A non-resolving cough in a 41-year-old woman: a case of familial pulmonary fibrosis

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Shareable abstract (@ERSpublications)
Identification of cases of familial pulmonary fibrosis is important with the risk of a monogenic cause. Patients appear to be younger and may have a more progressive disease. Consideration for antifibrotics and early transplant referral should be made. https://bit.ly/42jJ3aO

Cite this article as: Carolan A, Ozaki M, Ng WL, *et al*. A non-resolving cough in a 41-year-old woman: a case of familial pulmonary fibrosis. *Breathe* 2025; 21: 240258 [DOI: 10.1183/20734735.0258-2024].

Received: 28 Nov 2024
Accepted: 13 Jan 2025

A 41-year-old woman, who was a never-smoker with a past medical history of gastro-oesophageal reflux disease, allergic rhinitis and childhood asthma, presented to a respiratory outpatient clinic. She had a worsening chronic cough despite optimal medical management of her comorbidities. She worked as an allied health professional and had no occupational exposure. She did not have any pet birds.

A respiratory examination revealed bibasal crepitations and no finger clubbing. Her body mass index was 27.7 $kg \cdot m^{-2}$. There was no evidence of any rheumatological disease on physical examination. A plain film chest radiograph was completed and was normal. To further investigate, high-resolution computed tomography (HRCT) of the thorax (figure 1) and pulmonary function testing (table 1) were performed.

Task 1

Which of the following statements best describes the HRCT and pulmonary function test findings?

a) Normal appearance on HRCT, normal spirometry and normal gas transfer.
b) Mild centrilobular emphysema on HRCT, obstructed spirometry and reduced diffusing capacity of the lung for carbon monoxide (D_{LCO}).
c) Bronchiectasis on HRCT, restrictive spirometry and reduced D_{LCO}.
d) Nonspecific interstitial pneumonia pattern on HRCT, restrictive spirometry and reduced D_{LCO}.
e) Probable usual interstitial pneumonia pattern on HRCT, normal spirometry and reduced D_{LCO}.

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A working diagnosis of idiopathic pulmonary fibrosis (IPF) was made based on the probable UIP radiological pattern demonstrated on HRCT. No clinical features of other causative systemic diseases were found. The patient had a strong family history of interstitial lung disease (ILD) (figure 2). Her maternal aunt received a lung transplant for ILD at 69 years of age, the patient's maternal grandmother died from

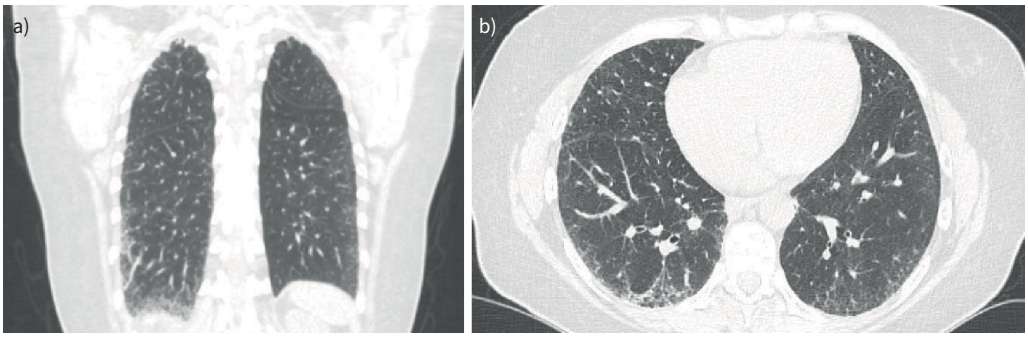

FIGURE 1 High-resolution computed tomography (HRCT) of the thorax at presentation. a) Sagittal and b) coronal images taken from the HRCT performed at presentation.

TABLE 1 Results of pulmonary function tests carried out at presentation

	Predicted value	Best measurement	% predicted (best/pred)	Post-bronchodilator measurement
FEV_1 (L)	3.54	3.01	85%	3.19
FVC (L)	4.08	3.62	89%	3.63
FEV_1/FVC (%)		83.19		87.54
D_{LCO}# ($mmol \cdot min^{-1} \cdot kPa^{-1}$)	10.09	5.03	50%	

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide. #: D_{LCO} assumes a normal haemoglobin of 13.5 $g \cdot 100mL^{-1}$.

