Genetics in ILD

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Conflicts of interest

- None related to this presentation

Topics

- Is ILD Genetic?
- Known Genetic basis for ILD
- Features of familial ILD
- Typical family tree for familial ILD
- Process for requesting genomic testing
- UK tests currently available
- Need for Genetic counselling
- Developing best practices for ILD-Genetics services

Prevalence & numbers

- About 20% PF is FPF
- About 30% relatives of sporadic IPF have ILA
- 10-fold increase in disease prevalence in families of patients with a diagnosis of IPF
- ? ILA found on lung cancer screening (~7%)

"ILD is a genetic disease"

Genes and Telomeres

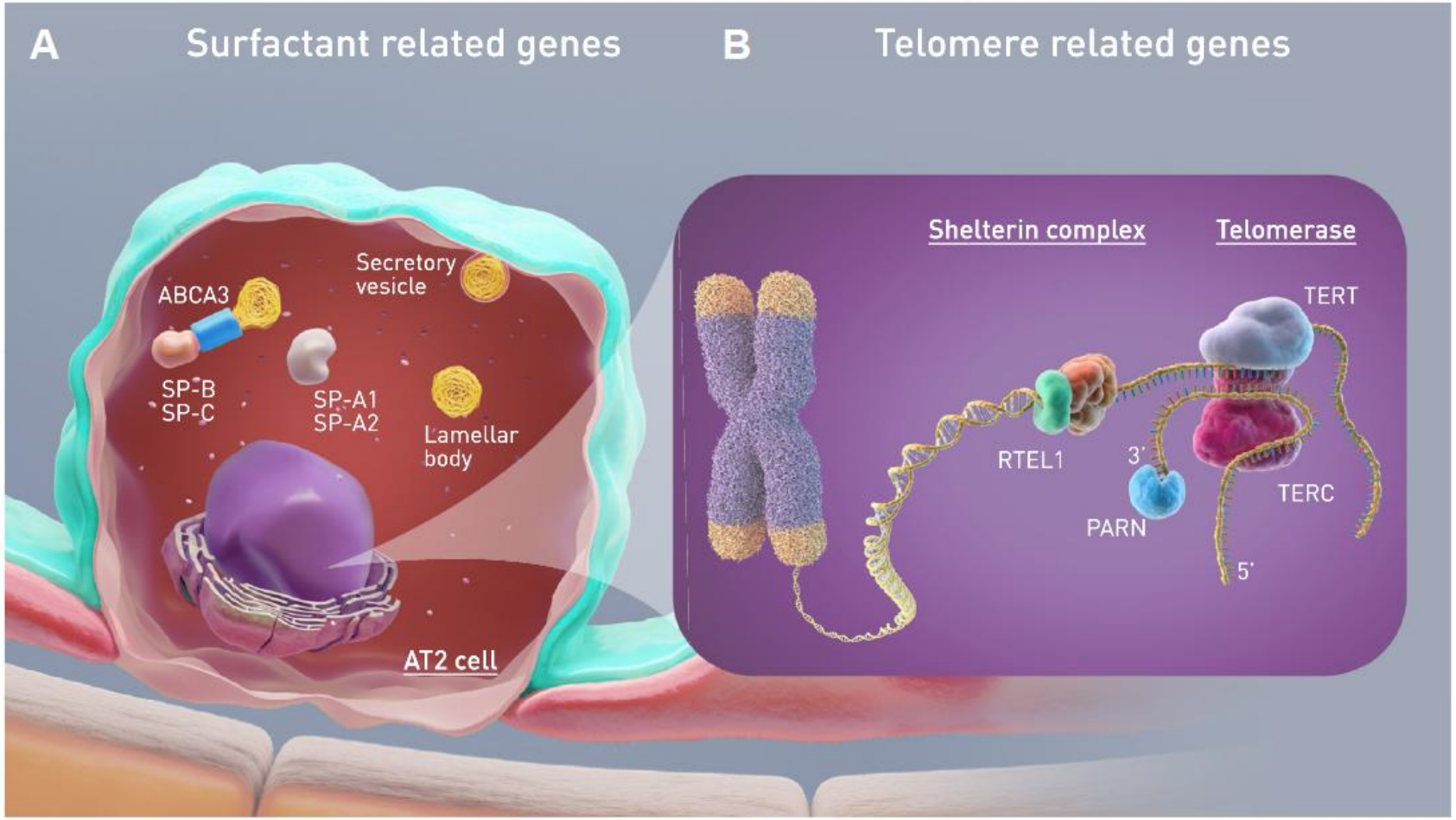
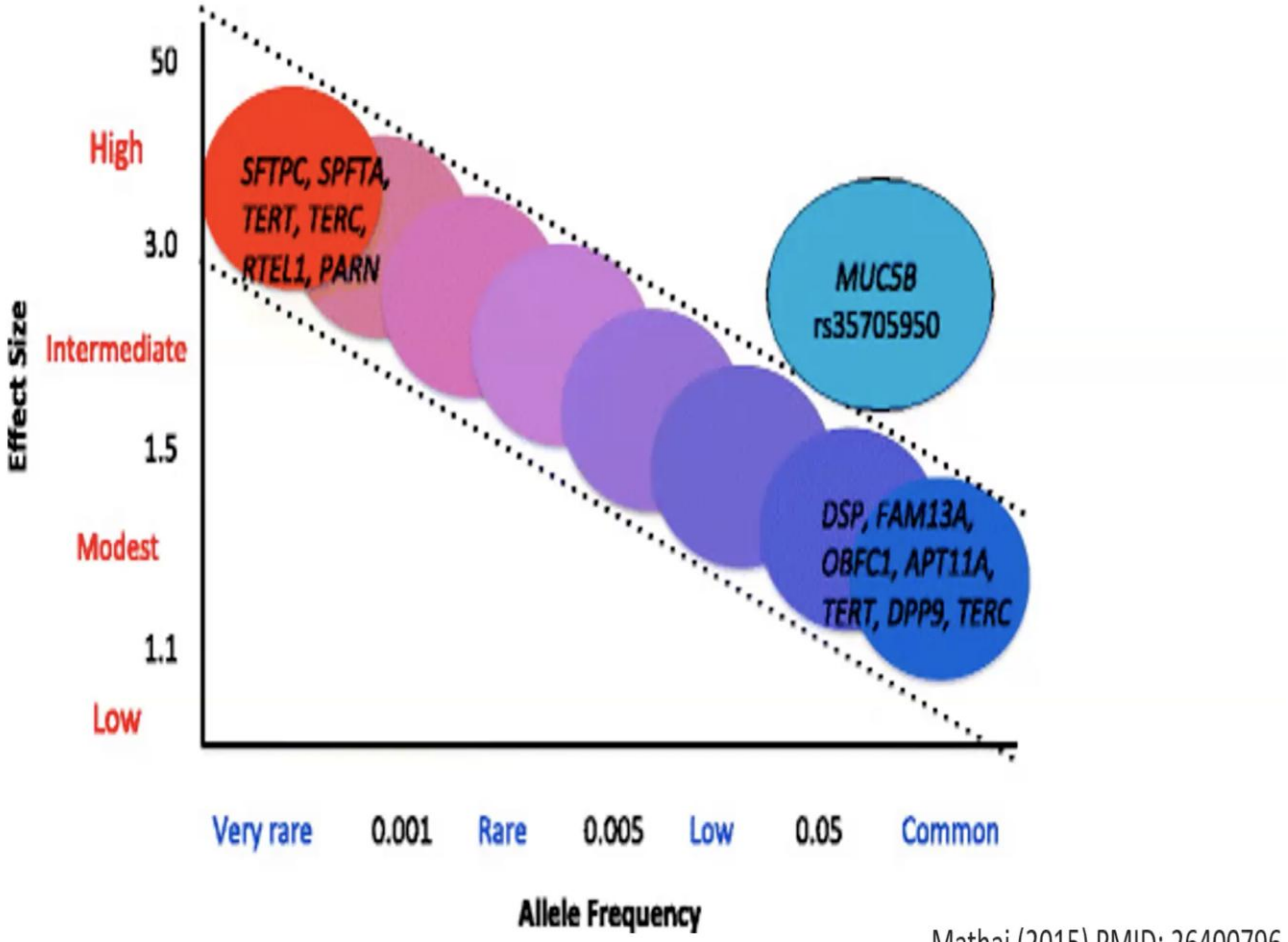


