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Primary ciliary dyskinesia: A multicenter survey on clinical practice and patient management in Italy

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Abstract

Introduction: There are no recent data on primary ciliary dyskinesia (PCD) distribution, diagnosis and treatment in Italy.

Methods: A descriptive study based on a survey questionnaire. It consisted of three sections (patients, diagnosis, and treatment), and sent to all the Italian PCD Centers.

Results: Questionnaires obtained from 20/22 centers in 12/20 regions showed that the total number of PCD patients treated at the participating centers was of 416. Out of all centers, 55% follow <20 patients, two centers have >40 patients, and 75% follow both pediatric and adults. Age at diagnosis was between 4 and 8 years in 45% of the centers, <3 years in three centers. Nasal nitric oxide, transmission electron microscopy and ciliary high-speed video microscopy are performed in 75%, 90%, and 40% of centers, respectively. Immunofluorescence is available in five centers. Genetic analysis is offered in 55% of the centers, and in seven centers >50% of the patients have a known genetic profile. Patients treated at all centers receive inhaled saline solutions, corticosteroids and chest physiotherapy. Prophylactic antibiotics and mucolytics are prescribed in 95% and 50% of the centers, respectively. Pseudomonas infection is treated with oral or inhaled antibiotics.

Conclusions: Many Italian centers care for a small number of pediatric and adult patients, and diagnosis is often delayed. We found a great variability in the available diagnostic procedures, as well in the prescribed therapies. Our study will help to uniform diagnostic algorithm and share treatments protocols for PCD in Italy and allowed to set specific national goals.

KEYWORDS
children, diagnosis, management, primary ciliary dyskinesia, treatment

1 | INTRODUCTION

Primary ciliary dyskinesia (PCD; MIM 244400) is a rare genetic disorder of motile cilia preferentially transmitted via autosomal recessive modality.[1] Recurrent-to-persistent upper and lower respiratory tract infections due to impaired mucociliary clearance are the hallmark of PCD; these often present with bronchiectasis and chronic obstructive airway disease, male infertility, and organ laterality (50% of cases).[2] Early diagnosis of PCD is mandatory to avoid progressive clinical and lung function decline.[3] However, as patients may experience a long delay before diagnosis, or may not be diagnosed at all, many cases remain undiagnosed and undertreated.[4] The main reason is a limited awareness of PCD among physicians who see few affected patients or do not recognize uncommon manifestations.[5] Indeed, confirmation of diagnosis requires methods that are not as widespread as they should be, particularly in countries with health expenditure inequality or a poor knowledge of the technology.[3,5] The prevalence of PCD is estimated to be 1:10.388 to 1:20 000 in non-Finnish European countries?.[6] The true value may be even higher because 30% of cases present with abnormal or nondiagnostic findings.[7]

Twelve years ago, a survey of patients younger than 20 years across Europe highlighted that the prevalence of PCD was underestimated in several countries, including also Italy.[3] This was due to the low response rates of hospitals and lack of modern diagnostic procedures; however, patients treated by either adult pulmonologists or ear, nose and throat (ENT) physicians were missing.

To the best of our knowledge, no recent data on PCD diagnostic approaches and treatment for PCD in Italy have been published.[3] To collect baseline data on the situation and increase awareness of PCD, we created a PCD subgroup within the main "PCD and Non-Cystic Fibrosis bronchiectasis," belonging to the Italian Society of Pediatric Respiratory Disease (SIMRI), and conducted a national survey on PCD. The aims were multifold: first, the study provides updated data on the distribution and size of PCD centers including also patients' age at diagnosis. Second, we identify modalities for PCD screening and diagnosis in Italy. Third, we report on therapeutic regimens preferred in the Italian centers. In our intention, this should facilitate discussion, exchange information, and share knowledge among the members in the PCD group and improve the care of affected patients. Future and ambitious plans should include a comprehensive centralized plan to obtain real national prevalence data, the use of a common uniform diagnostic algorithm and uniform guidelines for the treatment of PCD in Italy.