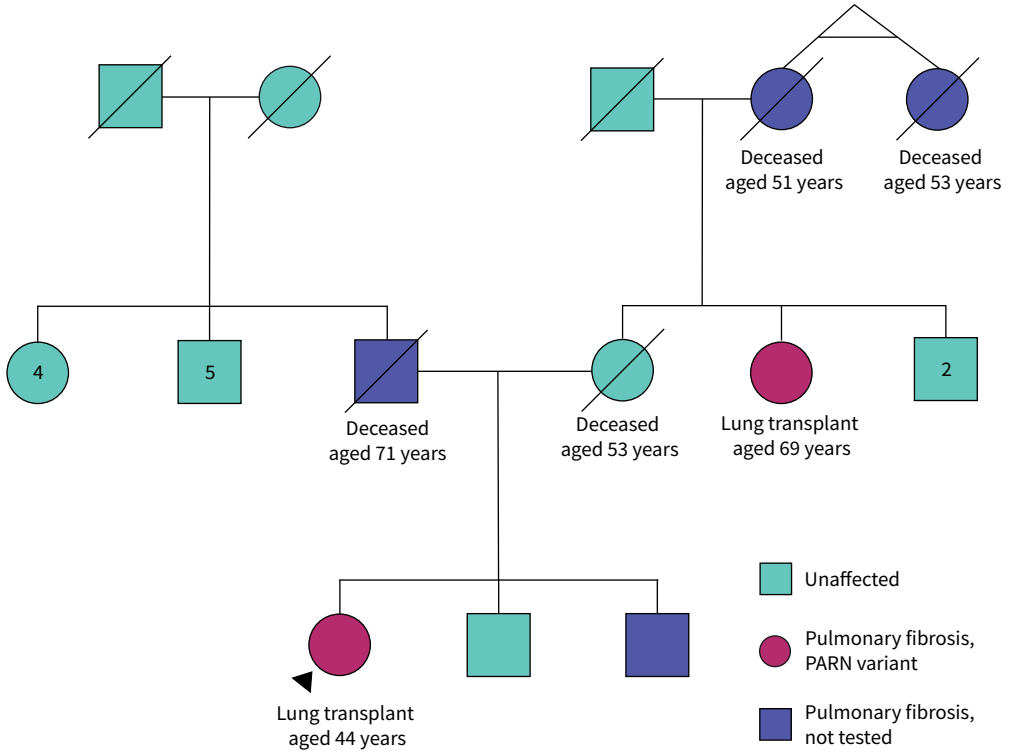

FIGURE 2 Family pedigree. Six family members are known to have had pulmonary fibrosis. Those with known pulmonary fibrosis and who carry the pathogenic PARN variant are depicted in magenta. Those with pulmonary fibrosis and whose PARN variant status is unknown have been depicted in purple. Unaffected family members have been depicted in cyan.

ILD at 51 years of age, and her grandmother's identical twin sister died from ILD at 53 years of age. Her mother, a smoker, died of lung cancer at 53 years of age. Her father was diagnosed with ILD at 64 years of age.

Task 2

Which of the following test(s) would be appropriate to carry out next in investigating this case?

a) Next-generation genetic sequencing.
b) Karyotyping (G banding).
c) Laboratory investigations, including rheumatoid factor, anti-cyclic citrullinated peptide antibody, a myositis panel and antinuclear antibodies.
d) ILD multidisciplinary meeting (MDM).
e) Fluoroscopic transbronchial lung biopsy.
f) Sanger sequencing.

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An ILD autoimmune and connective tissue disease blood panel was negative. NGS was performed and identified an intronic heterozygous variation of PARN (poly(A)specific ribonuclease) (c.388+5G>T), a telomere-related gene (TRG). This PARN variant had not been described previously. Segregation analysis was performed, and her maternal aunt with ILD was found to have the same PARN variant (figure 2). Telomere length was measured using flow fluorescence *in situ* hybridisation and compared to age-matched controls (figure 3). Her mean lymphocyte telomere length (MTL) was 4.5 kb or less than the first percentile for age. Telomere length in naïve T cells and B cells was also less than the first centile, and memory T cell and natural killer cell MTL was less than the 10th centile.

Given the patient's maternal history of lung cancer, and the rare association of surfactant protein A (SFTPA) variants with both ILD and lung cancer [3], further targeted next-generation sequencing was carried out for surfactant-related genes. A heterozygote ABCA3 (ATP-binding cassette transporter A3) variant, c.2125C>T, was identified but was not thought to be pathogenic [4].