Fig. 1: **Gene mutations and disease pathways found in familial pulmonary fibrosis (FPF)**: (**A**) Surfactant is a mixture of phospholipids and proteins produced by type 2 alveolar epithelial (AT2) cells, which prevents alveolar collapse at the end of expiration. The lipidic transporter ATP-binding cassette family A member 3 (ABCA3) is involved in the transport and storage of surfactant proteins (SP) into lamellar bodies. Secreted SP and phospholipids form the surfactant film at the air-liquid interface of the alveolar space. To date, in chILD, mutations have been described in genes encoding SP-C (*SFTPC*), ABCA3 (*ABCA3*), TTF1 (*NKX2-1*), SP-B (*SFTPB*), and in adult FPF, in genes encoding SP-A (*SFTPA1* and *SFTPA2*), SP-C, ABCA3 and TTF1. (**B**) Telomeres are nucleoprotein structures at the ends of linear chromosomes which protect genomic DNA. The activation of telomerase, composed of TERT and its RNA component TERC, prevents the attrition of chromosome ends during cell replication. Besides the telomerase complex, telomere homeostasis also requires the shelterin complex. In patients with FPF, mutations in the genes encoding telomere components, the most frequently identified being in *TERT, TERC, PARN* and *RTEL1*, result in alterations in telomere homeostasis and shortened telomeres in cells, such as AT2 cells.

