International consensus statement on routine blood testing in primary ciliary dyskinesia

Sarah Altaraihi[1], June K. Marthin[1], Pinelopi Anagnostopoulou[2,3], Mieke Boon[4,5], Siobhan B. Carr[6], Silvia Castillo-Corullón[7], Eleonora Dehlink[8], Damien M.S. Destouches[9], Jamie Duckers[10], Eric G. Haarman[11], Bülent Karadag[12], Christina Kavouridou[13], Michael R. Loebinger[14], Bernard Maitre[15], Henryk Mazurek[16], Lucy Morgan[17], Heymut Omran[18], Ugur Ozcelik[19], Daniel Peckam[20], Massimo Pifferi[21], Petr Pohunek[22], Tavs Qvist[23], Johanna Raidt[18], Phillipe Reix[24,25], Felix C. Ringshausen[26,27], Phil Robinson[28], Evie Robson[29], Jobst Röhmel[30,31,32], Francesca Santamaria[33], Anne Schlegtendal[34], Nicola Ullmann[35], Woolf Walker[36,37], Panayiotis Yiallouros[2,3], Guillaume Thouvenin[38], Suzanne Crowley[39] and Kim G. Nielsen[1,40]

[1]Danish PCD Centre Copenhagen, Paediatric Pulmonary Service, Department of Paediatrics and Adolescent Medicine, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark. [2]Medical School, University of Cyprus, Nicosia, Cyprus. [3]Pediatric Pulmonology Unit, Hospital "Archbishop Makarios III", Nicosia, Cyprus. [4]Department of Pediatrics, Pediatric Pulmonology, University Hospital Leuven, Belgium. [5]Department of Development and Regeneration, Woman and Child Unit, KU Leuven, Leuven, Belgium. [6]Royal Brompton Hospital and Imperial College London, London, UK. [7]Pediatric Pulmonology, Hospital Clinico de Valencia, Valencia, Spain. [8]Department of Paediatrics, Division of Paediatric Pulmonology, Allergology and Endocrinology, Medical University of Vienna, Vienna, Austria. [9]Association Dyskinésie Ciliaire Primitive, St Etienne, France. [10]University Hospital Llandough, Cardiff and Vale University Health Board, Cardiff, UK. [11]Department of Pulmonary Medicine, Amsterdam University Medical Centre location AMC, University of Amsterdam, Amsterdam, The Netherlands. [12]Division of Pediatric Pulmonology, Marmara University, Istanbul, Turkey. [13]Queen Silvias Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden. [14]Royal Brompton Hospital and National Heart and Lung Institute, Imperial College London, London, UK. [15]Service de Pneumologie, Centre Hospitalier Intercommunal de Créteil, Unité de Pneumologie, GH Mondor, AP-HP, Créteil, France. [16]Department of Pneumonology and Cystic Fibrosis, National Tuberculosis and Lung Diseases Institute, Rabka Zdrój, Poland. [17]Macquarie University Hospital, Sydney, Australia. [18]Department of General Paediatrics, University Children's Hospital Muenster, Muenster, Germany. [19]Department of Pediatric Pulmonology, Hacettepe University Medical Faculty, Ankara, Turkiye. [20]Leeds Institute of Medical Research, University of Leeds, Leeds, UK. [21]Department of Pediatrics, University Hospital of Pisa, Pisa, Italy. [22]Pediatric Pulmonology, Pediatric Department, Second Faculty of Medicine and University Hospital Motol, Prague, Czech Republic. [23]Danish PCD Centre Copenhagen, Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark. [24]Centre de Référence des Maladies Respiratoires Rares de l'Enfant, Service de Pneumologie Pédiatrique, Hospices Civils de Lyon, Lyon, France. [25]UMR 5558, Equipe EMET, Université Claude Bernard Lyon 1, Villeurbanne, France. [26]Department of Respiratory Medicine and Infectious Diseases, Hannover Medical School, and Biomedical Research in End-Stage and Obstructive Lung Disease Hannover, German Center for Lung Research (DZL), Hannover, Germany. [27]European Reference Network on Rare and Complex Respiratory Diseases, Frankfurt, Germany. [28]Respiratory Medicine, Royal Children's Hospital and University of Melbourne, Melbourne, Australia. [29]North of England PCD Management Service, Leeds Teaching Hospitals NHS Trust, Leeds, UK. [30]Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany. [31]Berlin Institute of Health at Charité – Universitätsmedizin Berlin, Berlin, Germany. [32]German Center for Lung Research (DZL), associated partner site, Berlin, Germany. [33]Department of Translational Medical Sciences, Pediatric Pulmonology Unit, Federico II University, Naples, Italy. [34]Department of Paediatric Pneumology, University Children's Hospital Bochum, Bochum, Germany. [35]Pneumology and Cystic Fibrosis Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy. [36]Primary Ciliary Dyskinesia Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK. [37]Clinical and Experimental Sciences, University of Southampton Faculty of Medicine, Southampton, UK. [38]Service de Pneumologie Pédiatrique, Hôpital Trousseau, AP-HP, Sorbonne Université, INSERM, Centre de Recherche Saint-Antoine, CRSA, Paris, France. [39]Paediatric Department of Allergy and Lung Diseases, Oslo University Hospital, Rikshospitalet, Oslo, Norway. [40]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.

Corresponding author: Sarah Altaraihi (sarah.altaraihi.02@regionh.dk)

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This is the first international consensus on routine blood testing in primary ciliary dyskinesia (PCD). It highlights blood tests that may be relevant to conduct at diagnosis, annually and at exacerbation in people with PCD. https://bit.ly/4gKDk1o

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Abstract

Background Primary ciliary dyskinesia (PCD) is a rare genetic disorder characterised by dysfunction of motile cilia. Symptoms include recurrent and chronic airway infections which can lead to deteriorating lung function and inflammatory destructive lung disease in the form of persistent atelectasis and bronchiectasis. Routine blood testing may be used as a tool for disease monitoring and management. However, currently there are no consensus-based guidelines within the field of PCD. BEAT-PCD together with the ERN-LUNG PCD-Clinical Trial Network aimed to develop an international expert consensus statement on which routine blood tests should be conducted in patients with PCD.