Task 3

Which of the following patient(s) should be considered for genetic testing?

a) A 70-year-old patient with IPF who has a sister with a diagnosis of fibrotic ILD.
b) A patient with a diagnosis of IPF at the age of 61 years.
c) A patient whose mother carries a pathogenic variant in the RTEL1 gene.
d) A patient with cryptogenic liver cirrhosis and IPF.

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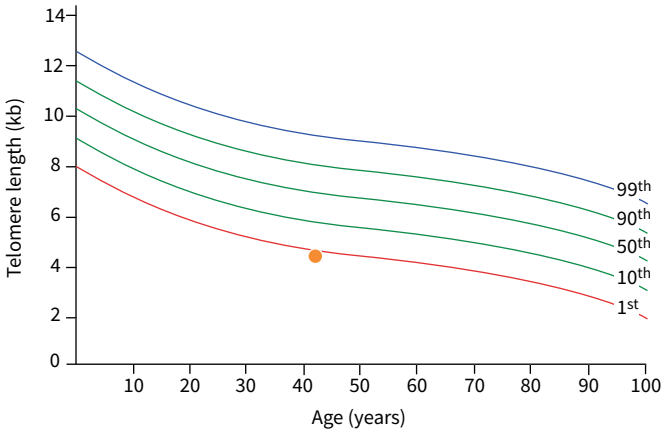

FIGURE 3 Lymphocyte telomere length measurement centile graph. Centile graph showing lymphocyte mean telomere length, measured using flow fluorescence *in situ* hybridisation, compared to age-matched controls. Telomere length was below the first centile in lymphocytes.

The case was discussed first at an ILD MDM. A diagnosis of familial pulmonary fibrosis (FPF) was made. No tissue biopsy was recommended. Following this, the results were discussed at a specialist pulmonary genetics MDM. The consensus at this meeting was that the PARN variant, although never previously described, was thought to be pathogenic.

Subsequently, the patient reported that her brother was diagnosed with early pulmonary fibrosis on a HRCT scan.

Task 4

What type of genetic testing would be offered to the patient's brother?

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Task 5

Which of the following, in combination with pulmonary fibrosis, is not associated with STS?

a) Myelodysplasia
b) Cryptogenic liver cirrhosis
c) Diabetes mellitus type 2
d) Early hair greying (before the age of 30 years)
e) Acute leukaemia

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The patient started on pirfenidone but continued to deteriorate clinically. Her progression is demonstrated on follow-up HRCT of the thorax (figure 4), which shows a definite UIP pattern with honeycombing. Over 3 years, her ppD_{LCO} dropped from 50% to 28%, and her ppFVC from 89% to 57%. Her 6-min walk test suggested ambulatory hypoxaemia, and she was prescribed ambulatory oxygen.

Task 6

What would be the next step in managing this patient?

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The patient continued to deteriorate clinically and went on to receive a double lung transplantation 3.5 years after diagnosis. Tissue samples from the explanted lung tissue show histopathological features typical of UIP pattern pulmonary fibrosis (figure 5).

Discussion

Up to 20% of patients with IPF have at least one family member with pulmonary fibrosis, referred to as FPF [5]. Genetic factors are increasingly recognised as an important cause of pulmonary fibrosis. Up to 40% of cases of FPF are suspected to have a monogenic cause, with TRGs encompassing the largest group

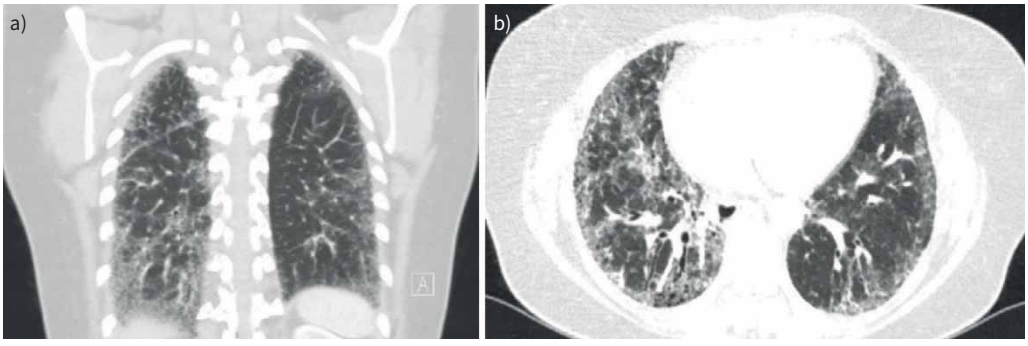

FIGURE 4 Follow-up high-resolution computed tomography (HRCT) scan of the thorax. a) Sagittal and b) coronal images taken from a HRCT scan completed 3 years after the images shown in figure 1. Clear progression from the previous images is demonstrated.

