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ARTICLE

Educational needs in diagnosing rare diseases: A multinational, multispecialty clinician survey

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ABSTRACT

Purpose: Recognizing rare diseases (RDs) and initiating appropriate investigation and referral is critical for timely diagnosis. Unfortunately, patients with RDs experience significant diagnostic delays, potentially leading to inappropriate or harmful testing or treatment and disease progression.

Methods: A 14-question survey assessing clinician knowledge, experience, and educational needs in RDs was emailed to US and European Union Medscape member clinicians. The survey was available from April 1, 2021, through August 2, 2021.

Results: The respondents included 978 clinicians across 16 specialties. Two-thirds of the respondents considered RDs to be 50 to 500 times rarer than standard European Union or US definitions, and despite a point prevalence of 3.5% to 5.9%, 59% said they never or rarely (1× or 2× per year) see patients with RDs. Although 87% have been involved in an RD diagnosis, only 19% were mostly or very confident in making a diagnosis. In addition, 38% to 44% reported diagnostic barriers such as knowledge of signs/symptoms, time to investigate, guideline availability, test access, and referrals. Highest RD education preferences included a comprehensive online learning platform with current education and resources and case-based, text-based, and short formats (≤15 minutes) taught by world-renowned clinicians.

Conclusion: This research study identified RD knowledge gaps, highlighting the need for education to shorten the diagnostic odyssey, which can enable earlier referral and treatment.

Introduction

Although rare on an individual level, collectively, rare diseases (RDs) are common, with a point prevalence of 3.5% to 5.9%—equating to 263 to 446 million people—being affected at any time point.[1] This includes an estimated 36 million people in the European Union (EU) and 30 million people in the United States.[2,3] The categorization of a

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disease as "rare" is based on its prevalence, and this definition varies by region. For example, the US Food and Drug Administration Orphan Drug Act defines an RD as having a prevalence of <200,000 people[4] in the United States (equating to about <1 in 1648 people) and the European Commission as a prevalence of ≤5 in 10,000 or ≤1 in 2000 people.[5] As of the most recent update in 2020, Orphanet contained information on 6172 unique RDs, 71.9% being genetic and 69.9% with an exclusively pediatric onset.[1]

Despite representing thousands of RDs, people living with RDs report a collective experience of common challenges, including a long and convoluted route to diagnosis, often referred to as the diagnostic odyssey.[6] During this time, patients often consult multiple different primary care providers and specialists, are given an average of 2 or 3 misdiagnoses,[7,8] and experience a delay of an average 4 to 5 years and sometimes more than 10 years between the first symptom onset and a correct diagnosis[8-12]

Nonspecific and heterogeneous symptoms associated with many RDs are often the cause of misdiagnoses and/or delayed diagnoses. This is highly problematic because undiagnosed patients are at risk of unnecessary medical interventions and surgeries as well as disease progression, which can be life-threatening.[13,14] Generally, RDs are progressive and severely physically and/or mentally disabling, leading to a substantially decreased quality of life for both patients and family/caregivers and often a shortened life expectancy.[14] In fact, an estimated 30% of patients with RDs die before 5 years of age.[15] There is also a massive economic impact: for example, in the United States, the aggregate financial burden of RDs is estimated to be greater than that associated with chronic diseases.[16] Another study conducted in Western Australia showed that although patients with RDs accounted for 2% of the population studied, they accounted for 10.5% of inpatient hospital costs, which the authors deemed likely to be an underestimate of the overall cost because this did not include social and economic implications for patients, carers, and family members, as well as outpatient costs and other physician/allied health service costs.[17]

It is impossible for any individual clinician to be familiar with all of the estimated 10,000 different RDs.[18] Of the >5300 diseases that have been defined by a point prevalence, 84.5% have a prevalence of less than one in 1 million.[15] That said, approximately 78% to 80% of the population burden of RDs can be attributed to about 149 diseases within the most common prevalence range of 1 to 5 per 10,000.[1]

The European Commission's strategic objectives for RDs focus on improving access to diagnosis, information, and care by supporting individual national plans, the European Reference Networks (facilitating RD interactions between health care providers in Europe), the designation and authorization of orphan medicinal products, research, and patient organizations. But despite this effort, national plan and policy implementation across Europe differ considerably.[19,20] In the United States, 3 key programs are integral to the national policy on RDs: the Orphan Drug Act, which incentivizes the development of RD drugs; the Rare Disease Act, which increases funding for new RD drugs; and the National Institutes of Health research programs, which support RD research.[2,21]

It is hypothesized that a lack of basic knowledge about what constitutes an RD and what that might mean in terms of approach to diagnosis and management hampers diagnosis.[22-28] However, it is currently unclear exactly what clinicians do understand about RDs, which is particularly important as countries endeavor to tackle this hypothesized education gap. Clinicians need sufficient knowledge to suspect an RD and need trusted and comprehensive sources of information to facilitate prompt diagnosis and appropriate referral for disease management. Several studies have assessed the need for RD education but have only surveyed approximately 300 to 400 clinicians at most and have not covered a broad range of clinical specialties or geographical regions and are therefore limited in their outcomes.[29-32]

To better understand what clinicians across a variety of different disciplines know about RDs, their experience in diagnosing and treating RDs, what they perceive as barriers, and how they want to learn about RDs, we conducted a large survey of physicians and nurses in the United States and 5 European countries (France, Germany, Italy, Spain, and the United Kingdom).