Methods An international panel of 33 PCD experts from 17 countries was established to generate consensus on routine blood testing in PCD. A modified Delphi technique with three e-survey rounds was used to reach consensus, which was defined as ⩾80% agreement for each statement. Two patient representatives were included in the consensus process.

Results The expert panel reached consensus on 51 out of 101 statements (50%) on routine blood testing in children and adults with PCD to be performed at diagnosis, annually and on exacerbation. The statements include biomarkers for inflammation, haemoglobin, iron status, vitamin D, immune function, inhalant allergies, liver and kidney function, and allergic bronchopulmonary aspergillosis.

Conclusions This is the first international consensus on routine blood testing in PCD. It highlights blood tests that may be relevant to perform at diagnosis, annually and on exacerbation in people with PCD. Further research on the clinical usefulness of routine blood testing in PCD is needed.

Introduction

Primary ciliary dyskinesia (PCD) is a rare heterogenous genetic disorder characterised by dysfunction of motile cilia [1]. The disorder commonly causes neonatal respiratory distress in term infants, conductive hearing impairment, chronic persistent wet cough and chronic rhinosinusitis. Further common symptoms are recurrent and chronic upper and lower respiratory infections, deteriorating lung function, and destructive airway disease manifesting as persistent lobar or segmental atelectasis and bronchiectasis. Additionally, situs anomalies and subfertility/infertility are frequent in PCD [1–4]. Multiple variants in genes linked with PCD, of which there are more than 50 known, predominantly follow autosomal recessive inheritance; however, X-linked recessive and autosomal dominant inheritance have also been reported [1, 5, 6]. The overall global prevalence is reported to be 1 in 7554 individuals [7].

There is presently no curative treatment for PCD. Due to the scarcity of evidence-based treatments for PCD, management is often based on similar diseases such as cystic fibrosis (CF) [8, 9]. Recently, however, a randomised clinical trial on oral azithromycin maintenance therapy in PCD provided the first evidence-based treatment recommendation [10]. Further, a recently published study on a nebulised epithelial sodium channel blocker has also shown promising results [11].

Routine blood testing in people with CF is recommended as part of European and American management guidelines [12–15] and has an impact on disease management even in pre-school children [16]. However, European PCD management guidelines make no mention of blood testing as part of routine care [9]. In contrast, the American PCD Foundation consensus recommendations for diagnosis, treatment and monitoring propose testing for allergic bronchopulmonary aspergillosis (ABPA) by measuring total IgE levels at diagnosis, with new-onset wheezing and unexplained clinical decline [17]. Further, the European paediatric bronchiectasis management guidelines recommend full blood count and immunological tests at diagnosis [18], while the European adult bronchiectasis management guidelines recommend differential blood count, serum immunoglobulins and testing for ABPA at diagnosis [19].

Routine blood testing in patients with PCD may be used as a tool for disease monitoring and guide its management. Regular monitoring of various parameters assessable in the blood could play a role in achieving optimal long-term outcomes in PCD. Thus, there is a need to investigate and identify which, if any, blood tests should be performed in patients with PCD, and their indication and frequency.

We conducted a modified Delphi study to develop an expert, international consensus statement on routine blood testing in children and adults with PCD. The consensus statement aims to provide suggestions to clinicians on which routine blood tests could be relevant to perform and to standardise blood testing across different sites, thus increasing the data available for future studies on the clinical usefulness of routine blood testing in patients with PCD.

Methods

Participants

The panel was invited with the intention of ensuring representation of a wide range of countries and experts, who had experience in managing children and adults with PCD. 37 experts from 17 countries and two patient representatives were invited to the panel. Those invited were mostly engaged in either BEAT-PCD (Better Experimental Approaches to Treat PCD; a European Respiratory Society (ERS) Clinical Research Collaboration) [20] or the European Reference Network on Rare and Complex Respiratory Diseases (ERN-LUNG) PCD-Clinical Trial Network [21]. They worked in highly specialised PCD centres and had several years of clinical experience in the treatment of patients with PCD, although no minimum threshold had been established. The coordinating group facilitating the activities of the panel were volunteers. Some participated in the Delphi e-survey (S.C. and K.G.N.), while two did not (S.A. and J.K.M.) in an effort to reduce bias in their roles of facilitators and coordinators of the project.

Study design

At the BEAT-PCD annual meeting held online on 9 September 2021, the topic of routine blood testing in confirmed PCD was discussed. The coordinating group worked afterwards to plan and facilitate a consensus statement on the topic derived from a Delphi survey methodology. This methodology involves conducting a series of sequential survey questionnaire rounds. The purpose of these is to gather anonymous expert opinion to create consensus on subjects where evidence is lacking or uncertain [22–24].

An online start-up meeting was held in June 2023 where all panellists were invited. After discussion at this meeting, it was decided to have separate statements for children and adults with PCD and categorise the blood tests by when they should be performed, *e.g.* at confirmed diagnosis, annually or on exacerbation. Furthermore, due to differing experience, practice and opinions on the matter of routine blood testing in PCD, and the limited amount of literature in this field, it was decided to distribute an introductory survey. In this survey, the expert panellists could describe which blood tests they conducted as routine in patients with PCD, including their indications and frequency. The answers from the introductory survey and a literature search served as the foundation for formulating the statements of the first Delphi survey round. To be as unbiased as possible, all blood tests mentioned in the introductory survey were included.

A modified Delphi method was then performed. Three rounds of e-surveys, based on the REDCap web application (https://project-redcap.org), were conducted. After each round a maximum of three reminders were sent after the initial invitation. A 5-point Likert scale was used to assess agreement on each statement, in which participants could respond “Strongly agree”, “Agree”, “Neutral”, “Disagree” or “Strongly disagree”. It was also possible to select “Cannot answer (not my field of expertise)”; this answer was not included in the calculation towards the final agreement percentage. If the participants were neutral or disagreed, they were prompted to offer a reason. This was to ensure that statements in subsequent survey rounds could be adjusted based on these comments.