2 | MATERIALS AND METHODS

2.1 | Study design and population

Italian patients with PCD are usually followed in pediatric pulmonology centers. A group of experts on PCD, in agreement with the Italian Association A.I.D. Kartagener Onlus (https://www.pcdkartagener.it/), designed a survey questionnaire to be sent to all Italian pediatric PCD

centers. To involve, the highest number of care centers, the current members of SIMRI and all the acknowledged regional referral centers for PCD and CF were contacted. Questionnaires were sent by email between October 2020 and February 2021, and answers were collected until the end of June 2021. All contacted physicians were invited to forward the questionnaire to other centers or other groups within the same hospital that treated patients with PCD.

2.2 | Questionnaire

The six-page questionnaire was in Italian and consisted of three sections:

1. Patients section included the numbers of patients seen in each center and sub-grouped into the following:

a. ≤10 patients
b. ≥11–20 patients
c. ≥21–40 patients
d. >40 patients

2. Diagnosis section included data on the mean age at diagnosis and the diagnostic procedures either in situ or from other centers.
3. Treatment section included data on treatments and care in each center.

2.3 | Analysis

This is a descriptive study on the data extrapolated from the questionnaires obtained from the participating centers. Data were entered into a database. The mean and standard deviation (SD) were calculated for a descriptive analysis of the continuous variables, and the frequencies were reported for dichotomous and qualitative variables. Data were analyzed using Statistical Analysis System 9.4 software.

The survey only included general information. As no sensitive data from individual patients have been disclosed, we did not request a formal approval from the Ethical Committees.

3 | RESULTS

We received 20 questionnaires from 22 contacted centers (91% answer rate) in 12 out of 20 Italian regions; two centers never replied.

3.1 | Patients

The Italian National Healthcare system currently does not centralize the care for PCD. Our survey reached 12 out of 20 Italian regions, with 6 regions including more than one PCD center (Figure 1). The

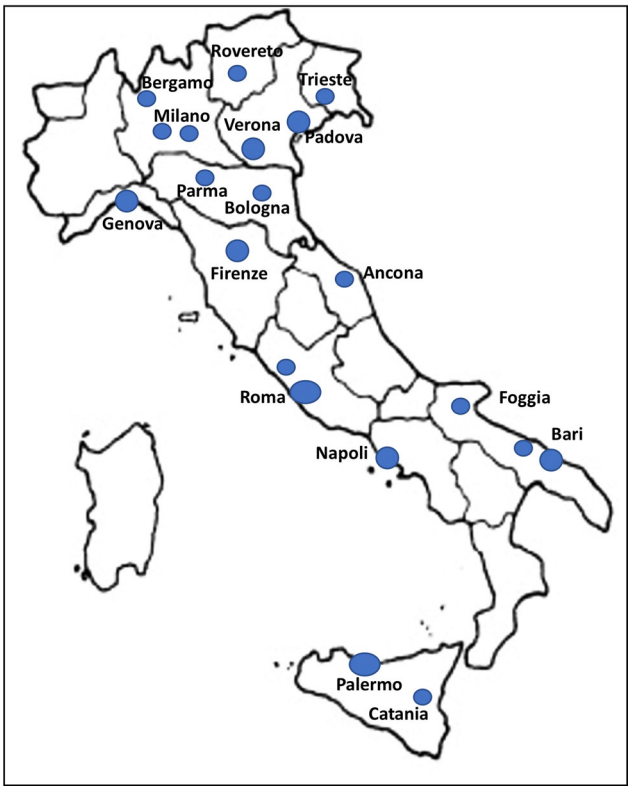

FIGURE 1 All centers and their distribution in Italy

patients' characteristics were reported by all centers and summarized in Table 1. Overall, the total number of PCD patients treated at the participating centers was of 416 and included both pediatric (<18 years-old) and adult subjects. Six centers followed less than 10 patients, 5 between 11 and 20 patients, 7 between 21 and 40 cases, and only two centers cared for more than 40 patients. Four out of the 20 centers (20%) treated only pediatric patients, and one center only adults. The remaining (75%) followed both pediatric and adult patients.