Materials and Methods

Study design

A 14-question survey was developed by 1 author after a review of the literature that reports results of other similar surveys[9,13,26,29,30,32] and reviewed by co-authors who have experience developing similar surveys,[26] as well as the Medscape survey development team, which reviews and manages an average of 113 clinician surveys per year.

Participants and setting

Initial online survey questions served to screen for physicians and nurses only (all other health care providers were excluded), including those specializing in cardiology, critical/intensive care, dermatology, emergency medicine, gastroenterology/hepatology, hematology/oncology, infectious disease, medical genetics, nephrology, neurology, obstetrics and gynecology (OB-GYN), ophthalmology, pediatrics, primary care, psychiatry, and transplant medicine. Other specialists were not invited to participate but were not excluded. Physicians had to practice in the EU or the United States to be eligible to participate.

Research tools

The survey employed an online questionnaire consisting of 14 questions in the English language. Statistical analysis for

the survey data was conducted using R version 4.1.3 (R Foundation for Statistical Computing).

Data collection

Medscape, LLC collected all clinician survey data between April 1, 2021, and August 2, 2021. Survey links were sent via email to Medscape members who met inclusion criteria as described above. Each clinician was remunerated US $25 (nurses) or $35 (physicians) in their local currency for their participation. Respondent confidentiality was maintained, and responses were deidentified and aggregated before analyses.

Measures and data analysis

To assess knowledge of the prevalence of RDs, clinicians were asked how they define "RD" and given a set of multiple-choice responses from which to select.

To assess their experience, clinicians were asked how often they see patients who have an RD, how confident they are in their ability to diagnose an RD (using a 5-point Likert scale: 5 = "Very confident" and 1 = "Not at all confident"), whether they have been involved in an RD diagnosis and how many cases, which roles they have had regarding RDs (diagnosis, specialist referral, routine management, prescribing medications, managing complications, or other), and how often they experience barriers to diagnosing RDs in their practice. The latter included sufficient knowledge regarding signs and symptoms that should trigger suspicion, sufficient time to investigate properly, availability of diagnostic guidelines, access to diagnostic tests, or knowing where to refer the patient, and it was assessed with a 5-point Likert scale (5 = "Always a barrier" and 1 = "Never a barrier").

Sources of knowledge about RDs were assessed by asking where clinicians have gained knowledge about RDs (medical/nursing school, seminars/meetings, continuing medical education [CME]/continuing education activities, specialty websites, published literature, or other) as well as which are their current top 3 resources for finding information needed to help with an RD diagnosis (options included PubMed or specific journals, search engines [Google, etc], RD specialty/society websites, Medscape, Orphanet, OMIM, National Organization for Rare Disorders [NORD], specialist colleagues, or other).

Finally, to assess what kind of RD education clinicians want, they were asked about the top 3 formats they find most effective in terms of the time required and gaining knowledge to inform themselves about an RD. They were asked to rank their preference for learning about RDs, from most to least—from a world-renowned expert, a local clinician/expert, or a patient advocate—and they were asked which top 3 resources for RD diagnosis they would be most likely to use.

Data analysis

Univariate analyses were conducted to describe the respondents' knowledge, experience in RD identification and management, confidence, barriers, and needs and preferences for CME. Subanalyses by specialty were only conducted if there was a minimum n of 50. This was possible for 14 specialty areas. Some analyses included "generalists," consisting of primary care physicians and pediatricians or "specialists," consisting of all physicians except generalists. When there were no substantial differences between countries or specialties, data were grouped. The term "clinicians" refers to all respondents, whereas the term "physicians" excludes nurses/advanced practice nurses.

Certain variables were recoded for analysis. For defining RD prevalence, clinicians who chose the correct option were coded as "correctly defined RD as 1," otherwise were coded as "0." For confidence in RD diagnosis, we coded both "very confident" equal to 5 and "mostly confident" equal to 4 as "1" or "high confidence," indicating that the respondents are confident in making an RD diagnosis. All other responses were coded as "0," suggesting that the respondents have "low confidence" in making an RD diagnosis. For sources used to gain knowledge about RDs, if respondents checked "published literature," we coded "the use of published literature" as "1" and other responses as "0." The same coding procedure was applied to other sources.