Hurley K, 2024 – PMID: 38718684

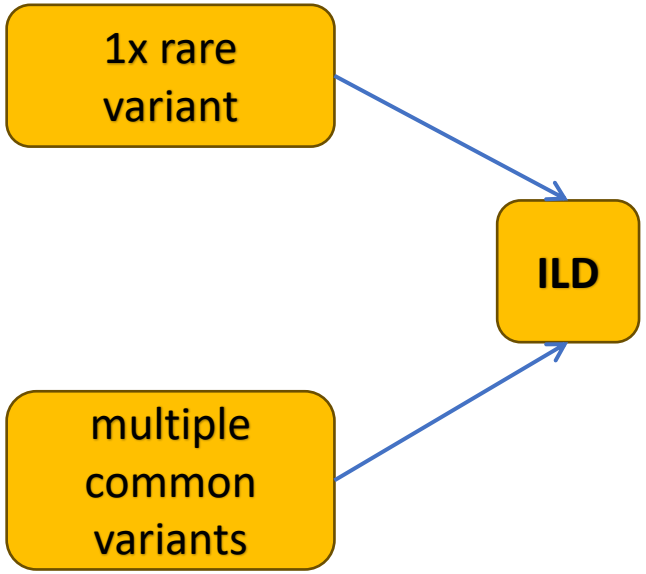
Gene “variants” – rare and common



Mathai (2015) PMID: 26400796

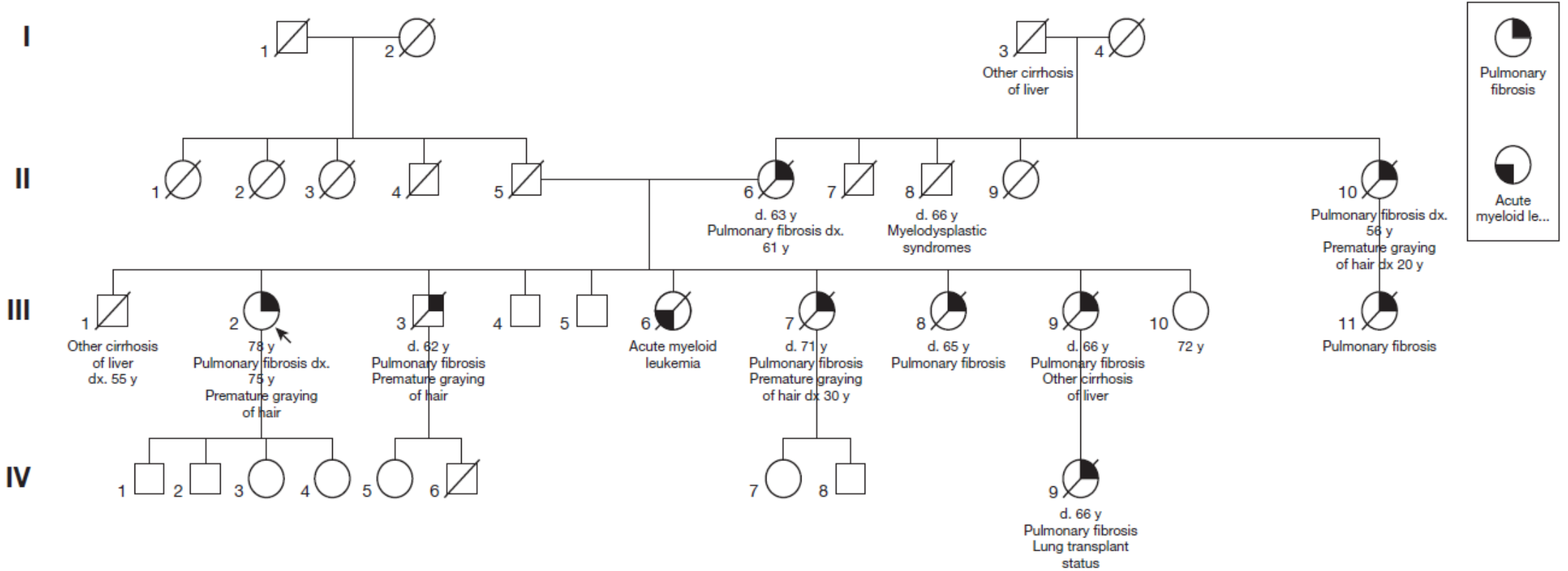
Classification:

- Pathogenic
- Likely pathogenic
- **Variant of uncertain significance (VUS)**
- Likely benign
- Benign



Clinical features of familial ILD

- ILD of unknown cause < 50 y.o. (?60)
- Unusual ILD presentations – atypical CT scans or clinical features
- Unexplained liver disease
- Haematological disease / abnormalities (MDS, leukaemia, high MCV, low PLT, persistent anaemia)
- Rapidly progressive ILD
- Poor tolerance to immunosuppression (haematological)
- Autoimmune disease / abnormalities
- Early hair greying
- Early menopause
- High frequency of lung cancer (? surfactant gene variants)



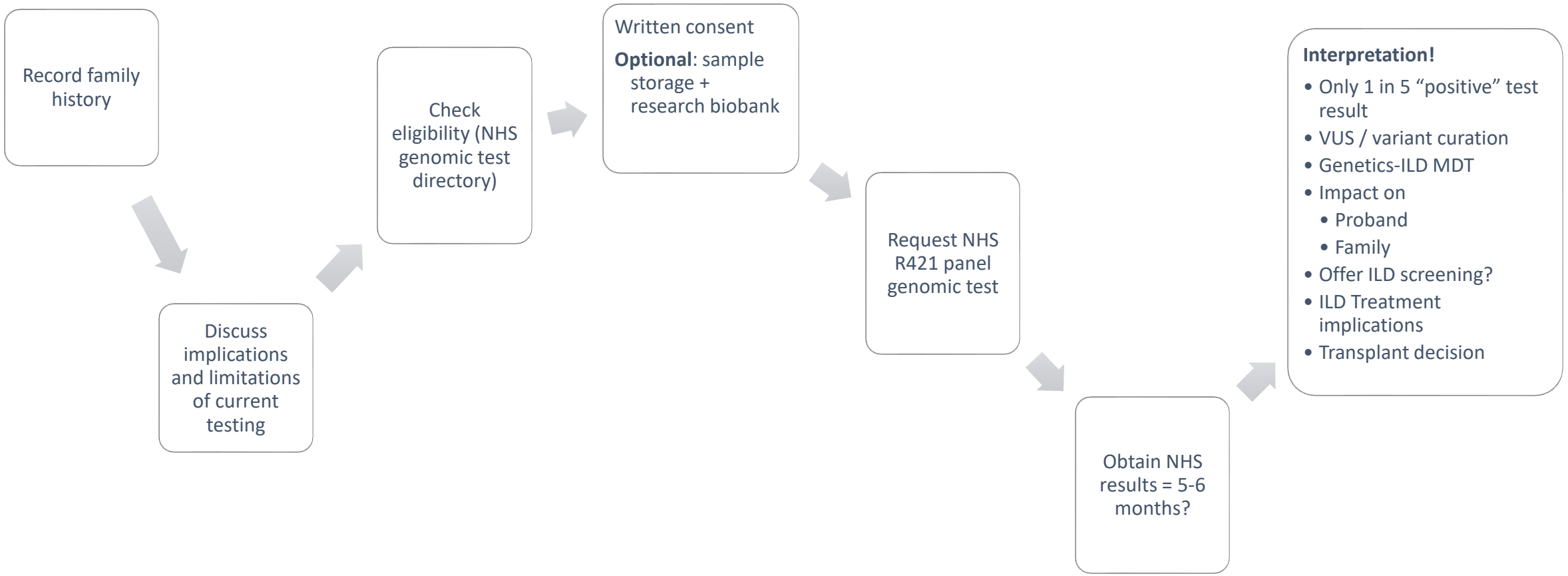
I 3. Diagnoses: Other cirrhosis of liver
II B. Diagnoses: Myelodysplastic syndromes
II 10. Diagnoses: Premature graying of hair - Diagnosed at 20 y
III 1. Diagnoses: Other cirrhosis of liver - Diagnosed at 55 y
III 2. Diagnoses: Premature graying of hair
III 3. Diagnoses: Premature graying of hair
III 7. Diagnoses: Premature graying of hair - Diagnosed at 30 y
III 9. Diagnoses: Other cirrhosis of liver
IV 9. Diagnoses: Lung transplant status