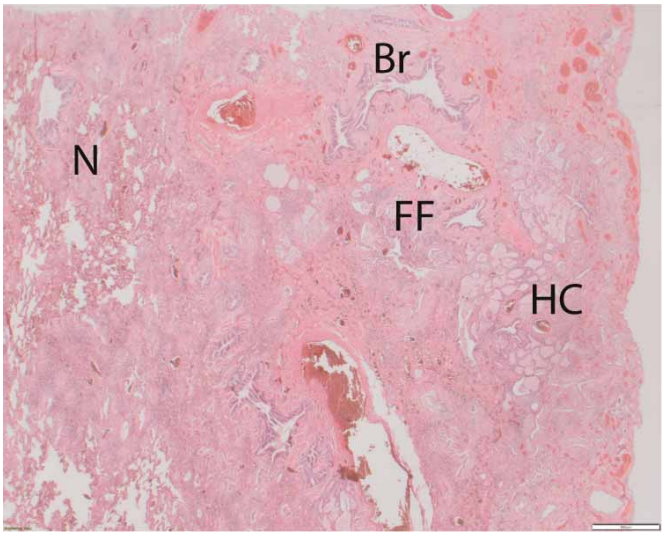

FIGURE 5 Slide of a representative sample of explanted lung tissue. This slide of explanted lung tissue shows areas of normal lung (N) on the left surrounded by an area with features typical of usual interstitial pneumonia pattern fibrosis: honeycombing (HC), fibroblastic foci (FF) and bronchiolectasis (Br). Scale bar=1000 μm.

and contributing 25–30% of cases. Surfactant-related genes are less common, contributing 3–5%, and other complex syndromes contribute a further 3–5% [6]. 12 TRGs are currently associated with FPF, including TERT (15–22%), TERC (2–5%), RTEL1 (5–10%) and PARN (2–5%). Other rarer variants in DKC1, T1NF2, NOP10, NHP2, ACD, NAF1, ZCCHC8, RPA and POT1 have also been associated with FPF [3]. Genetic sequencing of people with FPF focuses on TRGs and surfactant-related genes with analysis for additional genes considered depending on the patient's phenotype.

Telomeres are repeat DNA sequences that extend for thousands of bases at the chromosome ends, forming a cap that protects chromosome integrity during cell replication (figure 6). Premature shortening of telomeres below a critical threshold can lead to cell senescence and apoptosis [7]. The enzyme telomerase counteracts this process by adding repeat sequences to the 3′ end of telomeres. Variants in PARN lead to a reduction in telomerase activity [8]. Telomere shortening occurs during the normal process of ageing. Approximately 40% of adults with FPF and 27% with sporadic IPF have short telomeres [9]. Pathogenic variants in genes governing telomere homeostasis can lead to premature telomere shortening. TRGs are associated with a heterogeneous group of diseases, such as pulmonary fibrosis, liver disease, dyskeratosis congenita, aplastic anaemia and bone marrow failure [10]. This patient had a very short initial mean telomere length of 4.5 kb or less than the first percentile and went on to have a rapidly progressive clinical course. This is consistent with the observation that telomere length at presentation may better predict progression than type of gene variant [11].

Variants in the gene encoding PARN have recently been implicated in developing pulmonary fibrosis [12, 13]. The PARN variant reported in this case, c.388+5G>T, was predicted to disturb donor splice sites. The PARN variant c.388+5G>T had not previously been described in public databases and, therefore, had no established pathogenicity. The American College of Medical Genetics and Genomics has recognised standards and guidelines for interpreting sequence variants [4]. Weighted evidence is used to classify variants into five categories: benign, likely benign, variants of unknown significance, likely pathogenic and pathogenic. As new evidence is found, a variant's classification can change. Factors that supported the pathogenicity of the variant, in this case, included the co-segregation of the PARN variant in her affected maternal aunt and the very short telomere length measured in this patient. Following the specialist genetics MDM, the consensus was that the PARN c.388+5G>T variant should be classified as pathogenic.