3.2 | Diagnostic

The mean age of patients at diagnosis was less than 3 years in three centers (15% of the total); it was between 4 and 8 years in nine (45%), between 9 and 12 years in five (25%), between 13 and 18 years in two (10%) and >18 years in one center. The procedures for screening and confirming PCD, regardless of whether the test was performed in the center or rather patients were referred to another hospital, are reported in Table 2. No significant correlation was found between the size of centers and age at diagnosis. Fifteen centers (75%) reported to study patients suspected of having PCD through nasal nitric oxide (nNO) measurement via a stationary chemiluminescence analyzer using the closed velum technique. We have ascertained a great variability between centers on the available equipment for nNO analysis. However, the diagnostic cut-off value was fairly similar

TABLE 1 Summary of the referring centers and overview of the characteristics of the study population

Centers	Region	City	No of pts	% of pts followed at each center			Age at diagnosis (yrs)
				<6 yrs	6–18 yrs	>18 yrs	
1	Campania	Napoli	35	0	60	40	4–8
2	E.-Romagna	Bologna	5	60	40	0	9–12
3		Parma	26	15.5	23	61.5	<3
4	Friuli V. Giulia	Trieste	5	20	60	20	4–8
5	Lazio	Roma[a]	28	0	20	80	9–12
6		Roma[b]	60	10	77	13	4–8
7	Liguria	Genova	29	8	52	40	9–12
8	Lombardia	Bergamo	5	0	100	0	4–8
9		Milano[c]	9	10	80	10	<3
10		Milano[d]	18	0	50	50	<3
11	Marche	Ancona	12	40	60	0	4–8
12	Puglia	Bari[e]	23	0	20	80	13–18
13		Bari[f]	10	50	50	0	4–8
14		Foggia	7	0	0	100	>18
15	Sicilia	Catania	8	10	80	10	4–8
16		Palermo	48	3	21	76	13–18
17	Toscana	Firenze	21	4	57	39	4–8
18	Trentino A. Adige	Rovereto	15	10	30	60	9–12
19	Veneto	Padova	28	20	70	10	4–8
20		Verona	24	4	9	87	9–12

Abbreviations: pts, patients; yrs, years.

[a]Roma, Policlinico Umberto I.

[b]Roma, Bambino Gesù Children's Hospital.

[c]Milano, Pediatric Unit Policlinico.

[d]Milano, Cystic Fibrosis Unit Policlinico.

[e]Bari, Pediatric Unit University.

[f]Bari, Hospital Giovanni XIII.

among centers and in accordance with literature (250 ppb–77 nl/min). Samples of ciliated cells to perform either high speed video microscopy (HSVM) and/or transmission electron microscopy (TEM) were mainly obtained by nasal brushing (60% of centers) while a smaller proportion (25%) of them could also perform bronchial brushing in site when endoscopy was indicated. Only two centers (12%) obtained the sample with a scraping spoon instead of using a simple nasal brush. TEM was performed to examine cilia ultrastructure in 90% of the centers, with some declaring to send out samples to another center for analysis; 40% of the centers performed TEM to all patients with highly suggestive clinic presentation, 47% to patients with suggestive clinical picture and low nNO, 13% to patients with altered HSVM, while 72% of them declared to perform EM in more than 50% of patients seen for suspected PCD.

Only 40% of centers assessed ciliary HSVM. Seventy-five percent of the centers performed HSVM once or twice, while the remaining repeated the exam at least three times for confirmation. Genetic analysis was available in 55% of the centers but a wide discrepancy was found according to the genes tested (at the time of the survey: 34–42 genes). Figure 2 shows that seven centers (35%) reported that a genetic characterization was obtained in >50% of their patients. The relatively low number of patients with a genetic diagnosis could be explained by the fact that many centers developed genetic panels more recently when tests had become less expensive and more easily available. Therefore, not all patients with a previous ME diagnosis underwent new testing.

From our data TEM and genetic panels were the diagnostic tests more frequently performed by Italian centers in patients visited for suspected PCD, especially when typical symptoms and pathological nNO were found.

Immunofluorescence was available in only 25% of the centers. None of the participating centers cultured ciliated epithelium.

3.3 | Treatment

All treatments are summarized in Table 3: 50% of the centers used mucolytic agents (such as N-acetylcysteine, DNase, ambroxol), either administered nasally or inhaled through a facial mask. All centers prescribed isotonic and/or hypertonic NaCl solution through nasal irrigation or inhaled via a facial mask (3% hypertonic saline preferred, few centers using 7% solution). All centers prescribed inhaled corticosteroids (ICS) especially when airway reactivity or atopy was confirmed (75%). Airway clearance techniques, including positive expiratory pressure mask, autogenic drainage, oscillating positive expiratory pressure, and manual maneuvers were prescribed as a daily treatment in all centers. The vast majority of centers (95%) prescribed prophylactic antimicrobial therapy (namely, azithromycin) preferably during the winter season in patients with ≥3 exacerbations who had required antibiotic treatment in the previous 6 months.