We conducted a series of χ^2 tests (formula provided below) to compare the characteristics of respondents who correctly defined "RD" and those who did not, whether there was an association between seeing patients with an RD on a weekly basis and sources of gaining knowledge about RDs, and whether having confidence in making an RD diagnosis was associated with sources of gaining knowledge about RDs.

$$\chi^2 = \frac{\sum (O_i - E_i)^2}{E_i}$$

where O_i = observed value

E_i = expected value

Results

Survey responders

Of the 69,317 clinicians who were contacted, 978 clinicians who specialize in 16 different therapeutic areas completed the survey (1.4% response rate). Among them, 927 (94.8%) were physicians, and 51 (5.2%) were nurses or advanced practice nurses. Fifty percent of the respondents were from the United States and 50% were from Europe (Table 1).

Table 1 Characteristics of respondents ($N = 978$)

Variable	Total *n* (%)
Profession	
Physician	927 (94.8)
Nurse/advanced practice nurse[a]	51 (5.2)
Regions	
Europe	489 (50.0)
France	11 (1.1)
Germany	24 (2.5)
Italy	151 (15.4)
Spain	88 (9.0)
United Kingdom	215 (22.0)
United States	489 (50.0)
Physician specialties	
Pediatricians	55 (5.9)
Primary care physicians[b]	55 (5.9)
Obstetrician-gynecologists	60 (6.5)
Cardiologists	58 (6.3)
Dermatologists	62 (6.7)
Nephrologists	60 (6.5)
Infectious disease specialists	60 (6.5)
Gastroenterologists/hepatologists	116 (12.5)
Hematologists/hematologist oncologists	60 (6.5)
Neurologists	62 (6.7)
Psychiatrists	62 (6.7)
Ophthalmologists	62 (6.7)
Emergency medicine physicians	61 (6.6)
Critical/intensive care specialists	54 (5.8)
Medical geneticists	35 (3.8)
Transplant specialists	5 (0.5)

[a]Excluded from physician analysis.
[b]Primary care physicians refer to physicians practicing family practice, general practice, internal medicine, and geriatrics.

Table 2 Overall survey findings ($N = 978$)

Variable	%
Able to correctly define RD prevalence	
Yes	30
No	70
Underestimated by 50-fold	46
Underestimated by 500-fold	20
Overestimated	1
Own description	2
Confidence in making an RD diagnosis	
High confidence	19
Low confidence	81
Previous involvement in an RD diagnosis	
Yes	87
No	13
Sources for gaining knowledge about RDs (respondents selected all that applied)	
Published literature	71
Medical school	70
Seminars/meetings	61
CME activities	54
Specialty websites	48
Type of RD education considered most effective (respondents selected top 3 choices)	
Case-based education (on a single disease)	65
Short-format education (≤15 min)	58
Text-based education	56
Case-based education (on multiple diseases)	43
60- to 90-min seminars/symposia	38
Face-to-face workshops/seminars	26

RD, rare disease.

Clinician knowledge in RD

Overall, only 30% of respondents defined an RD as per the EU and US definitions (a prevalence of ≤1 in 2000 or >200,000 people, respectively) (Table 2). When broken out by profession, 29% of physicians and 38% of nurses correctly identified the respective definitions. The correct definition was selected by only 8% of US respondents, 13% in Germany, 20% in the United Kingdom, 32% in Italy, 34% in Spain, and 36% in France (Table 3). Depending on their specialty, 64% to 92% of physicians and 58% of nurses vastly underestimated the definition, by 50- or 500-fold (selecting a prevalence of <1 in 100,000 or <1 in 1,000,000), including 77% of pediatricians and 78% of primary care physicians.

Clinician experience in RD

The relatively high underestimation of RD prevalence correlated with low physician experience in RD. Overall, 80% of nurses and 57% of physicians said they never or rarely (1 or 2 times per year) see patients who have RDs, 43% of physicians reported that they see these patients at least monthly, and 12% reported that they see them at least weekly (Figure 1). One in 5 nurses reported seeing a patient with an RD at least monthly. Specialists (45%) reported that they see more patients with RDs monthly or weekly compared with pediatricians or primary care practitioners (PCPs) (31%), and this was similar between the US and European countries. However, as many as 8% of US and 7% of European pediatricians report actually never seeing a patient with an RD, with 68% of US pediatricians and 60% of European pediatricians reporting seeing patients with RDs only rarely (1 or 2 times per year). At least half of the responding ophthalmologists (57% in the United States and 59% in Europe) and neurologists (58% in the United States and 53% in Europe) and about one-third of responding OB-GYNs, cardiologists, and hematologist/oncologists reported that they see patients who have an RD at least once a week or once a month. There was a trend for French physicians seeing patients with RD more frequently compared with those from other countries (Figure 2A).

In a χ^2 analysis to determine whether there was a correlation between correctly defining the prevalence of RDs and perceived/self-reported RD patient caseload, we found that respondents who said they see patients with an RD more often (eg, weekly), were significantly more likely to correctly define the prevalence (36.8%) compared with those who report seeing these patients less often (eg, monthly or less; 16.5%) (χ^2 [1, $N = 978$] = 27.6, $P < .001$) (Table 4).

Table 3 Survey question: how do you define rare disease?