The most common radiological pattern seen in cases of FPF is a UIP pattern [14, 15], as was described in this case. However, Newton *et al.* [16] have reported that just under half of ILD cases involving TRGs have an MDM diagnosis of IPF, a wide range of ILD diagnoses are made, from unclassifiable to chronic hypersensitivity pneumonitis – with discordant diagnoses within the majority of families. Suspicion of a TRG should not be reserved for a diagnosis of IPF only.

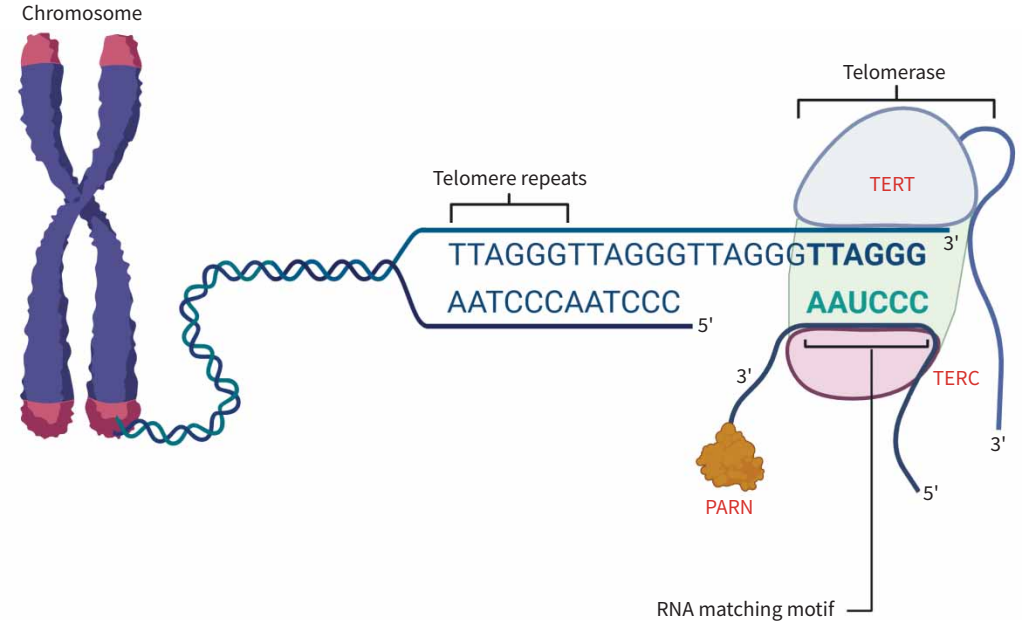

FIGURE 6 The addition of nucleotide repeats to the 3′ end of the telomere. Telomerase is made up of two components: the RNA component, TERC, and the reverse transcriptase component, TERT. PARN is involved in the maturation of the TERC component, which acts as a template for nucleotide additions. Created with BioRender.com.

Antifibrotic treatment should be started for patients in accordance with international guidelines, in those with IPF or progressive pulmonary fibrosis [1, 3]. As lung transplantation is the only intervention that prolongs survival in IPF, it should be considered early. However, caution should be used as those with a TRG are at high risk of haematological complications following lung transplantation [17, 18]. This should be considered carefully when deciding on the post-transplantation immunosuppression regime, including careful drug monitoring. Although there is no specific guidance available, where possible, cytotoxic drugs such as azathioprine should be avoided [3].

Our patient did not demonstrate any extrapulmonary features of STS (table 2). Cases of haematological disorders and liver disease have been reported in patients with a PARN variant [19], although the prevalence is lower when compared to other TRGs, TERT and TERC [14, 16].