Newton CA, 2022 – PMID: 35337808

Legend: ○ = Females; □ = Males; ⊘ = Deceased; ◨ = Pulmonary fibrosis; ◪ = Acute myeloid leukemia; Arrow points to the Proband or index case; Roman Numerals represent the generations from oldest to youngest; Individuals are identified by Roman numeral generation and number in order (e.g., III.7)

Figure 1 – *Example of a pedigree demonstrating features of short telomere syndrome across multiple generations. Arrow points to the proband or index patient. Roman numerals represent the generations from oldest to youngest. Individuals are identified by Roman numeral generation and number in order (eg, III.7).*

How is NHS genomic testing requested?



1. Early onset of disease	Yes/No	
2. Familial Pulmonary Fibrosis/ILD	Yes/No	
3. Personal or family history of	Yes/No	
3a. Haematological disease or unexplained haematological abnormalities (i.e., aplastic anaemia)		
3b. CTD/autoimmune features		
3c. Cryptogenic liver cirrhosis or unexplained liver function abnormalities		
3d. Frequent cancer diagnosis (i.e., head and neck cancer, lung cancer)		
3e. Early hair greying (<30 years)		
3f. Early menopause (<45 years) or recurrent miscarriage		
3g. GI disease such as oesophageal stenosis, enteropathy, enterocolitis		
4. Family history of dyskeratosis congenita (major clinical features: mucocutaneous triad, bone marrow failure)?		

Other details:

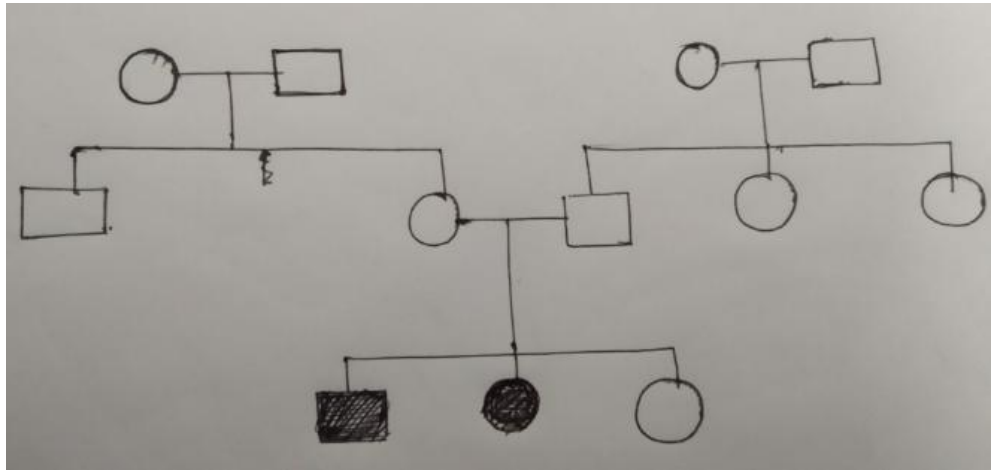
Environmental exposures:

Smoking status:

Personal history of Osteoporosis: (Yes/No)

Family history – details:

Siblings	
Mother	
Father	
Mother's siblings	
Father's siblings	
Maternal grandparents	
Paternal grandparents	
Children	
Partner	



Pedigree can be difficult to draw during clinic

First name	NHS number (or postcode if not known)
Last name	Date of birth (d d / m m / y y y y)

01-NGID-ROD (v4.03)

Record of Discussion Regarding Genomic Testing

This form relates to the person being tested. One form is required for each person.

All of the statements below remain relevant even if the test relates to someone other than yourself, for example your child.

I have discussed genomic testing with my health professional and understand the following

Family and wider implications

1. The results of my test may have implications for me and members of my family. I understand that my results may also be used to help the healthcare of members of my family and others nationally and internationally. This could be done in discussion with me or through a process that will not personally identify me.

Uncertainty

2. The results of my test may have findings that are uncertain and not yet fully understood. To decide whether findings are significant for myself or others, my data may be compared to other patients' results across the country and internationally. I understand that this could change what my results mean for me and my treatment over time.

Unexpected information

3. The results of my test may also reveal unexpected results that are not related to why I am having this test. These may be found by chance and I may need further tests or investigations to understand their significance.

DNA storage

4. Normal NHS laboratory practice is to store the DNA extracted from my sample even after my current testing is complete. My DNA might be used for future analysis and/or to ensure that other testing (for example that of family members) is of high quality.

Data storage

5. The data from my genomic test will be securely stored so that it can be looked at again in the future if necessary.

Health records

6. Results from my genomic test will be part of my patient record, a copy of which is held in a national system only available to healthcare professionals.