Answer Choice	France (n = 11)	Germany (n = 24)	Italy (n = 151)	Spain (n = 88)	United Kingdom (n = 215)	United States (n = 489)
A prevalence of 1 in 200	0%	0%	1%	1%	2%	0%
A prevalence of 1 in 2000[a]	36%	13%	32%	34%	20%	12%
A condition affecting <200,000 people[b]	9%	17%	7%	10%	9%	8%
A prevalence of 1 in 100,000	36%	34%	31%	34%	48%	47%
A prevalence of 1 in 1,000,000	18%	34%	24%	15%	19%	18%
Other	0%	0%	5%	6%	2%	4%

[a]Correct answer for Europe.
[b]Correct answer for the United States.

When asked about the roles clinicians have had in RDs, 89% of physicians and 41% of nurses said they have been involved in diagnosis. There was a trend for French physicians having been more often involved in the diagnosis of RDs compared with other countries (Figure 2B). Overall, 59% of physicians and 25% of nurses have been involved in specialist referrals for RDs; generalists were more likely to make referrals (especially in the United States [84%] vs Europe [61%] compared with specialists in the United States [68%] and Europe [48%]). Overall, physicians (46%) and nurses (41%) were comparably involved in the routine management of patients with RD. Although US physicians (49% generalists and 53% specialists) were more likely to be involved in the routine management of RDs compared with European physicians (38% generalists and 41% specialists), the rates did not differ significantly between generalist and specialist care. In the United States, more specialists said they prescribe medications (50%) and/or manage complications for RDs (50%) vs generalists (33% and 31%, respectively). However, in European countries, similar proportions of specialists and generalists prescribe medications (45% vs 54%, respectively) and manage complications (48% vs 51%, respectively). Differences between countries were not significant (Figure 2C).

Barriers in the diagnosis of RDs

Despite a high proportion of physicians having been involved in an RD diagnosis, few felt "very" or "mostly" confident in making a diagnosis of an RD: 23% in the United States and 17% in Europe. Another 40% of physicians in the United States and 38% in Europe were only "moderately" confident. This result was particularly stark for pediatricians: despite 85% of all pediatricians having been involved in an RD diagnosis, only 9% were "mostly confident" in making such a diagnosis and none felt "very confident." Similarly, although 95% of gastroenterologists/hepatologists have been involved in an RD diagnosis, only 27% were "mostly" or "very" confident in making such a diagnosis.

A χ^2 analysis revealed that clinicians who had high confidence in making an RD diagnosis were significantly

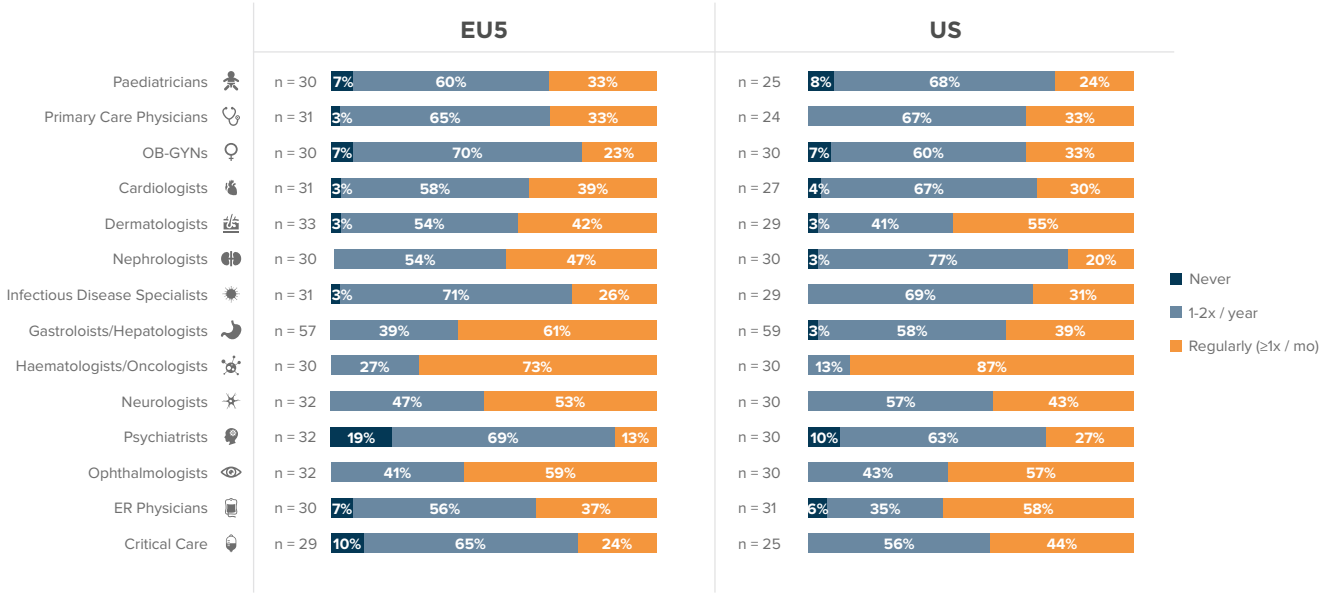

Figure 1 **How often are physicians seeing patients with rare diseases?** *ER*, emergency room; *EU*, European Union; *OB-GYN*, Obstetrics and Gynecology.