After each survey round, anonymous data were analysed quantitatively using appropriate descriptive statistics.

Consensus was defined as $\geqslant$80% agreement (“Agree” and “Strongly agree”), and statements where agreement was $\geqslant$80% were accepted without any further editing. Statements with 40–80% agreement would proceed to the next survey round with proposed adjustments, to see if they could reach consensus in an edited version. Before each survey round, the coordinating group met to write and define the statements. Statements that reached $\leqslant$40% agreement were discarded and did not progress to any subsequent rounds. Between the second and third survey round, an online meeting was held wherein all expert participants were invited. Anonymous results so far were presented, and all statements where agreement was 40–80% were discussed for adjustments for the third and final survey round. Due to the adjustment process, some statements did not have a rationale included, because they reached consensus in the first round without discussion. However, later rounds included rationale considerations, leading to revised statements with rationales.

After the third round the coordinating group made a rationalisation step. If a blood test was agreed to be conducted annually or during exacerbations, it should also be performed at confirmed diagnosis of PCD as a baseline measure. These blood tests were added in the confirmed diagnosis of PCD category as suggestions from the coordinating group.

Results

Panel characteristics

Among the 37 experts invited, 33 accepted the invitation to be part of the panel. Of the two patient representatives invited, one answered the survey, while the other opted to comment on statements. Of the

expert panellists, 42% had experience in treating children with PCD, 18% had experience in treating adults with PCD, while 39% had experience in treating both children and adults with PCD. Furthermore, 78% had expertise in paediatric pulmonology, 34% had expertise in adult pulmonology, while 3% had expertise in infectious diseases (not mutually exclusive). Most experts (97%) had a practice setting in academic/tertiary hospitals. The mean±SD length of clinical experience in treatment of patients with PCD in the expert group was 18.3±8.36 years. The panellists were located across different regions of the world, with 35% working in Western Europe (table 1).

Delphi process

The first round was conducted from 1 to 28 September 2023. All 34 (100%) panellists responded to the first round. In the survey, 100 statements were presented. Of the presented statements, 23 (23%) reached consensus, while 61 (61%) statements scored between 40% and 80% and went on to the next round. On most of these statements, adjustments were made, some statements were combined and six new statements were formulated. Further, 16 statements had ⩽40% agreement and were discarded.

The second round was conducted from 12 to 27 October 2023 and 33 (97%) of the panellists responded to the 61 statements presented for the round, of which 20 (33%) reached consensus. Further, 39 (64%) statements reached 40–80% agreement and went on to the next round rephrased and adjusted, while one new statement was formulated. Two statements had ⩽40% agreement and did not progress to the third round. The third round was conducted from 2 to 13 December 2023. In this final round, 33 (97%) panellists responded and 40 statements were presented, of which eight additional statements reached consensus. In total, 51 out of 101 statements reached consensus and were included in the final consensus statement. A flowchart of the Delphi process is presented in figure 1.

Routine blood tests that should be conducted in children with PCD

A summary of the statements that reached consensus on routine blood testing in children with PCD is presented in table 2. Detailed results, including the percentage of agreement for each statement, are provided in supplementary table S1.

The panel agreed that the following blood tests should be conducted at confirmed diagnosis of PCD in children: differential white blood cell count, haemoglobin, iron status, vitamin D status, biomarkers for ABPA (total IgE levels, *Aspergillus fumigatus* specific IgE and IgG), pneumococcal antibodies,

TABLE 1 Delphi panel

Expert participants	33 (97)
Physician with experience in treatment of children with PCD	14 (42)
Physician with experience in treatment of adults with PCD	6 (18)
Physician with experience in treatment of both children and adults with PCD	13 (39)
Field of expertise of expert participants[#,¶]	
Paediatric pulmonology	25 (78)
Adult pulmonology	11 (34)
Infectious diseases	1 (3)
Years of clinical experience in treatment of patients with PCD[+]	18.3±8.36
Number of patients with PCD at expert participants' site[§,f]	120 (54–202)
Practice setting of expert participants[#,¶]	
Academic/tertiary hospital	31 (97)
Regional hospital	1 (3)
Research	4 (13)
Private practice	0 (0)
Patient representative	1 (3)
Location of panellist	
Western Asia	4 (12)
Australia	2 (6)
Northern Europe	10 (29)
Western Europe	12 (35)
Eastern Europe	2 (6)
Southern Europe	4 (12)

Data are presented as n (%), mean±SD or median (interquartile range). [#]: not mutually exclusive; [¶]: 32/33 expert panellists; [+]: self-reported; [§]: 31/33 expert panellists; [f]: genetically confirmed and not confirmed patients with PCD.