TABLE 2 Summary of the screening and diagnostic procedures of primary ciliary dyskinesia performed in the Italian centers

	Centers	
	Numbers out of 20	%
Nasal nitric oxide	15	75
Nasal brush only	12	60
Nasal and bronchial brush	5	25
TEM	18	90
HSVM	8	40
IF	5	25
Genetic analysis	11	55

Note: Data are presented as number and % of the total.

Abbreviations: HSVM, high speed video microscopy; IF, immunofluorescence; TEM, transmission electron microscopy.

Most centers tried to eradicate *Pseudomonas aeruginosa* when first detected in sputum culture. Antibiotics were prescribed intravenously, orally or by inhalation (the latter by appropriate inhalation device) in 45%, 90% and 95% of the centers, respectively (Figure 3A). Finally, when *Haemophilus influenzae* was found in sputum culture, 20% of the centers tried to eradicate it by intravenous antibiotics, whereas 75% used oral treatment (Figure 3B).

TABLE 3 Summary of the therapeutic interventions prescribed to patients with primary ciliary dyskinesia at the Italian centers

	Centers	
	Numbers out of 20	% of the total
Mucolytics (nasal or inhaled)	**10**	**50**
Isotonic NaCl solution	**20**	**100**
Nasal	1	5
Inhaled	2	10
Nasal and inhaled	18	90
Hypertonic NaCl solution	**20**	**100**
NaCl 3%	12	60
NaCl 7%	3	15
NaCl 3% or 7%	5	25
Inhaled corticosteroids	**20**	**100**
In all patients	5	25
If airway reactivity or atopy	15	75
Prophylactic antibiotics	**19**	**95**
Airway clearance techniques[a]	**20**	**100**

[a]Including: Positive expiratory pressure mask, autogenic drainage, oscillating positive expiratory pressure, manual maneuvers.