Research

7. I understand that I have the opportunity to take part in research which may benefit myself or others, now or in the future. An offer to join a national research opportunity is available on the following page.

For any further questions, my healthcare professional can provide information. More information regarding genomic testing and how my data is protected can be found at www.nhs.uk/conditions/genetics

Please sign on page three to confirm your agreement to the genomic test

NHS Genomic Medicine Service. Record of Discussion Form version 4.03.

First name	NHS number (or postcode if not known)
Last name	Date of birth (d d / m m / y y y y)

Genomics england

01-NGID-ROD (v4.03)

The National Genomic Research Library

The NHS invites you to contribute to the National Genomic Research Library, managed by Genomics England.

Genomics England was set up in 2013 by the Department of Health and Social Care to work with the NHS to build a library of human genomes for researchers to study. Combining data from many different patients helps researchers to better understand disease and spot patterns in the data.

By agreeing to share your data you might get results which could lead to your own diagnosis, a new treatment, or offers to take part in clinical trials. Your taking part could enable diagnoses for people who don't have one.

Please read the following statements. Feel free to ask any questions before making a decision.

By saying 'yes' to research, I understand the following

The National Genomic Research Library

1. NHS England, on behalf of the Trusts that provided your genomic test, will allow Genomics England to access my personal data including my genomic record.

Security

2. Any samples and data stored by Genomics England and the NHS will always be stored securely. Genomics England will take all reasonable steps to ensure that I cannot be personally identified.

Re-contact

3. My clinical team or Genomics England together with my clinical team, can contact me if the data or samples reveals any clinical trials or other research that I might benefit from.

4. If something is relevant to me or my family, there is a process by which this will be shared with my NHS clinical team.

Data and sample usage

5. Researchers may include national or international scientists, healthcare companies and NHS staff. To access the data, these researchers must all be approved by an independent committee of experts, including health professionals, clinical academics and patients. There will be no access to the data by personal insurers and marketing companies.

Data storage

6. Genomics England will collect different aspects of my health data from the NHS and other data from organisations listed at https://www.genomicsengland.co.uk/privacy-policy/. The collection and analysis of my health data for research will continue across my entire lifetime and beyond.

Withdrawal

7. I can change my mind about taking part at any time.

More information regarding research in the National Genomic Research Library can be found at www.genomicsengland.co.uk For any further questions, my healthcare professional can provide information.

Please use page three to indicate your research choices.

First name	NHS number (or postcode if not known)
Last name	Date of birth (d d / m m / y y y y)

Genomics england

01-NGID-ROD (v4.03)

Confirmation of Your Genomic Test and Research Choices

I confirm that I have had the opportunity to discuss information about genomic testing, I agree to the genomic test, and my research choice is indicated below.

A. **I have discussed taking part in the National Genomic Research Library** ☐ YES | NO ☐
   If your answer to A is NO then please ignore B and sign directly below

B. **I agree that my data and remainder sample may contribute to the National Genomic Research Library** ☐ YES | NO ☐

Patient name	Signature	Date
		d d / m m / y y y y

If you are signing this form on behalf of someone else (children, adults without capacity or deceased patients) then please sign below.

Parent | Guardian | Consultee name* *please amend as appropriate	Signature	Date
		d d / m m / y y y y

Healthcare professional use only

To be completed by the healthcare professional recording the patient's choices.

Patient category	☐ Adult (made their own choices) ☐ Adult lacking capacity (choices advised by consultee) ☐ Child (parent or guardian choices)	☐ Clinician has agreed to the test (in the patient's best interests) ☐ Deceased (choices made on behalf of deceased individual)
Test type	☐ Rare and Inherited Diseases - WGS	☐ Cancer (paired tumour normal) - WGS
If answer to research choice A is *NO*	☐ Patient would like to discuss at a later date ☐ Patient lacks capacity and no consultee available	☐ Inappropriate to have discussion ☐ Other
Remote consent	☐ Recorded remotely by clinician, no patient signature	
Responsible clinician		
Hospital number		

Healthcare professional name	Signature	Date
		d d / m m / y y y y

Département de Génétique - Pr. Catherine Boileau
HUPNVS – Hôpital Bichat Claude Bernard- 46 rue Henri Huchard 75877 Paris cedex 18

Consentement pour l'examen des CARACTERISTIQUES GENETIQUES d'une personne et la conservation des échantillons dans une banque d'ADN ou un centre de ressources biologiques

IDENTIFICATION du PATIENT (étiquette ou nom, prénom et date de naissance)	**IDENTITE du REPRESENTANT LEGAL (Si patient mineur ou majeur sous tutelle)** **Nom :** **Prénom :** **Lien avec le patient :**

Je soussigné(e) reconnais avoir été informé(e) par le : ☐ Dr.....
☐ Conseiller en génétique .....sous la responsabilité du Dr.....

quant à l'examen des caractéristiques génétiques qui sera réalisé à partir :
☐ Du (des) prélèvement(s) pratiqué(s) sur moi-même
☐ Du (des) prélèvement(s) pratiqué(s) sur mon enfant mineur ou sur la personne majeure placée sous tutelle

Pour (préciser obligatoirement le nom de la pathologie ou l'indication de l'examen réalisé, et sa nature) :

Je reconnais avoir reçu l'ensemble des informations permettant la compréhension de cet examen et sa finalité.
Le résultat de l'examen me sera rendu et expliqué en l'état actuel des connaissances par le médecin qui me l'a prescrit. Ce dernier m'expliquera les moyens de prise en charge nécessaire le cas échéant.