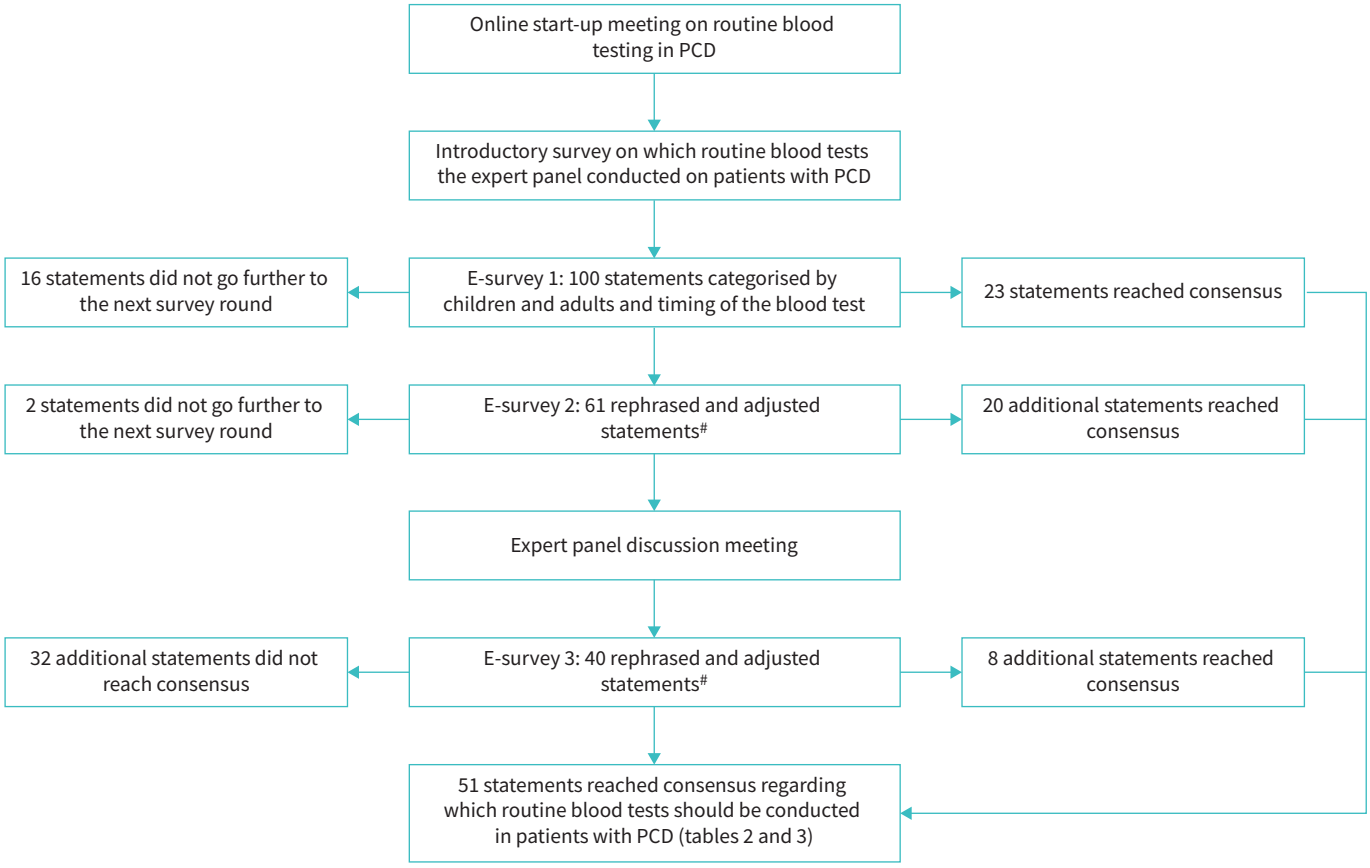

FIGURE 1 Flowchart of the Delphi process on routine blood testing in primary ciliary dyskinesia (PCD). Consensus was reached on statements with ⩾80% agreement. "Rephrased and adjusted statements": no consensus yet (40–80% agreement), the statements will go to the next survey round, with adjustments, to see if they can reach consensus. "Statements did not go further": ⩽40% agreement. A total of 51 statements out of 101 reached consensus. #: throughout the process some statements were combined, new statements were formulated and adjustments were made.

immunoglobulins (IgA, IgM, IgG and IgG subclasses) and specific IgE for a panel of common inhalant allergens. Additionally, at the rationalisation step, the coordinating group added C-reactive protein (CRP) and creatinine. Further, the panel agreed that blood tests which should be conducted annually were differential white blood cell count, CRP, haemoglobin, iron status, vitamin D status, total IgE as a marker for ABPA, biomarkers for liver function when using macrolides as maintenance treatment and creatinine. For an exacerbation not responding to treatment with oral antibiotic treatment, the panel agreed that CRP, differential white blood cell count, haemoglobin and biomarkers for ABPA (total IgE levels, *A. fumigatus* specific IgE and IgG) should be performed.

Rejected statements are presented in supplementary table S3.

Routine blood tests that should be conducted in adults with PCD

A summary of the statements that reached consensus on routine blood testing in adults with PCD is presented in table 3. Detailed results, including the percentage of agreement for each statement, are provided in supplementary table S2.

The panel agreed that the following blood tests should be performed at confirmed diagnosis of PCD in adults: differential white blood cell count, CRP, haemoglobin, vitamin D status, biomarkers for ABPA (total IgE levels, *A. fumigatus* specific IgE and IgG), immunoglobulins (IgA, IgM, IgG and IgG subclasses) and specific IgE for a panel of common inhalant allergens. Additionally, at the rationalisation step, the coordinating group added platelets, creatinine and albumin. Moreover, the panel agreed that blood tests which should be performed annually in adults were differential white blood cell count, CRP, platelets, haemoglobin, iron status, vitamin D status, biomarkers for ABPA (total IgE levels, *A. fumigatus* specific IgE and IgG), creatinine, albumin and biomarkers for liver function when using macrolides as maintenance

TABLE 2 Summary of consensus statements on routine blood testing in children with primary ciliary dyskinesia (PCD)

Blood tests	At confirmed diagnosis of PCD	Annually	At exacerbation not responding to oral antibiotic treatment
Differential white blood cell count	X	X	X
C-reactive protein	(X)	X[§]	X
Haemoglobin	X	X	X
Iron status (ferritin and transferrin receptors)	X	X[f]	
Vitamin D status	X	X	
Total IgE	X	X	X
Aspergillus fumigatus specific IgE	X		X
Aspergillus fumigatus specific IgG[#]	X		X
Antibody levels towards *Streptococcus pneumoniae*[¶]	X		
IgA, IgM, IgG and IgG subclasses	X		
Specific IgE towards a panel of common inhalant allergens[¶]	X		
Aspartate aminotransferase, alanine aminotransferase, bilirubin[+]		X	
Creatinine	(X)	X	

[#]: if available at health facility; [¶]: if not conducted previously; [+]: when using macrolides as maintenance treatment; [§]: if there is clinical decline; [f]: in patients with previous anaemia. Blood tests in brackets were included at a rationalisation step by the coordinating group (blood tests conducted annually or during exacerbations should also be performed at confirmed diagnosis as a baseline measure).

treatment. For an exacerbation not responding to oral antibiotic treatment, the panel agreed that CRP, differential white blood cell count, haemoglobin, biomarkers for ABPA (total IgE levels, *A. fumigatus* specific IgE and IgG) and creatinine should be conducted. Finally, the panel agreed that after initiation of maintenance macrolide treatment, the blood test for alanine aminotransferase (ALAT) should be conducted.