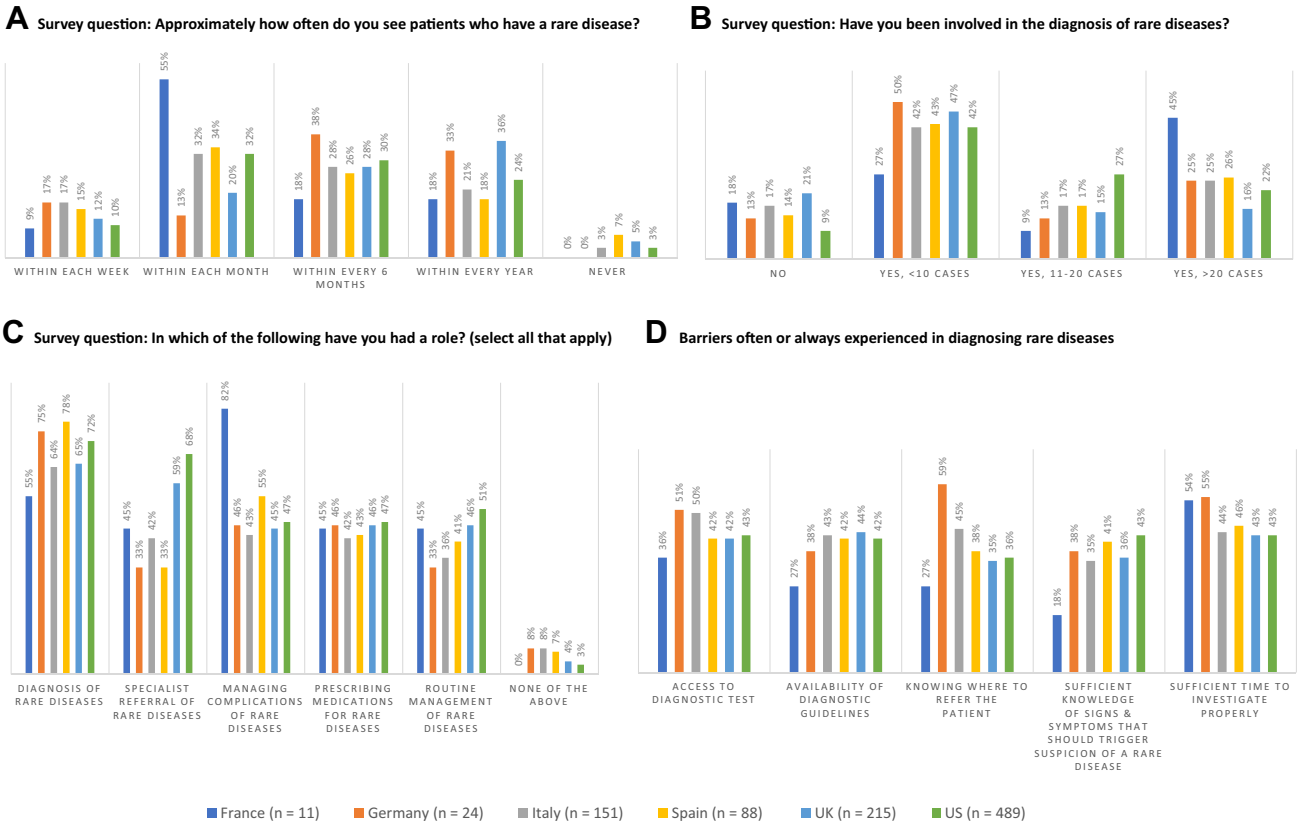

Figure 2 **Data analysis by country.** A. Survey question: Approximately how often do you see patients who have a rare disease? B. Survey question: Have you been involved in the diagnosis of rare diseases? C. Survey question: In which of the following have you had a role? (select all that apply). D. Barriers often or always experienced in diagnosing rare diseases.

more likely to correctly define RD (24%) compared with those who had low confidence (17.7%) (χ^2 [1, N = 978] = 12.5, P < .01) (Table 4).