*Je souhaite être informé du résultat de l'examen réalisé oui ☐ non ☐

*J'autorise, dans le respect du secret médical :
- La transmission des informations de mon/son dossier médical nécessaires aux médecins concernés par cet examen des caractéristiques génétiques. oui ☐ non ☐
- La conservation d'un échantillon de matériel biologique issu de mes/ses prélèvements et son utilisation ultérieure pour poursuivre les investigations dans le cadre de cette même démarche diagnostique, en fonction de l'évolution des connaissances. oui ☐ non ☐
- La conservation des données utiles à la gestion de la démarche diagnostique et de mon/son dossier dans des bases de données informatiques déclarées à la CNIL. oui ☐ non ☐

J'ai compris que si une anomalie génétique pouvant être responsable d'une prédisposition ou d'une affection grave était mise en évidence, je devrai permettre la transmission de cette information au reste de ma/sa famille. J'ai été averti que mon silence pouvait leur faire courir des risques ainsi qu'à leur descendance, dès lors que des mesures de prévention, y compris de conseil génétique ou de soins, peuvent être proposées. Ainsi, lors du rendu des résultats, je devrai choisir entre :
- Assurer moi-même cette diffusion d'information génétique aux membres de ma/sa famille.
- Autoriser le médecin prescripteur à cette diffusion d'information génétique aux membres de ma/sa famille.

D'ores-et-déjà, j'autorise, dans le respect du secret médical, l'utilisation des résultats par le médecin prescripteur au profit des membres de ma/sa famille si ces résultats apparaissent médicalement utiles pour eux. oui ☐ non ☐

Des informations génétiques sans lien direct avec ma/sa pathologie mais pouvant avoir un impact sur ma/sa santé ou celle de mes apparentés peuvent être révélées.
Je souhaite que mon/son médecin me tienne informé(e) oui ☐ non ☐

Dans le cadre de la démarche diagnostique, une partie de mon/son prélèvement peut ne pas être utilisée. Elle peut être importante pour la recherche scientifique. Ainsi, sans que l'on puisse me recontacter :
J'autorise le stockage de mon/son prélèvement et son utilisation pour la recherche oui ☐ non ☐

Conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, je dispose d'un droit d'opposition, d'accès et de rectification par l'intermédiaire du Dr.....

Les items comportant un astérisque (*) doivent être obligatoirement renseignés
Tout consentement non signé empêche la réalisation de l'examen.

Fait à	**Le**
Nom, prénom et signature du patient ou de son représentant légal : **Signature du patient mineur ou majeur sous tutelle (si possible) :**	**Signature et cachet du médecin ou du conseiller en génétique :**

SMR020115

NSW GOVERNMENT Health

Facility:

FAMILY NAME	MRN
GIVEN NAME	☐ MALE ☐ FEMALE
D.O.B. ____/____/____	M.O.
ADDRESS	
LOCATION / WARD	
COMPLETE ALL DETAILS OR AFFIX PATIENT LABEL HERE	

CONSENT: GENETIC TESTING

(for all types of genetic and genomic testing for ADULTS, MATURE MINORS and MINORS)

CONSENT FOR GENETIC TESTING is provided by (please tick an option below):

☐ **An adult** (a patient with capacity)

☐ **A mature minor** (a patient with capacity)
I *(the health practitioner)* have assessed this patient to be a minor with capacity to give consent as they have demonstrated sufficient maturity and intellect to fully understand what is proposed.

☐ **A parent / guardian of a minor without capacity**

PROVISION OF INFORMATION TO PATIENT / PARENT / GUARDIAN — To be completed by Health Practitioner

I _____
INSERT NAME OF HEALTH PRACTITIONER

have discussed with *this patient/ parent/ guardian* the reason for conducting the proposed genetic test*. I have informed *this patient/ parent/ guardian* of the nature, possible results, limitations and material risks of the proposed genetic test*, as confirmed on this form by this *patient/ parent/ guardian*.
This patient/ parent/ guardian has been offered additional written information and/or reference to online resources about the genetic testing.

Genetic testing is being conducted for _____

_____
INSERT NAME OF CONDITION(S) OR CLINICAL INDICATIONS

***TYPE OF GENETIC TEST (please tick an option below):**

☐ **Carrier Testing:** a genetic test performed on a person to identify if they carry a gene change.

☐ **Diagnostic Testing:** a genetic test performed on a person to identify a specific genetic condition.

☐ **Predictive/Presymptomatic Testing:** a genetic test performed on a person with a family history of a genetic condition, who does not usually have symptoms at the time of testing, to determine if they have inherited that condition or susceptibility to that condition.

☐ **Prenatal Testing:** a genetic test to identify possible genetic conditions in an unborn baby.

☐ Other (please specify): _____

INTERPRETER PRESENT ☐ Yes ☐ No

_____ _____
INSERT NAME OF INTERPRETER SIGNATURE

____/____/____ ____:____ AM/PM _____
DATE TIME EMPLOYEE ID / PROVIDER NUMBER

_____ ____/____/____
SIGNATURE OF HEALTH PRACTITIONER DATE

NHR00574 20119

CONSENT: GENETIC TESTING (for all types of genetic and genomic testing for ADULTS, MATURE MINORS and MINORS)

SMR020.115

Holes Punched as per AS2828.1: 2012 BINDING MARGIN - NO WRITING

NO WRITING

NSW GOVERNMENT Health

Facility:

FAMILY NAME	MRN
GIVEN NAME	☐ MALE ☐ FEMALE
D.O.B. ____/____/____	M.O.
ADDRESS	
LOCATION / WARD	
COMPLETE ALL DETAILS OR AFFIX PATIENT LABEL HERE	

CONSENT: GENETIC TESTING
(for all types of genetic and genomic testing for ADULTS, MATURE MINORS and MINORS)

PATIENT / PARENT / GUARDIAN CONSENT — To be completed by Patient / Parent / Guardian