Rejected statements are presented in supplementary table S4.

Discussion

In this Delphi consensus study, we achieved formulation of 51 statements concerning routine blood testing for children and for adults with PCD categorised by their indication and timing. The panel agreed that blood tests should be performed routinely in the domains of inflammation, iron status, vitamin D, ABPA and immunodeficiency at confirmed diagnosis. Published data on blood testing in PCD are limited, and we were unable to find any other studies addressing routine blood testing specifically in PCD. Knowledge on

TABLE 3 Summary of consensus statements on routine blood testing in adults with primary ciliary dyskinesia (PCD)

Blood tests	At confirmed diagnosis of PCD	Annually	At exacerbation not responding to oral antibiotic treatment	After initiation of maintenance macrolide treatment
Differential white blood cell count	X	X	X	
Platelets	(X)	X		
C-reactive protein	X	X	X	
Haemoglobin	X	X	X	
Iron status (ferritin and transferrin receptors)		X[+]		
Vitamin D status	X	X		
Total IgE	X	X	X	
Aspergillus fumigatus specific IgE and *A. fumigatus* specific IgG	X	X[§]	X	
IgA, IgM, IgG and IgG subclasses	X			
Specific IgE towards a panel of common inhalant allergens[#]	X			
Creatinine	(X)	X	X	
Albumin	(X)	X		
Aspartate aminotransferase, bilirubin[¶]		X		
Alanine aminotransferase		X[¶]		X

[#]: if not conducted previously; [¶]: when using macrolides as maintenance treatment; [+]: in patients with previous anaemia; [§]: if available at health facility. Blood tests in brackets were included at a rationalisation step by the coordinating group (blood tests conducted annually or during exacerbations should also be performed at confirmed diagnosis as a baseline measure).

the clinical usefulness on these blood tests in patients with PCD is therefore lacking. The results of this consensus statement can support clinicians in standardising routine blood testing in PCD across different sites. This will help increase the data available for future analyses and provide more knowledge on this topic. In the following text, we will discuss the aforementioned blood tests in the context of PCD.

A study has shown that CRP can be used as a marker of systemic inflammation and disease severity in adult patients with bronchiectasis [25], and it also found no correlation between total white blood count and disease severity. The panel agreed that inflammatory burden should be assessed, with the measurement of CRP and differential blood cell count. However, consensus on indication of testing in children and adults differed. In contrast to bronchiectasis, published data on systemic inflammation in patients with PCD showed no elevation in CRP, or white blood cell count, nor change in these parameters after 6 months of azithromycin treatment in children and adults [10]. However, in a different study, characterising the nutritional status of 36 children with PCD, the mean CRP was slightly elevated [26].

The panel also reached consensus on the annual measurement of blood platelets in adults. Platelets have a role in haemostasis, thrombosis and the immune response to inflammation [27, 28]. In adults with bronchiectasis, platelet levels have shown a positive correlation with disease severity and mortality [29]. No data exist for adults or children with PCD, and the findings in adults with bronchiectasis may not be applicable.

Iron deficiency is the most common nutritional deficiency, for which neonates, pre-school children and adolescents (particularly females) are predisposed [30]. Iron deficiency anaemia can increase the vulnerability to infection [31]. The panel agreed that iron status (ferritin and transferrin receptors) should be checked at confirmed diagnosis in children and annually in both children and adults with anaemia. However, some panellists argued that it can be difficult to interpret iron status in patients with chronic infection. The only published results of iron status in a group of 36 children with PCD reported normal group mean values. The study gave no further details, although the magnitude of standard deviation for serum iron inferred that some had iron deficiency [26]. The same study also reported normal group mean values of albumin in children with PCD. Nonetheless, albumin has been negatively associated with disease severity in non-CF bronchiectasis in two studies [32, 33], one of which included a single patient with PCD [32]. The panel agreed albumin should be measured annually in adults with PCD.

Vitamin D has an important role in innate immunity and calcium metabolism [34, 35]. Increased prevalence of vitamin D deficiency and insufficiency has been reported in children and adults with PCD and is associated with poorer quality of life [36]. In a cohort of children with PCD, low vitamin D levels weakly correlated with fat-free mass index [26], which is a better measure of nutritional status than body mass index [37]. However, using vitamin D as a marker for nutritional status is not an established practice. Further, vitamin D deficiency has been associated with poorer lung function in adults with bronchiectasis, although the mechanism is unclear [38]. The panel agreed that monitoring of vitamin D levels would seem to be appropriate. However, as some panellists commented, monitoring vitamin D levels may be overzealous given the high prevalence of vitamin D deficiency in PCD, rather physicians could simply prescribe vitamin D supplements to all patients with PCD. Still, this could be considered an additional treatment burden, and although rare, might be harmful if toxic doses are taken [39].

ABPA is a complex immunological pulmonary response caused by sensitisation to *A. fumigatus*. The symptomatic clinical manifestations may vary, but productive cough, wheezing, haemoptysis and reduced lung function are usual [40]. In CF, it is underdiagnosed, and in PCD, there are two published case reports of ABPA in adults [41–43] and a case series with two children [44]. This suggests that ABPA may be either underdiagnosed or uncommon in PCD, and there are no prevalence data available.

Recommended biomarkers for the diagnosis or early detection of ABPA in CF are total serum IgE, and specific IgE and specific IgG to *A. fumigatus* [41, 45, 46]. As mentioned earlier, the European adult bronchiectasis management guidelines recommend testing for ABPA at diagnosis. Further, the American PCD Foundation consensus recommendations suggest measuring total IgE, with or without evidence of aspergillus specificity, if new-onset wheezing and unexplained clinical decline are present [17]. Given the potential seriousness of ABPA, in this consensus statement the panel similarly agreed with measuring total IgE, but also specific IgE and specific IgG (if available) against *A. fumigatus*.