Unfortunately, there is no consensus for the screening and monitoring of extrapulmonary involvement, such as liver and haematological involvement, in FPF. However, Team Telomere, a group with the goal of advocacy and education for telomere biology disorders, has created guidelines for diagnosing and managing telomere biology disorders. These guidelines offer guidance for all telomere biology disorders, some of which are more severe in their manifestations than FPF. A full blood count (FBC) every 6–12 months is recommended to monitor for haematological involvement in patients with a normal FBC. The frequency of FBC monitoring should increase if any abnormality is found, for example, every 3–4 months if a mild low count is present. Liver function tests (LFTs), including synthetic function, should

TABLE 2 Criteria to suspect a short telomere syndrome

Pulmonary fibrosis and one or more of the following in the patient and/or family members:
Haematological abnormalities: macrocytosis, neutropenia, lymphopenia, thrombocytopenia, myelodysplasia, acute leukaemia
Hepatic abnormalities: cryptogenic elevated liver enzymes, portal hypertension, hepatopulmonary syndrome, liver cirrhosis
Early hair greying (significant greying before age 30 years)
Recognised telomere disease such as dyskeratosis congenita

Adapted from [3].

be performed at baseline and at least once a year, and more frequently if LFTs or clinical signs suggest liver disease. If liver disease is suspected, an ultrasound of the abdomen and/or a measure of liver stiffness, such as a transient elastography (fibroscan), should be performed to evaluate further [20].

Here, we present a newly identified splice mutation in the PARN gene that led to pulmonary fibrosis in a young woman. The MDM plays a central role in diagnosing new cases of ILD. The importance of taking a family history for all patients with ILD is highlighted. Patients with FPF tend to be younger and may have a more progressive disease [3, 21], making the identification of familial patients important from a clinical perspective. A comprehensive genetic assessment should be performed, and specialist advice should be sought when a causative variant is identified. Antifibrotic therapy should be started for patients with FPF in accordance with international guidelines. Lung transplantation should be considered early, particularly in those patients with progressive disease and short telomeres at diagnosis.

Answer 1

e) would be the most appropriate answer. The HRCT showed a probable usual interstitial pneumonia (UIP) pattern: mild basal predominant subpleural reticulation with some evidence of traction bronchiectasis. However, no definite honeycombing was seen. Honeycombing is a hallmark of UIP and must be present for a diagnosis of definite UIP [1]. Pulmonary function testing demonstrated normal spirometry with a percentage predicted forced vital capacity (ppFVC) of 89%. There was a notably reduced percentage predicted D_{LCO} (ppD_{LCO}) of 50%. These pulmonary function tests were performed before publication of the new European Respiratory Society/American Thoracic Society guidelines on interpreting spirometry [2]; therefore, the lower limit of the normal and Z-score were not reported.

<< Go to Task 1

Answer 2

Answers a), c) and d) would be appropriate for investigating this patient. An ILD autoimmune and connective tissue disease blood panel should be taken to screen for potential causes of ILD. The panel for this patient included extranuclear antibodies, antinuclear bodies, rheumatoid factor, anti-cyclic citrullinated peptide and an extended myositis panel. Due to this patient's family history of ILD, which suggests familial pulmonary fibrosis, as well as her young age at presentation, we proceeded with next-generation sequencing (NGS) of the patient's DNA to assess if there was a monogenic cause for her ILD.

In the past Sanger sequencing was the gold standard for detecting pathogenic variants in a patient. However, it has largely been replaced by NGS, which has a higher capacity for interrogating many targets simultaneously. Sanger sequencing is now primarily used for predictive testing, to assess an asymptomatic person's risk of developing a disease, for confirmation of pathogenic variants identified through NGS, and for familial screening for a known variant.

NGS takes the form of gene panel sequencing, whole exome sequencing (WES) or whole genome sequencing (WGS). Gene panels take a targeted look at specific regions chosen based on variants' association with clinical phenotypes. WES looks at all the coding regions in the genome (the exome). WGS looks at all coding and non-coding areas of the genome. The method chosen depends on a number of factors, including the clinical question, cost and if there is a requirement for the detection of copy number variants.

Karyotyping, or G banding, shows a visual representation of the number and structure of chromosomes in a cell. It gives information on the structure and position of chromosomes. It is used for diagnosing chromosomal disorders such as Down syndrome (trisomy 21). However, it would not give us the genetic information we need for this patient.

Given the radiological diagnosis of probable UIP in this case, it would be reasonable to discuss the case at an ILD MDM before proceeding with any tissue diagnosis, which may not be required. If it is determined that a lung biopsy is needed, depending on the centre's expertise, either transbronchial cryobiopsy or surgical lung biopsy would be carried out, not fluoroscopic transbronchial lung biopsy.