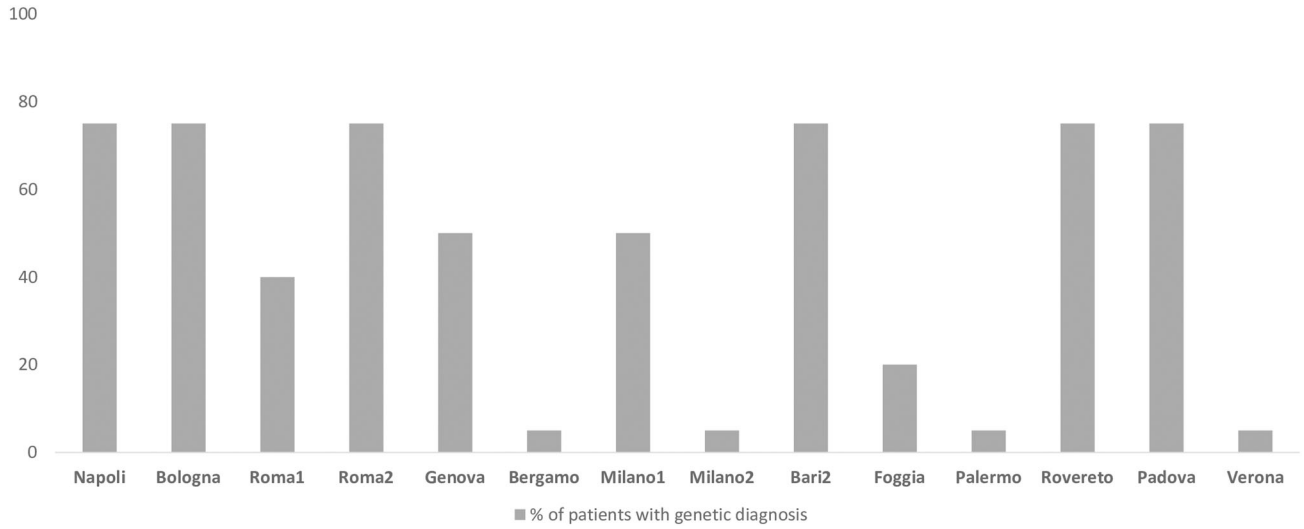

FIGURE 2 Percentage of patients with genetic diagnosis for each center

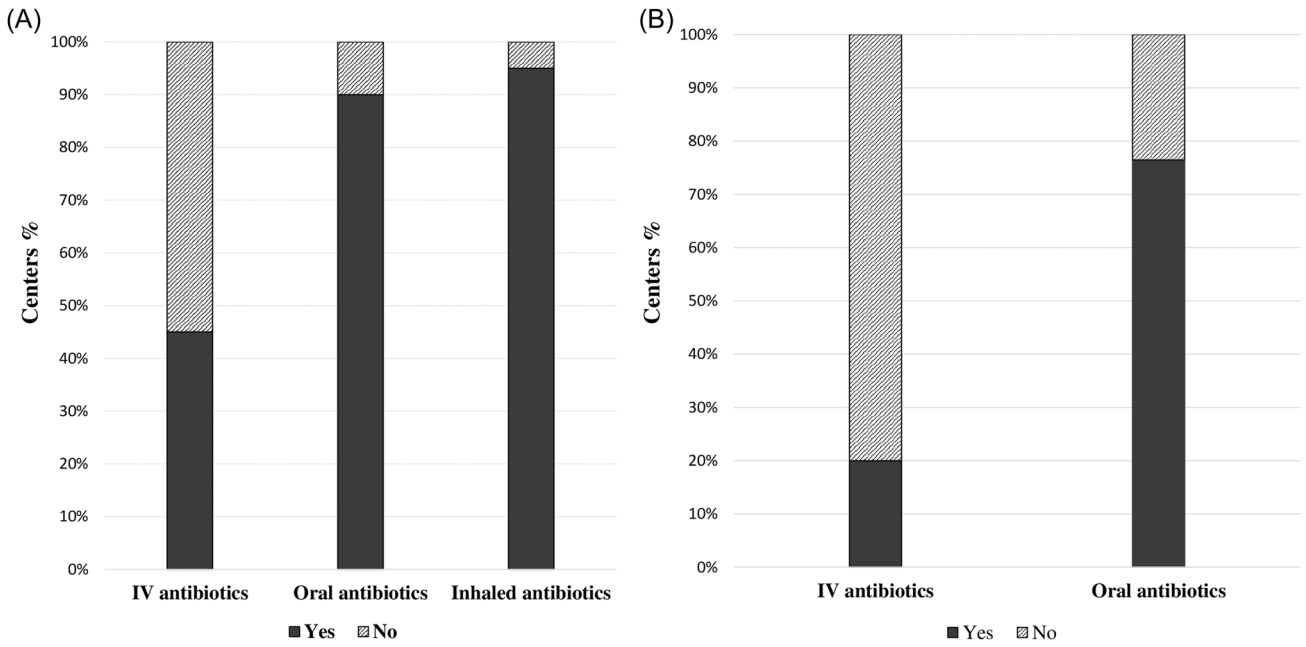

FIGURE 3 (A) Eradication strategy of *Pseudomonas aeruginosa* infection in patients with primary ciliary dyskinesia. (B) Eradication strategy of *Haemophilus influenzae* infection in patients with primary ciliary dyskinesia.

4 | DISCUSSION

We analyzed data on PCD from 20 specialized Italian centers. A previous European survey also including Italy did not include specific national sub analysis. Therefore, the goal of our study was to provide updated information on screening, diagnosis and treatment of PCD in Italy to optimize patient care.[7–9]

The total number of PCD patients treated at the participating centers was of 416, and 70% of the centers followed more than 11 affected individuals. This data can help us estimate that the proportion of PCD patients per center has increased compared to a previously reported proportion of eight patients per center in Italy.[10] Possible explanations are the spread on the national territory of the diagnostic methods to detect the disease, a great dissemination of the recent international PCD guidelines and the creation of novel networks such as the ERN Lung and the BEAT-PCD that improved the access to diagnosis and treatment of PCD patients.[11,12] Therefore, improvements in knowledge about PCD in the Italian scientific community might have led primary care physicians to refer more cases to a specialized center. Indeed, some centers may still have limited experience because of the relatively small number of patients followed. Therefore, a centralized healthcare system would determine that subjects highly suspected of having PCD would be referred to more specialized centers to undergo appropriate diagnostic tests. Moreover, patients would have more opportunities to be included in international research programs.[10] In fact, the distribution of PCD centers appears unbalanced in our national healthcare system, with 6 out of the 20 regions of which Italy is composed (30% of the total) having more than one center and others (8 regions) having none. Consequently, patients need to move between regions to reach the closest referral center and receive appropriate care.