Conversely, some panellists argued that ABPA in children with PCD was rare, and suggested to routinely only test for total IgE, as it has been proposed as a primary indicator for ABPA in CF [46]. In children younger than pre-school age, ABPA could be even more rare, and testing routinely at all for ABPA in this age group may not be relevant.

The ERS paediatric and adult bronchiectasis management guidelines recommend immunological testing at diagnosis of bronchiectasis [18, 19]. Similarly, the American PCD Foundation recommends the quantitative measurement of immunoglobulins in patients with suspected PCD to rule out immunodeficiency [17]. Even though the patients considered in the current consensus statement have a confirmed diagnosis of PCD, it is nonetheless important to evaluate potential immunodeficiency. An increased prevalence of humoral immunodeficiency has been reported in a cohort of 68 patients with PCD [47]. The panel agreed that measuring of IgA, IgM, IgG and IgG subclasses should be performed at confirmed diagnosis, but further testing for immunodeficiency by measuring antibody levels towards tetanus and diphtheria and measuring T- and B-cell subsets was rejected.

Moreover, patients with PCD are susceptible to pneumococcal infections, and the European PCD management guideline recommends pneumococcal immunisation [9]. The panel agreed that antibody levels towards *Streptococcus pneumoniae* should be measured at the time of diagnosis to assess protection state against pneumococcal infections in children with PCD. However, testing for *S. pneumoniae* antibody levels at diagnosis in infants would not be relevant, as they have not yet been vaccinated. The assessment can be done at a later time.

Consensus was also reached for the measurement of specific IgE for a panel of common inhalant allergens at confirmed diagnosis. Allergic rhinitis is frequent in the general population and presents somewhat similar nasal symptoms to PCD, including anterior and posterior rhinorrhoea and nasal congestion [1, 48]. The panel regarded the detection of potential allergic sensitisation to be important in the interpretation of symptoms, as patients with PCD can have concurrent allergic rhinitis, which can be treated. However, testing for potential allergic sensitisation in children younger than pre-school age does not seem to be appropriate, as it would be unlikely for them to have developed allergic rhinitis [49].

The consensus panel agreed that creatinine should be measured annually in patients with PCD and at exacerbation in adults. Intravenous aminoglycosides, colistin, piperacillin/tazobactam, vancomycin and age are all significant risk factors for acute and chronic kidney injury in CF [50], but prolonged intravenous aminoglycoside exposure in CF is probably not associated with chronic renal dysfunction [50, 51]. However, no data have been published on renal function in patients with PCD, despite the relatively high prevalence of chronic infection with non-tuberculous mycobacteria and *Pseudomonas aeruginosa* [1], necessitating similar treatment regimens to CF. However, routinely testing for creatinine in young children who are not in consideration for intravenous antibiotic treatment may be excessive. Renal involvement is typically a feature of primary ciliopathies, which are syndromic disorders caused by malfunction of sensory cilia. Moreover, it is becoming evident that some ciliopathy genes can cause an overlapping motile ciliopathy (PCD-like) phenotype [52, 53], making the investigation of renal function even more pertinent.

The risk of azithromycin-induced hepatotoxicity, predominantly hepatocellular damage, in patients without PCD is low and the vast majority recover [54]. However, chronic liver damage severe enough to require transplantation may ensue [54]. In the aforementioned randomised clinical trial on azithromycin maintenance therapy in PCD, ALAT was raised to abnormal levels after 6 months of azithromycin treatment in three of 90 patients (one patient with a value more than double the upper limit of normal range) [10]. Speculation about the use of azithromycin as early as in infancy to prevent long-term structural lung damage [10] should include monitoring for potential hepatotoxicity, although most liver injury occurs within 3 weeks of starting treatment [54]. Consensus was reached regarding the monitoring of liver function only when using macrolides as maintenance treatment.

Limitations

In this study, consensus was generated using the Delphi method, where within-group bias can be reduced. There was a high participation rate through all three survey rounds. Furthermore, the panel included experts based in highly specialised PCD centres from many countries and a patient representative. However, there were some limitations to our study design. Most of the expert panellists were paediatric pulmonologists, which might result in an underrepresentation of adult PCD treatment expertise. However, paediatricians have, in the past especially, often managed the care of adult patients with PCD in many PCD centres. While 34% of the expert panellists' field of expertise was adult pulmonology, 57% had experience in treating adults with PCD (table 1). Furthermore, we separated the statements for children and adults, and those who did not have expertise in one or the other could select "Cannot answer (not my field of expertise)" in the survey. Moreover, the panel was largely from Europe, and therefore the consensus statement is likely not globally generalisable.

Importantly, due to the current lack of evidence in the field of PCD, many of the statements were formulated based on literature in CF and bronchiectasis. However, we also distributed an introductory

survey, where all expert panellists could list blood tests that were already routinely conducted at their site in patients with PCD; these were also included in the Delphi surveys. Additionally, the economic aspects and the availability of the specific blood tests at the site of the panellists may have influenced their response in the Delphi survey. Additionally, it should be emphasised that many rejected statements were close to reaching consensus. Even though consensus was not reached on these statements in this Delphi study, it does not imply that these tests are not relevant in certain patients. Finally, it is important to note that statements on children with PCD did not differentiate on age at diagnosis. Age is an important factor, and certain routine blood tests may not be relevant to perform in certain age groups. Clinicians should always assess whether a routine blood test is appropriate for each individual patient to minimise the blood volume necessary for analysis. In addition, some of the blood tests mentioned in the statement can be costly, and not all sites may be able to conduct all the tests which have reached consensus.

Routine blood testing in PCD could be excessive and may not change the management of patients. However, PCD is a chronic disorder that can lead to deteriorating lung function and inflammatory destructive airway disease, manifesting as persistent lobar or segmental atelectasis and bronchiectasis [1]. Although, as mentioned earlier, data on the clinical usefulness of routine blood testing are lacking, the increased surveillance of patients with PCD seems appropriate. Routine blood tests may help detect subclinical conditions and identify patients who are at risk of developing complications. Hopefully, the current consensus statement can help to standardise blood testing in PCD across different sites, which can then facilitate further data, research and knowledge on this topic. The FOLLOW-PCD study, which is a consensus on standardised clinical data from patients with PCD, makes no mention of blood testing [55]. In the consensus study on a core outcome set for pulmonary disease interventions in PCD, there was an interest in exploring blood testing as an outcome in clinical trials; however, there was no agreement or further discussion on this subject [56]. This is the first ever attempt to assess the topic of routine blood testing specifically in PCD.