<< Go to Task 2

Answer 3

The answers a), c) and d) are correct. The European Respiratory Society's (ERS) statement on familial pulmonary fibrosis recommends offering genetic testing to any patient with fibrotic ILD who has one or more first- or second-degree family members with a diagnosis of fibrotic ILD [3]. It also recommends offering testing to any patient with an idiopathic fibrosing ILD before the age of 50 years. Other indications include evidence of a short telomere syndrome (STS) or another relative carrying a pathogenic or likely pathogenic variant known to cause ILD.

<< Go to Task 3

Answer 4

The brother is a relative of a person with a known pathogenic variant. Therefore, Sanger sequencing or molecular testing for the specific variant would be appropriate to assess whether he is a carrier of the pathogenic PARN variant.
The inheritance of the variants implicated in pulmonary fibrosis is generally autosomal dominant, meaning that children of a carrier of a pathogenic variant have a 50% chance of inheriting the variant. Screening can be offered to asymptomatic first-degree relatives of those with a pathogenic variant, dependent on local practice and health regulations [3].

<< Go to Task 4

Answer 5

Answer c) is not suggestive of a STS. All the other answers should raise the suspicion of STS if identified in a patient with a fibrotic ILD. The ERS has highlighted criteria that should lead to the suspicion of STS (table 2). This patient had no other manifestations associated with STS (table 2). Her liver enzymes and full blood count were within normal range. A liver fibroscan was carried out and was found to be normal.

<< Go to Task 5

Answer 6

Given the rapid clinical deterioration, workup for lung transplantation was started.

<< Go to Task 6

Acknowledgements: The authors wish to acknowledge the patient discussed in this case for her consent to this publication, as well as her ongoing interest and support for research and education dedicated to pulmonary fibrosis.

Conflict of interest: A. Carolan reports support for the present manuscript from Scholar on RCSI StAR MD programme with Bon Secours Hospital Dublin; and support for attending meetings from GSK. M. Ozaki reports grants from Irish Research Council Starting Laureate Award IRCLA/2022/1572; and support for attending meetings from GSK. W.L. Ng reports support for the present manuscript from Royal College of Surgeons in Ireland. J. Ryan reports consultancy fees from Bond Biosciences, Pfizer, Gilead and Kyowa kirin; payment or honoraria for lectures, presentations, manuscript writing or educational events from Falk and Kyowa kirin; and a leadership role with Irish Liver Foundation Charity. M.W. O'Reilly reports grants from Health Research Board, RCSI Seed fund, Spruce and Inventia; consultancy fees from Roche; payment or honoraria for lectures, presentations, manuscript writing or educational events from HRA Pharma, Roche and Bayer; and support for attending meetings from Pfizer 2023. N. Nathan reports grants from 2024: CORTICONEHI (Clinical trial: Efficacy of methylprednisolone pulses in neuroendocrine cells hyperplasia of infancy: an early phase study); 2023: Million Dollar Bike Ride project for Neuroendocrine Cell Hyperplasia of Infancy: Genetic basis of neuroendocrine cell hyperplasia of infancy; 2022: Chancellerie des Universités: Legs Poix, Molecular and phenotypic characterization of interstitial lung disease n° 2022000594; 2022: RespiFIL grant for the development of an elearning module for CT-scan in childhood interstitial lung diseases (15 000 €); 2022: RespiFIL grant for the development of an online platform for the collection of quality of life and transition questionnaires in rare lung disease (15 000 €); payment or honoraria for lectures, presentations, manuscript writing or educational events from La lettre du Pneumologue; support for attending meetings from European Respiratory Society; a Leadership role as 2021–2025 Head of the ERS Clinical research collaboration for childhood ILD (CRC-chILDEU), 2017–2023 Treasurer of the Société française de pédiatrie (SFP), 2023– Treasurer and Scientific committee of the Société de Pneumologie Pédiatrique et d'Allergologie (SP2A), 2023– Scientific and Scientific committee of the Société de Pneumologie de Langue Française (SPLF). R. Borie reports consultancy fees from Boehringer Ingelheim, Ferrer and Sanofi; payment or honoraria for lectures, presentations, manuscript writing or educational events from Boehringer Ingelheim; and support for attending meetings from Boehringer Ingelheim. K. Hurley reports support for the present manuscript from Health Research Board, Ireland, Emerging Clinical Scientist Award (ECSA-2020-011) and the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (101078300 - STAR-TEL). K. Hurley reports grants from Moderna; payment or honoraria for lectures, presentations, manuscript writing or educational events from Boehringer Ingelheim and patientMpower. The remaining authors have nothing to disclose.

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