Specific barriers in the diagnosis of RD differed between specialists and generalists and between the United States and Europe. Specialists in the United States identified access to diagnostic tests and sufficient knowledge regarding signs and symptoms that should trigger suspicion as the top 2 barriers to RD diagnosis, whereas more specialists in Europe found sufficient time to investigate properly a barrier, followed by access to diagnostic tests. Over half of European pediatricians, US PCPs, and European/US critical care specialists said both insufficient knowledge and insufficient time were frequent barriers, and 58% of cardiologists reported inadequate time as a frequent barrier. Apart from US PCPs, a significant proportion of respondents (≥40%) reported that availability of diagnostic guidelines and access to diagnostic tests are frequent barriers to diagnosing RDs. At least 33% of most specialty groups (excluding US pediatricians and European critical care specialists) said that knowing where to refer the patient is a frequent barrier. Overall, 33% to 50% of all clinicians said they "often" or "always" experience barriers to diagnosis and referrals for RDs. Emergency medicine physicians in both Europe (70%)

Table 4 Association between knowledge of RD prevalence and confidence in RD diagnosis or seeing patients with RDs weekly (N = 978)

Variable	Defined Prevalence of RD Correctly		χ^2 (df = 1, N = 978)	P Value
	Yes, n (%)	No, n (%)		
High confidence in making an RD diagnosis	46 (24.0)	146 (76.0)	12.5	.006
Low confidence in making an RD diagnosis	139 (17.7)	647 (82.3)		
Seeing patients with RDs weekly	43 (36.8)	74 (63.2)	27.6	<.001
Seeing patients with RDs monthly or less often	142 (16.5)	719 (83.5)		

RD, rare disease.

Table 5 Sources for gaining knowledge about RDs according to weekly RD patient load and confidence in diagnosing RDs ($N = 978$)

Sources of Gaining Knowledge About RD (Check All That Apply)	Seeing Patients With RDs Weekly				Confidence in Making an RD Diagnosis			
	Yes, *n* (%)	No, *n* (%)	χ^2 (df = 1, $N = 978$)	*P* Value	Yes, *n* (%)	No, *n* (%)	χ^2 (df = 1, $N = 978$)	*P* Value
Published literature								
Yes	94 (80.3)	597 (69.3)	6.0	.014[a]	159 (82.8)	532 (67.2)	17.0	<.001[a]
No	23 (19.7)	264 (30.7)			33 (17.2)	254 (32.3)		
Medical school								
Yes	85 (72.6)	603 (70.0)	0.3	.0561	137 (71.4)	551 (70.1)	0.1	.733
No	32 (24.7)	258 (30.0)			55 (28.6)	235 (29.9)		
Seminars/meetings								
Yes	86 (73.5)	515 (59.8)	8.1	<.004[b]	150 (78.1)	451 (57.4)	28.0	<.001[c]
No	31 (26.5)	346 (40.2)			42 (21.9)	335 (42.6)		
CME activities								
Yes	71 (60.7)	453 (52.6)	2.7	.101	134 (69.8)	390 (49.6)	25.2	<.001[c]
No	46 (39.3)	408 (47.4)			58 (30.2)	396 (50.4)		
Specialty websites								
Yes	66 (56.4)	405 (47.0)	3.6	.057	110 (57.3)	361 (45.9)	8.0	.005[b]
No	51 (43.6)	456 (53.0)			82 (42.7)	425 (54.1)		

CME, continuing medical education; *RD*, rare disease.
[a]$P < .05$.
[b]$P < .01$.
[c]$P < .001$.

and the United States (81%) said insufficient time to investigate properly was a barrier for them. Analysis by country revealed few differences; however, there was a trend for French physicians experiencing fewer barriers overall (except regarding sufficient time to investigate properly) and knowing where to refer the patient being a more frequent barrier for German physicians (Figure 2D).

Resources used to learn about RDs

Almost three-quarters of physicians (73%) learned about RDs in medical school. Published literature was the most popular source beyond medical school (72%) for gaining additional knowledge, with other important sources including seminars or meetings (62%), CME activities (54%), and specialty websites (48%).

When asked what physicians' current main resources are for finding information needed to help with an RD diagnosis, PubMed/specific journals was the top resource, with 81% choosing this option. Medscape was the second-highest resource for European physicians (55%) and an important resource for US physicians (37%). Of note, 68% of infectious disease specialists in Europe identified Medscape as a primary resource for information on diagnosing RDs, more than the overall survey group. More US generalists (51%) sought information from specialist colleagues compared with European generalists (34%); search engines (eg, Google) were also popular resources for US physicians (60%), more so than for European physicians (45%). Orphanet and NORD may be used to narrow down a diagnosis but were infrequently used: 4% of US generalists relied on Orphanet and 16% on NORD, and 23% and 5% of European generalists relied on Orphanet or NORD, respectively. A similar percentage of generalists (14% in the United States and 13% in Europe) relied on OMIM.

χ^2 analyses showed that respondents who see patients with RDs more often (weekly) were significantly more likely to consult published literature to gain knowledge about RDs (80.3%) compared with those who do not see patients with RDs weekly (69.3%) (χ^2 [1, $N = 978$] = 6.0, $P < .05$) and were more likely to gain their RD knowledge from seminars or meetings (73.5%) vs respondents who do not see patients with RDs weekly (59.8%) (χ^2 [1, $N = 978$] = 8.1, $P < .01$) (Table 5).