Conclusions

This consensus statement study, using the Delphi technique, provides suggestions on which blood tests should be conducted in adult and paediatric patients with PCD. Moreover, it may harmonise blood testing data across different sites, thus providing an impetus for research on the clinical usefulness of routine blood testing in PCD.

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References

1 Wallmeier J, Nielsen KG, Kuehni CE, *et al.* Motile ciliopathies. *Nat Rev Dis Primers* 2020; 6: 77.
2 Goutaki M, Meier AB, Halbeisen FS, *et al.* Clinical manifestations in primary ciliary dyskinesia: systematic review and meta-analysis. *Eur Respir J* 2016; 48: 1081–1095.

3 Lucas JS, Davis SD, Omran H, *et al.* Primary ciliary dyskinesia in the genomics age. *Lancet Respir Med* 2020; 8: 202–206.
4 Nielsen KG, Holgersen MG, Crowley S, *et al.* Chronic airway disease in primary ciliary dyskinesia – spiced with geno-phenotype associations. *Am J Med Genet C Semin Med Genet* 2022; 190: 20–35.
5 Davis SD, Rosenfeld M, Lee HS, *et al.* Primary ciliary dyskinesia: longitudinal study of lung disease by ultrastructure defect and genotype. *Am J Respir Crit Care Med* 2019; 199: 190–198.
6 Loges NT, Marthin JK, Raidt J, *et al.* A range of 30–62% of functioning multiciliated airway cells is sufficient to maintain ciliary airway clearance. *Eur Respir J* 2024; 64: 2301441.
7 Hannah WB, Seifert BA, Truty R, *et al.* The global prevalence and ethnic heterogeneity of primary ciliary dyskinesia gene variants: a genetic database analysis. *Lancet Respir Med* 2022; 10: 459–468.
8 Kuehni CE, Goutaki M, Rubbo B, *et al.* Management of primary ciliary dyskinesia: current practice and future perspectives. *In:* Chalmers JD, Polverino E, Aliberti S, eds. *Bronchiectasis (ERS Monograph)*. Sheffield, European Respiratory Society, 2018; pp. 282–299.
9 Lucas JS, Alanin MC, Collins S, *et al.* Clinical care of children with primary ciliary dyskinesia. *Expert Rev Respir Med* 2017; 11: 779–790.
10 Kobbernagel HE, Buchvald FF, Haarman EG, *et al.* Efficacy and safety of azithromycin maintenance therapy in primary ciliary dyskinesia (BESTCILIA): a multicentre, double-blind, randomised, placebo-controlled phase 3 trial. *Lancet Respir Med* 2020; 8: 493–505.
11 Ringshausen FC, Shapiro AJ, Nielsen KG, *et al.* Safety and efficacy of the epithelial sodium channel blocker idrevloride in people with primary ciliary dyskinesia (CLEAN-PCD): a multinational, phase 2, randomised, double-blind, placebo-controlled crossover trial. *Lancet Respir Med* 2023; 12: 21–33.
12 Castellani C, Duff AJA, Bell SC, *et al.* ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros* 2018; 17: 153–178.
13 National Guideline Alliance (UK). Cystic Fibrosis: Diagnosis and Management. London, National Institute for Health and Care Excellence, 2017.
14 Lahiri T, Hempstead SE, Brady C, *et al.* Clinical practice guidelines from the cystic fibrosis foundation for preschoolers with cystic fibrosis. *Pediatrics* 2016; 137: e20151784.
15 Yankaskas JR, Marshall BC, Sufian B, *et al.* Cystic fibrosis adult care: consensus conference report. *Chest* 2004; 125: Suppl. 1, 1S–39S.
16 Jaffé A, Buchdahl R, Bush A, *et al.* Are annual blood tests in preschool cystic fibrosis patients worthwhile? *Arch Dis Child* 2002; 87: 518–520.
17 Shapiro AJ, Zariwala MA, Ferkol T, *et al.* Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD Foundation consensus recommendations based on state of the art review. *Pediatr Pulmonol* 2016; 51: 115–132.
18 Chang AB, Fortescue R, Grimwood K, *et al.* European Respiratory Society guidelines for the management of children and adolescents with bronchiectasis. *Eur Respir J* 2021; 58: 2002990.
19 Polverino E, Goeminne PC, McDonnell MJ, *et al.* European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017; 50: 1700629.
20 Goutaki M, Crowley S, Dehlink E, *et al.* The BEAT-PCD (Better Experimental Approaches to Treat Primary Ciliary Dyskinesia) Clinical Research Collaboration. *Eur Respir J* 2021; 57: 2004601.
21 Raidt J, Maitre B, Pennekamp P, *et al.* The disease-specific clinical trial network for primary ciliary dyskinesia: PCD-CTN. *ERJ Open Res* 2022; 8: 00139-2022.
22 Powell C. The Delphi technique: myths and realities. *J Adv Nurs* 2003; 41: 376–382.
23 Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. *J Adv Nurs* 2000; 32: 1008–1015.
24 Niederberger M, Köberich S. Coming to consensus: the Delphi technique. *Eur J Cardiovasc Nurs* 2021; 20: 692–695.
25 Coban H, Gungen AC. Is there a correlation between new scoring systems and systemic inflammation in stable bronchiectasis? *Can Respir J* 2017; 2017: 9874068.
26 Marino LV, Harris A, Johnstone C, *et al.* Characterising the nutritional status of children with primary ciliary dyskinesia. *Clin Nutr* 2019; 38: 2127–2135.
27 Thomas MR, Storey RF. The role of platelets in inflammation. *Thromb Haemost* 2015; 114: 449–458.
28 Chen Y, Zhong H, Zhao Y, *et al.* Role of platelet biomarkers in inflammatory response. *Biomark Res* 2020; 8: 28.
29 Aliberti S, Sotgiu G, Gramegna A, *et al.* Thrombocytosis during stable state predicts mortality in bronchiectasis. *Ann Am Thorac Soc* 2021; 18: 1316–1325.
30 Mattiello V, Schmugge M, Hengartner H, *et al.* Diagnosis and management of iron deficiency in children with or without anemia: consensus recommendations of the SPOG Pediatric Hematology Working Group. *Eur J Pediatr* 2020; 179: 527–545.
31 Cappellini MD, Musallam KM, Taher AT. Iron deficiency anaemia revisited. *J Intern Med* 2020; 287: 153–170.
32 Li L, Li Z, Bi J, *et al.* The association between serum albumin/prealbumin level and disease severity in non-CF bronchiectasis. *Clin Exp Pharmacol Physiol* 2020; 47: 1537–1544.