The current literature highlights that PCD diagnosis may be missed or delayed because of the heterogeneous clinical spectrum of the disease.[13] A recent large international cohort study showed that PCD is diagnosed at a median age of 9.8 years increasing to 12.4 years for patients without neonatal respiratory distress and situs solitus.[14] Our data confirm these findings with 70% of centers in Italy reporting a median age at diagnosis between 4 and 12 years. Apparently, larger centers did not report a significant lower age of diagnosis as it could have been expected. However, in Italy (where an early referral from small primary centers is not mandatory) larger and more known centers get to visit many grown-up patients coming from different regions and looking for more specific analysis and diagnostic assessments after years of being labeled with "chronic asthma" or "recurrent respiratory infections." Those patients often receive the final diagnosis later in life when they (or their caregivers) are tired of persistent symptoms or when they have to face complications such as bronchiectasis. PCD is a disorder of several organs and systems, and thus patients should be referred to a multidisciplinary team. Therefore, it is mandatory that neonatologists, general pediatricians and other adult or pediatric specialists such as ENT, cardiologists, gynecologists and andrologists are aware of typical presenting manifestations.

Two recent guidelines have concluded that the detection of cilia ultrastructural defects or the positive result of a genetic test can confirm PCD diagnosis.[8,15] However, a specialized PCD center should have the possibility to perform all the diagnostic procedures required to carry out PCD diagnosis. In particular, we believe that nNO measurement, ciliary (ultra)structure analysis at TEM, motility

evaluation by HSVM, and genetic analysis should be available in all centers. Most methods need high levels of expertise and are expensive, and this could partially explain the delay in the overall reported diagnosis.[16]

Our data show that nNO measurement is used for screening PCD (75%) in most centers in Italy; cilia ultrastructure or motility are investigated on a nasal or bronchial epithelium sample (85%). Methods used to confirm the diagnosis differ among our centers.[10] The cilia ultrastructure seen via TEM is evaluated in a relevant proportion (90%); HSVM constitutes 40% of centers. The higher prevalence of TEM use versus HSVM does not rule out that physicians obtain TEM from another national hospital without referring the patient. HSVM analysis requires that the epithelium specimen be rapidly processed in situ. The role of HSVM analysis is still debated. The test is feasible and recommended in Europe, whereas it is relatively rare and not recommended in North America.[17]

Molecular analysis for PCD associated gene mutations was performed for patients in more than half of the Italian centers (55%), either locally or by sending their sample to another laboratory; 50% of healthcare providers declared that more than half of their patients had a genetic diagnosis of PCD. Our findings indicate that many centers are increasingly relying on the genetic analysis to confirm the diagnosis including in the absence of TEM results either because of troubles in analyzing the epithelium specimen or in cases with normal TEM.[1,2,18] Genotyping patients is essential to design international studies that can develop new therapeutic options and personalized care.[19] Transcript or RNA therapy offered encouraging results in vitro and it could represent one of the future main field for research.[20]

Finally, immunofluorescence, which has not been recommended by recent official documents,[8,15] was available only in 25% of the Italian hospitals studied in our survey.

As previously shown in Europe,[21] Italian PCD centers (75% in our study) care for both children and adults. This finding indicates that national programs are needed to guarantee the transition from pediatric to adult care and should be implemented to meet the special needs of the adults with PCD and their families.