Similarly, respondents with high confidence in making an RD diagnosis were significantly more likely to use the following resources to gain knowledge about RDs: (1) published literature (82.8%) vs those with low confidence (67.2%) (χ^2 [1, $N = 978$] = 6.0, $P < .05$), (2) seminars or meetings (78.1%) vs those with low confidence (57.4%) (χ^2 [1, $N = 978$] = 28.0, $P < .001$), (3) CME activities (69.8%) vs those with low confidence (49.6%) (χ^2 [1, $N = 978$] = 25.2, $P < .001$), and (4) specialty websites (57.3%) vs those with low confidence (45.9%) (χ^2 [1, $N = 978$] = 8.0, $P < .01$) (Table 5).

What kind of RD education do physicians want?

When asked what type of education physicians find most effective to learn about RDs, in terms of time required and gaining knowledge, the greatest preferences were for single-disease, case-based education (64%) and short-format (<15

minutes) lectures (59%) followed by articles or publications (57%) and 60- to 90-minute seminars/symposia (38%).

The top 3 most-valued resources for learning about an RD rated by physicians were as follows: (1) a comprehensive online learning platform with educational materials and resources (83%), (2) a website that provides links to online resources for RDs (71%), and (3) a website that provides printable information about different RDs that can be used in practice (64%).

Regardless of where they practice, physicians said they wanted to learn about RDs primarily from a world-renowned expert, followed by a local expert/clinician and lastly from a patient advocate.

Discussion

Our findings support those of previous smaller, single-nation studies regarding clinician knowledge and experience with RDs. Specifically, it is apparent that most physicians in the United States and Europe, whether generalist or specialist, underestimate the prevalence of RDs, which may lead them to underestimate or under-recognize the number of patients with RDs in their existing clinical practices. Notably, two-thirds of physicians considered RDs on the order of 50- to 500-fold rarer compared with standard definitions in the EU (≤5 per 10,000) or the United States (<200,000 people in the United States). Being more familiar with the prevalence of RDs was associated with a perceived higher RD caseload, suggesting that awareness of the clinical relevance of RD is important. The low familiarity with RDs has previously been observed; for example, a survey-based study of Polish physicians found that 95% of physicians taking specialization courses perceived their knowledge of RDs to be "insufficient" or "very poor," and fewer than 5% felt prepared to care for a patient with an RD.[31]

Given a point prevalence of RDs of 3.6% to 5.9%,[1] and assuming that a physician sees approximately 100 patients in a week, 5 to 6 of those patients could be affected by an RD. Certainly, this will vary depending on specialty, but it may be higher, for example, in pediatric practice because approximately 70% of RDs have an onset exclusively in childhood. However, as many as 71% of the pediatricians reported that they never or rarely see patients with RDs, and 91% had low confidence in diagnosing patients with RDs, which is higher than the low confidence rate of 80% for the entire cohort. An Australian study reported that although a higher proportion of their cohort of pediatricians (93%) indicated that they had seen children with one of more than 350 RDs in their career, 28% felt unprepared to treat patients with RDs.[32]

Rare disease knowledge and experience varies across specialties and subspecialties,[33] but there are core competencies in knowing when to suspect a rare disease, and there are specialized RD-specific competencies. Primary care physicians are in a unique position to be the central repository of the patient/family history and they need to have that core competency, to recognize when a patient may be presenting with an RD, and competence in investigating and referring to an appropriate specialist.[9,15] However, our study showed that although the majority of PCPs have been involved in diagnosing RDs, few reported having sufficient access to diagnostic tests and sufficient knowledge of RDs. Results from a survey of general practitioners (GPs) in Belgium showed that GPs were the initial caregiver for 37% of patients with RDs and established a diagnostic referral for another 36%.[29] Although 59% of the GPs studied reported having an active patient with an RD, they felt they had only "moderate" knowledge of their patient's RD. However, similar to our study observation, only 15% of GPs relied on Orphanet, an important European RD resource, for information about their patients.[18] An older study from the United States found that 89% of family physicians in the study were the first clinicians to identify a patient's RD, 54% established the definitive diagnosis of the RD, 56% provided the initial acute care, and 76% were responsible for providing continuing care.[29] These physicians sought consultations from specialists for 85% of these cases.[34]

Most physicians reported learning about RDs in medical school; however, RDs are generally only minimally covered in medical schools across the United States and Europe.[9,13,32] In the United Kingdom, this is evidenced by the mandatory reporting of medical school syllabi to the General Medical Council, in which only 1 of 42 schools mention the term "rare disease."[35] A study in Spain reported that fewer than one-third of physicians received any training on RDs in medical school.[13] In the United States, the US Medical Licensing Examination syllabus does not mention the terms "rare," "uncommon," or "low prevalence." Where the term "genetic" is mentioned in a clinical context, it is related to prenatal genetic screening and specific metabolic and developmental disorders.[36] The exception may be France, where under the French Rare Disease Plan, RDs are incorporated into the examination that is taken by all medical students, with optional RD modules available on the multidisciplinary aspect of care.[37] The trends seen in our survey with regard to French clinicians seeing patients with RD more often and experiencing fewer barriers in RD diagnosis could be linked to this early training. From the authors' experience in the United Kingdom, when RD is included in medical education, this is largely as a method for teaching about scientific principles (ie, metabolic pathways and models of genetic inheritance, with only a small number of notable exceptions such as cystic fibrosis or Huntington disease). Evidence to date demonstrates that clinicians are not aware of how an RD is defined, when to consider an RD, how to establish a diagnosis, or how to differentiate an RD from a common disorder.[31,38]