33 Lee SJ, Kim HJ, Kim JY, *et al.* Serum albumin and disease severity of non-cystic fibrosis bronchiectasis. *Respir Care* 2018; 62: 1075–1084.
34 Aranow C. Vitamin D and the immune system. *J Investig Med* 2011; 59: 881–886.
35 Holick MF. The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. *Rev Endocr Metab Disord* 2017; 18: 153–165.
36 Mirra V, Caffarelli C, Maglione M, *et al.* Hypovitaminosis D: a novel finding in primary ciliary dyskinesia. *Ital J Pediatr* 2015; 41: 14.
37 Shypailo RJ, Wong WW. Fat and fat-free mass index references in children and young adults: assessments along racial and ethnic lines. *Am J Clin Nutr* 2020; 112: 566–575.
38 Chalmers JD, McHugh BJ, Docherty C, *et al.* Vitamin-D deficiency is associated with chronic bacterial colonisation and disease severity in bronchiectasis. *Thorax* 2013; 68: 39–47.
39 Marcinowska-Suchowierska E, Kupisz-Urbanska M, Lukaszkiewicz J, *et al.* Vitamin D toxicity – a clinical perspective. *Front Endocrinol* 2018; 9: 550.
40 Agarwal R, Chakrabarti A, Shah A, *et al.* Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy* 2013; 43: 850–873.
41 Li BCM, Huh SM, Prieto MD, *et al.* Biomarkers for the diagnosis of allergic bronchopulmonary aspergillosis in cystic fibrosis: a systematic review and meta-analysis. *J Allergy Clin Immunol Pract* 2021; 9: 1909–1930.
42 Sharma B, Sharma M, Bondi E, *et al.* Kartagener's syndrome associated with allergic bronchopulmonary aspergillosis. *MedGenMed* 2005; 7: 25.
43 Sehgal IS, Dhooria S, Bal A, *et al.* Allergic bronchopulmonary aspergillosis in an adult with Kartagener syndrome. *BMJ Case Rep* 2015; 2015: bcr2015211493.
44 Allaer L, Lejeune S, Mordacq C, *et al.* Primary ciliary dyskinesia and fungal infections: two cases of allergic bronchopulmonary aspergillosis in children. *Pediatr Pulmonol* 2022; 57: 1809–1813
45 Sunman B, Ademhan Tural D, Ozsezen B, *et al.* Current approach in the diagnosis and management of allergic bronchopulmonary aspergillosis in children with cystic fibrosis. *Front Pediatr* 2020; 8: 582964.
46 Stevens DA, Moss RB, Kurup VP, *et al.* Allergic bronchopulmonary aspergillosis in cystic fibrosis – state of the art: cystic fibrosis foundation consensus conference. *Clin Infect Dis* 2003; 37: Suppl. 3, S225–S264.
47 Boon M, De Boeck K, Jorissen M, *et al.* Primary ciliary dyskinesia and humoral immunodeficiency – is there a missing link? *Respir Med* 2014; 108: 931–934.
48 Nur Husna SM, Tan HTT, Md Shukri N, *et al.* Allergic rhinitis: a clinical and pathophysiological overview. *Front Med* 2022; 9: 874114.
49 Scadding GK, Smith PK, Blaiss M, *et al.* Allergic rhinitis in childhood and the new EUFOREA algorithm. *Front Allergy* 2021; 2: 706589.
50 Saad A, Young MR, Studtmann AE, *et al.* Incidence of nephrotoxicity with prolonged aminoglycoside exposure in patients with cystic fibrosis. *Pediatr Pulmonol* 2020; 55: 3384–3390.
51 Novel-Catin E, Pelletier S, Reynaud Q, *et al.* Aminoglycoside exposure and renal function before lung transplantation in adult cystic fibrosis patients. *Nephrol Dial Transplantat* 2019; 34: 118–122.
52 Hannah WB, DeBrosse S, Kinghorn BA, *et al.* The expanding phenotype of *OFD1*-related disorders: hemizygous loss-of-function variants in three patients with primary ciliary dyskinesia. *Mol Genet Genomic Med* 2019; 7: e911.
53 Bukowy-Bieryllo Z, Rabiasz A, Dabrowski M, *et al.* Truncating mutations in exons 20 and 21 of *OFD1* can cause primary ciliary dyskinesia without associated syndromic symptoms. *J Med Genet* 2019; 56: 769–777.
54 Martinez MA, Vuppalanchi R, Fontana RJ, *et al.* Clinical and histologic features of azithromycin-induced liver injury. *Clin Gastroenterol Hepatol* 2015; 13: 369–376.
55 Goutaki M, Papon JF, Boon M, *et al.* Standardised clinical data from patients with primary ciliary dyskinesia: FOLLOW-PCD. *ERJ Open Res* 2020; 6: 00237-2019.
56 Kos R, Goutaki M, Kobbernagel HE, *et al.* A BEAT-PCD consensus statement: a core outcome set for pulmonary disease interventions in primary ciliary dyskinesia. *ERJ Open Res* 2023; 10: 00115-2023.