Our survey showed that many different treatments are prescribed in Italy to mobilize airways secretions and control bacterial growth, including airway clearance techniques, systemic antibiotics, mucolytic agents, ICS, as well as isotonic and hypertonic solutions. Strong evidence for the most appropriate treatment of PCD is still severely lacking. Only two double-blind, randomized controlled trials have been published, specifically in the use of inhaled hypertonic saline and azithromycin, and the treatment for PCD patients is still usually based on experts opinion or extrapolated from CF, despite the differences in the underlying pathophysiology.[22,23] Unexpectedly, half of our centers used mucolytic agents (nasal or inhaled), although the clinical efficacy and safety have not yet been proven in PCD.[22] All centers regularly prescribed ICS, although no evidence for their effectiveness has been reported yet.[24] Most clinicians used ICS in cases of proven airway hyperreactivity or atopy (75%). The use of azithromycin to prevent respiratory exacerbations and reduce bacterial load was reported by almost all centers (95%).[23,25] The use of azithromycin; it could also be supported and justified by the known anti-inflammatory and immunomodulatory effect.[26]

Moreover, most Italian centers prescribe therapy for a prompt eradication of *Pseudomonas aeruginosa*, although no evidence is available to support dosing strategies or treatment duration.[24,27] Our results confirmed what Crowley et al. reported a few years ago with a survey specifically aimed at exploring treatment strategies for *Pseudomonas* and sent to 55 PCD centers in 36 European countries. The authors found that 87% of the European centers prescribed antibiotics for newly acquired PA.[21] The lack of clear indications on how to eradicate *Pseudomonas* may be the cause of the heterogeneity highlighted in our survey, with some centers prescribing antibiotics intravenously, orally or inhaled. This is likely on the basis of the individual clinical situation. Finally, the BEAT-PCD network suggested that *H. influenzae* should be treated if the patient is symptomatic, while in Italy the majority of centers tried to eradicate this infection by oral treatment.[28]

Our study has both strengths and drawbacks. The main strength is that it is the first multicenter and collaborative study that shows how PCD is currently managed in Italy. We had a very good response rate from many specialized centers; thus, the results likely represent the true national context. Although several efforts were made to contact all the centers, two sites of them did not respond. Despite the large proportion of patients evaluated in our study, Italian PCD patients might be even more numerous than shown: this has prevented us from providing prevalence data. Finally, we reported some discrepancies in managing Italian PCD patients in Italy. This is probably due to a lack of shared standardized diagnostic and treatment protocols amongst the care centers. However, there is no doubt that we are learning from the beneficial information that our study provided to increase awareness of the disease among health professionals, decrease its underestimation, and improve patients' quality of life and survival.

This national survey confirmed that PCD management in Italy is not centralized and that many centers care for a relatively small number of patients often including both children and adults. Programs that facilitate the transition from PCD childhood to adulthood are needed to reach an adequate management. We also showed a great variability in the available diagnostic procedures as well as the therapeutic interventions. We are confident that based on the current findings it will be possible to develop a joint program with the ambitious aim to better explore prevalence data, uniform diagnostic algorithm and share treatments protocols of PCD in Italy. Thanks to our results we could identify the most urgent and important goals that need to be set for our country, as listed below, that are to (a) obtain national prevalence data by elaborating a national registry; (b) uniform diagnostic algorithm and allow genetic testing in all centers; (c) uniform guidelines for treatment of PCD; (d) plan other national multicenter research studies; (e) organize national meetings with other specialists to increase awareness and knowledge of PCD in Italy; (f) improve collaboration with the Italian Association A.I.D. Kartagener Onlus; and finally (g) reduce patients' migrations between centers.

We are confident that this will be the first step for other future national collaborative studies to improve knowledge and care of patients affected by PCD.

AUTHOR CONTRIBUTIONS

Renato Cutrera, Nicola Ullmann, Francesca Santamaria, and Luigi Mappa contributed in the conceptualization, project development, writing, design of methodology and supervision. Nicola Ullmann, Annalisa Allegorico, Valentina Fainardi, and Melissa Borrelli contributed in the data curation and formal analysis. Renato Cutrera, Nicola Ullmann, Francesca Santamaria, Annalisa Allegorico, and Melissa Borrelli contributed in the paper supervision. Valentina A. Ferraro and Giuseppe F. Parisi contributed in the visualization and review process. Vittorio Romagnoli, Elena Proietti, Francesca Lucca, Marcella Gallucci, Mara Lelii, Doriana Amato, Laura Petrarca, Giuseppe Cimino, Oliviero Sacco, Claudia Calogero, Maria Francesca Patria, Annalisa Allegorico, Annalisa Ferlisi, Massimo Maschio, and Ahmad Kantar contributed in the writing and review process.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, they are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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

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