Consequently, patients with RDs continue to report long delays in their journeys to obtain an accurate diagnosis,[15,39] which sometimes may require collaboration with and

involvement of clinicians from across the globe.[40] Even if a treatment is not available, earlier diagnosis is important because it not only validates the patient's experience and symptoms but may provide genetic information that can inform prognosis and provide support and education to other family members.[15] In addition, an earlier diagnosis prevents unneeded testing and inappropriate treatments, which may be harmful to the patient and allows for the optimization of their long-term management and the opportunity to participate in research.

Strengths and limitations

The large sample size, which includes 16 different specialties across 6 key countries, is an important strength of this study, enabling robust outcomes as well as cross-country and cross-discipline comparisons for identifying the education needs for specific audiences.

There are some limitations, including the fact that all respondents were Medscape members; it may therefore introduce some bias regarding their sources for RD education/knowledge. Demographic information was available for some but not all participants; therefore, it was not included in this report. Self-declared clinical specialty also limits the generalizability of aggregated specialty results across different countries, for example, the role of a primary care physician can differ significantly from one country to another. All participants were from resource-rich countries; therefore, the findings may only be applied to these countries, which may have different educational goals compared with others. Furthermore, the numbers of participants from France and Germany were substantially lower than those from other countries, which is tied to another limitation of the survey being conducted in English only.

Practical implications

Education is needed to increase awareness of RD, including the likelihood of seeing a patient with an RD in any practice, and to address the common barriers in RD diagnosis that many clinicians experience, including knowledge of common patterns of presentation and signs and symptoms that should trigger suspicion of an RD. When suspicions are raised, resources should be available "just in time," which are concise, relevant for their specialty, and easily accessible to help guide suitable investigation and referral.[15] It has been shown that when knowledge and/or competence is improved or reinforced via online accredited education, there is an associated increase in confidence, which is correlated with higher commitment to intended practice changes.[41] This suggests that RD education can change clinical practice and reduce the diagnostic odyssey for patients. A comprehensive online learning platform for RDs where physicians can find the information they need, when they need it, where they are able to print RD information for patients or their own practice, and to find other sources on specific RDs, were all identified as valuable resources. These findings are consistent with those of prior surveys, which found that a majority of physicians want online educational modules in an online portal with which they are familiar.[26,30,32] In addition, this survey identified case-based, text-based, and short-format education as most useful for physicians; therefore, these should be prioritized as formats for future education.

From early medical education onward, clinicians need to be made aware of the unique profile of needs for the 3.5% to 5.9% of the population living with a rare condition. Disease agnostic education concentrates on core competency in RD, that is, definition, prevalence, collectively common challenges, and care pathways. An example of this type of education can be found in the course "Rare Disease 101."[42] This foundation of knowledge can be built on when considering specific rare conditions, but it is imperative that this information is up to date given the rapid changes in RD knowledge base. Education or information regarding specific RDs may be found using resources such as Orphanet,[43] NORD,[44] OMIM,[45] the UK Genomics Education Programme,[46] the RCGP Genomic toolkit,[47] Osmosis,[48] and others. Medscape.org provides accredited education on RD basics (ie, core competencies) as well as on specific RDs across 24 specialties.[49] Patient advocacy groups are frequently the most up-to-date providers of information given their multi-stakeholder links and work based on patient experience. However, for systematic change, national plans need to ensure that health care and medical education systems implement core competency as well as specialty-specific RD training across all career stages and cross-specialty.

Conclusions

Results from this survey were not unexpected. Physicians are generally poorly prepared to identify patients with RDs and this is reflected in patient-reported experiences. It follows that the physicians who underestimated the prevalence of RDs were less confident in their ability to diagnose and reported that they are less likely to see patients with RDs on a regular basis. Of concern is the lack of knowledge and confidence among pediatricians, in light of the predominance of RDs presenting in childhood. This educational research study highlights the need to develop education for physicians on recognizing RDs earlier, shortening the diagnostic odyssey, and enabling earlier referral and treatment.

Data Availability

The authors were unable to find a valid data repository for the data used in this study. These data are available from S. Christy Rohani-Montez at Medscape Education Global (srohani@medscape.net).

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Ethics Declaration

This study was exempt from institutional review board approval because it is not considered human subjects research under Title 45 Code of Federal Regulations Part 46. It does not obtain, use, study, analyze, or generate identifiable private information (United States Department of Health and Human Services, 2020).

Conflict of Interest

W.R.H.E. is a consultant or advisor for Intrabio and Orphazyme and is a speaker or member of the speakers' bureau for Takeda. All other authors declare no conflicts of interest.

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