I understand and acknowledge that:
- ✓ A blood, saliva or tissue sample will be used to test DNA;
- ✓ I will be told the results by a health practitioner;
- ✓ This is not a "general health test";
- ✓ Results are based on current knowledge that may change in the future;
- ✓ This test will not predict all future health problems;
- ✓ I can change my mind about having the test performed or about receiving genetic test results at any time by contacting the health practitioner;
- ✓ There are a number of different possible results from the testing and these can have implications for *me/my child* and *my/ my child's* family;
- ✓ The results may be of "unknown or uncertain significance", which means they cannot be understood based on current knowledge;
- ✓ There is a chance that some genetic tests could identify other medical conditions (or susceptibility to other medical conditions) as an incidental finding;
- ✓ The genetic test results may identify unexpected family relationships;
- ✓ The genetic test results may affect *my/my child's* ability to obtain some types of insurance (for example, life insurance);
- ✓ Further testing may be needed to finalise the result;
- ✓ The reason for testing and the potential benefits, consequences and limitations involved in the testing have been explained in a way I understand;
- ✓ I have had an opportunity to discuss the information, ask questions and have any concerns addressed and I am satisfied with the explanations and answers to my questions;
- ✓ *My/my child's* results are confidential and will only be released with my consent or as required or permitted by law.

RELEASE OF GENETIC TESTING RESULTS (please tick YES or NO)

► *My/my child's* test results can be shared with relevant health practitioners involved in the care of *my/my child's* family members (genetic relatives): ☐ Yes ☐ No

Genetic relatives are people who are related to an individual by blood, for example, a sibling, parent or descendant of the individual.
Please note: Genetic information can be used and disclosed without consent in order to lessen or prevent a serious risk to the life, health or safety of a genetic relative no further removed than third degree, and, only where the disclosure is made in accordance with the guidelines issued by the Information and Privacy Commission NSW.

► If I cannot be contacted, details of *my/my child's* test results can be released to a nominated individual: ☐ Yes ☐ No

Please provide contact details for an appropriate person:

Name: _____ Phone: _____

Relationship to Patient: _____

ADULT AND MATURE MINOR CONSENT (a patient with capacity)

I consent to genetic testing as discussed with _____
INSERT NAME OF HEALTH PRACTITIONER

_____ _____ ____/____/____
INSERT NAME OF PATIENT SIGNATURE OF PATIENT DATE

PARENT/GUARDIAN CONSENT (a parent / guardian of a minor without capacity)

I consent to genetic testing as discussed with _____
INSERT NAME OF HEALTH PRACTITIONER

for _____
INSERT NAME OF MINOR

_____ _____ ____/____/____
INSERT NAME OF PARENT/GUARDIAN SIGNATURE OF PARENT/GUARDIAN DATE

_____ _____
RELATIONSHIP TO MINOR OF PARENT/GUARDIAN ADDRESS

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SMR020115

DO NOT PRINT

NO WRITING

R421 Pulmonary Fibrosis Familial

Testing Criteria

Interstitial Lung Disease (ILD) and **ONE** of the following:

1. ILD, no identifiable cause or association, and age <50 years.
2. Family history of ILD regardless of identifiable cause or association
3. For suspected telomerase complex variants, testing to be considered in the absence of 1. and 2. above if one or more of the following are present in addition to ILD:
   - unexplained haematological abnormalities including macrocytosis, anaemia, thrombocytopenia, leukopenia and/or isolated lymphopenia;
   - unexplained haematological abnormalities including macrocytosis, anaemia, thrombocytopenia, leukopenia and/or isolated lymphopenia; premature greying,
   - or unexplained liver function abnormalities.
   - Consideration of lung transplantation

Other panels available that cover some of these genes – e.g. R91 Cytopenia

Genes tested
ABCA3
ACD
AP3B1
CSF2RA
CSF2RB
CTC1
DKC1
HPS1
HPS4
MARS
MUC5B **
NAF1
NHP2
NKX2-1
NOP10
PARN
RTEL1
SFTPA1
SFTPA2
SFTPB
SFTPC
TERC
TERT
TINF2
ZCCHC8
RPA1
HCK

UK national genomic test directory - v8.0 May 2025 – https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-inherited-disease-eligibility-criteria-v8.0.pdf

PanelApp UK - https://panelapp.genomicsengland.co.uk/panels/1174/

Genetic counselling is key!

Manage uncertainty of results

1 in 5 pathogenic results

Impact on:

- ILD follow-up frequency
- Supportive care
- ILD treatment (early antifibrotic +/- avoid high-dose immunosuppression)
- Lung transplant referral

Who else to test in the family?

Offer ILD screening (*via ILA pathway?*)

Research participation

Example 1

45 yo male

ILD diagnosis: PPFE

Other features: non-specific haematological abnormalities (high MCV)

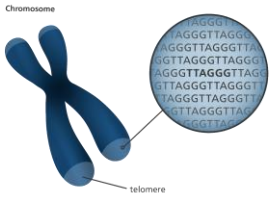
R421 panel: RTEL1 VUS

Telomere length < 1st percentile (critically short)

Mother and sister healthy – and each has different RTEL1 VUS

Progression:

- Referred for transplant – not eligible due to bone marrow abnormalities, severe anxiety
- Extremely rapid progression within 1 year
- Started on nintedanib – stopped due to stroke
- Severe weight loss
- Currently on best supportive care



Familial Interstitial Pneumonia (FIP) / Familial ILD clinics in the UK

NHS Manchester University NHS Foundation Trust — Manchester

NHS Royal Devon University Healthcare NHS Foundation Trust — Exeter

NHS Royal Papworth Hospital NHS Foundation Trust — Cambridge

Research

(i.e., leukocyte telomere length, biobanks, screening relatives)

Evaluation includes:

