8.2%)	1 (11%)	1 (10%)	0 (0%)	3 (9.7%)	2 (4.9%)	2 (29%)	0 (0%)	1 (14%)
No	10 (16%)	7 (78%)	0 (0%)	2 (18%)	1 (3.2%)	2 (4.9%)	0 (0%)	3 (50%)	5 (71%)
Yes	46 (75%)	1 (11%)	9 (90%)	9 (82%)	27 (87%)	37 (90%)	5 (71%)	3 (50%)	1 (14%)
No response / Unknown	3	1	0	0	2	2	0	1	0
Is prenatal diagnosis available for the most common RNDs available in your Country?									
I do not know	18 (28%)	1 (10%)	5 (50%)	2 (18%)	10 (30%)	15 (35%)	2 (29%)	0 (0%)	1 (14%)
No	18 (28%)	9 (90%)	2 (20%)	5 (45%)	2 (6.1%)	3 (7.0%)	3 (43%)	6 (86%)	6 (86%)
Yes	28 (44%)	0 (0%)	3 (30%)	4 (36%)	21 (64%)	25 (58%)	2 (29%)	1 (14%)	0 (0%)

¹ n (%);

² Fisher's exact test;

³ Bonferroni correction for multiple testing

Table 4.

RND treatment accessibility by region and income groups

Response	Regions					Income Groups					p-value ²	q-value ³
	Overall N=64 ¹	Africa N=10 ¹	Americas N=10 ¹	Asia/Oceania N=11 ¹	Europe N=33 ¹	Higher- income N=43 ¹	Upper- middle income N=7 ¹	Lower- middle income N=7 ¹	Lower- income N=7 ¹			
Is gene therapy for RNDs available in your Country ?												
I do not know	11 (17%)	0 (0%)	4 (40%)	0 (0%)	7 (21%)	<0.001	<0.001	2 (29%)	0 (0%)	0 (0%)	<0.001	<0.001
No	19 (30%)	9 (90%)	2 (20%)	6 (55%)	2 (6.1%)			2 (29%)	5 (71%)	7 (100%)		
Yes	34 (53%)	1 (10%)	4 (40%)	5 (45%)	24 (73%)			3 (43%)	2 (29%)	0 (0%)		
Is enzyme replacement therapy for RNDs available in your Country ?												
I do not know	10 (16%)	0 (0%)	3 (30%)	1 (9.1%)	6 (18%)	<0.001	<0.001	1 (14%)	0 (0%)	0 (0%)	<0.001	<0.001
No	14 (22%)	9 (90%)	2 (20%)	2 (18%)	1 (3.0%)			2 (29%)	5 (71%)	7 (100%)		
Yes	40 (63%)	1 (10%)	5 (50%)	8 (73%)	26 (79%)			4 (57%)	2 (29%)	0 (0%)		
Are specific drugs for RNDs available in your Country?												
I do not know	7 (11%)	2 (20%)	1 (10%)	2 (18%)	2 (6.3%)	0.010	0.3	0 (0%)	1 (14%)	2 (29%)	<0.001	0.002
No	10 (16%)	5 (50%)	1 (10%)	2 (18%)	2 (6.3%)			2 (29%)	3 (43%)	4 (57%)		
Yes	46 (73%)	3 (30%)	8 (80%)	7 (64%)	28 (88%)			5 (71%)	3 (43%)	1 (14%)		
No response / Unknown	1	0	0	0	1			0	0	0		
Are the costs for the specific RNDs treatments covered by the National Health Service?												
I do not know	7 (11%)	0 (0%)	2 (20%)	0 (0%)	5 (15%)	<0.001	<0.001	0 (0%)	0 (0%)	0 (0%)	<0.001	<0.001
No	18 (28%)	9 (90%)	5 (50%)	3 (27%)	1 (3.0%)			3 (43%)	5 (71%)	7 (100%)		
Yes, completely covered	22 (34%)	0 (0%)	1 (10%)	1 (9.1%)	20 (61%)			2 (29%)	0 (0%)	0 (0%)		
Yes, partially covered	17 (27%)	1 (10%)	2 (20%)	7 (64%)	7 (21%)			2 (29%)	2 (29%)	0 (0%)		

¹ n (%);² Fisher's exact test;³ Bonferroni correction for multiple testing