- Multidisciplinary team clinical visit (ILD nurse, physician +/- Genetic counsellor, Clinical Genetics physician, trainees etc.)
- Identify family history, family dynamics (!)
- Informed consent for genomic testing (R421 panel)
- Research consenting if applicable
- Follow-up visit to feed back results
- Offer Clinical Genetics referral / ILD screening – **need pathway (!)**

In Exeter:

- We accept national referrals
- Results are discussed in a **National Genetics-ILD MDT**
  - ILD nurses, physicians, coordinator
  - Genetic scientists, Haematology, Hepatology
  - International expertise

R421 Pulmonary Fibrosis Familial

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   - unexplained haematological abnormalities including macrocytosis, anaemia, thrombocytopenia, leukopenia and/or isolated lymphopenia; premature greying,
   - or unexplained liver function abnormalities.
   - Consideration of lung transplantation

Contact us:

Pilar Rivera-Ortega
p.riveraortega@nhs.net

Stefan Stanel
s.stanel@nhs.net

Problems

We are dealing with rare disorders, caused by potentially multiple gene variants (some unknown)

Clinical problems:

- No clear list of centres offering ILD genomic testing and associated services
- No agreed set of best practices internationally for arranging ILD genomic testing

Test interpretation problems:

- Slow procedure to classify variants of uncertain significance (VUS) – needs MDT discussion, better research databases

Genomic Testing of Patients with Interstitial Lung Disease: Current International Practice

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Rationale

- Gene-environment interactions play a significant role in the pathogenesis of interstitial lung disease (ILD), with 20-30% of ILD risk attributed to genetic predisposition.
- Genomic testing is not routinely integrated into ILD clinical practice or guidelines.
- There is no international consensus on best practices for ILD genomic testing.

Aims

- We aimed to explore current practices in ILD genomic testing on a global scale to identify barriers and inform strategies for broader implementation.

Methods

- Semi-structured interviews were conducted with ILD experts to understand current practice for genomic testing of ILD patients and predisposed relatives.
- Experts were selected based on their publication history or clinical experience with Genetics in ILD, ensuring wide international representation.
- Only one expert per center was interviewed to avoid duplication of responses.
- Interviews followed an open, semi-structured format using broad predefined topics including training and clinic infrastructure, familial ILD case finding, genomic tests and methods, impact on care (including relatives), research, and governance.
- Interview transcripts were analyzed using deductive qualitative methods.

Results

- Seventeen interviews were conducted, with a median duration of 39 minutes (range 32 – 61).
- A wide variety of approaches to genomic testing in ILD practice were identified.
- Four key theme groups emerged (further details in Table 1):

1. **Setting of testing:** The need for genetic counselling, documented informed consent and appropriate training of ILD clinicians to interpret the results, given the impact on ILD patients and their relatives
2. **Impact on clinical care:** The influence of genomic testing on clinical decisions, and support by multidisciplinary teams
3. **Specific tests:** Heterogeneity in the choice of tests (e.g. telomere length measurement, gene panels, sequencing) with the sequence of testing, sample types, and laboratory methods often determined by local availability and cost
4. **Data safety:** Concerns were raised on governance and data handling, with several experts highlighting gaps in how genomic data is shared and regulated.

Conclusions and next steps

- There is global heterogeneity in ILD genomic testing
- The themes identified in this study will help inform a framework to improve access to testing and define best practices
- The next steps are to conduct an *international mapping* of access to ILD genomic testing and a *Delphi survey* for consensus on the core features needed for familial ILD services.
- This work will help to raise awareness, increase worldwide collaboration and support the development of clinical pathways.

Table 1. Key themes identified in genomic testing for patients with ILD.

Training and experience
Continuing Medical Education (CME) in Genetics for ILD clinicians who want to request genomic tests is recommended
Training should cover relevant local governance and legal requirements
Experience is currently gained through observation, trial-and-error, mentoring, short Genetics courses, reading of published literature, involvement in research
Collaboration with Genetics specialists is recommended to increase skills
Service infrastructure
The clinician needs dedicated time for evaluating familial ILDs
Genetic counselling is necessary, but its availability is variable
Access to Genetics expertise to interpret uncertain results is required
Access to psychological support for patients is helpful
Managing the costs of testing can be difficult
Patients typically tested
Patients diagnosed with ILD having one or more relatives with ILD
Sporadic ILD cases with extrapulmonary features suggestive of telomeropathy
Young ILD patients (<50 years of age)
Tests requested
Genetic sequencing with standardized panel testing is generally available
Leukocyte telomere length measurement is considered useful, but its availability is low
The testing methods, sample types and the order of tests are considered important, but recommendations are based on local availability of tests
Impact on care
Multidisciplinary discussion of cases including input from Genetics is recommended
Genomic testing influences clinical decisions (i.e. choice of ILD treatment)
ILD patients with genomic findings may require multidisciplinary care for complex syndromes (hematology, hepatology, pediatrics, transplant etc.)
ILD screening of relatives is recommended, but there is no guidance on its implementation
Genetic evaluation of asymptomatic relatives is useful if the index case has a confirmed pathogenic genomic finding
Governance
Effective and honest communication with patients is essential
Patients should be counselled prior to testing and informed consent needs to be documented
Privacy and confidentiality need to be balanced against use of data to help other affected relatives
No consistent procedure exists to share genomic data to help in the care of relatives
Patients who are tested usually inform their relatives themselves
Consent forms for genomic testing should capture a nominated person other than the patient to receive results
Research
The majority of patients want to take part in research
Biobanking of samples is encouraged
Prospective registries would be helpful
Collaboration (including internationally) is needed for larger studies and to standardize tests
Raising awareness and community outreach can help increase research recruitment

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International mapping of ILD genomic testing

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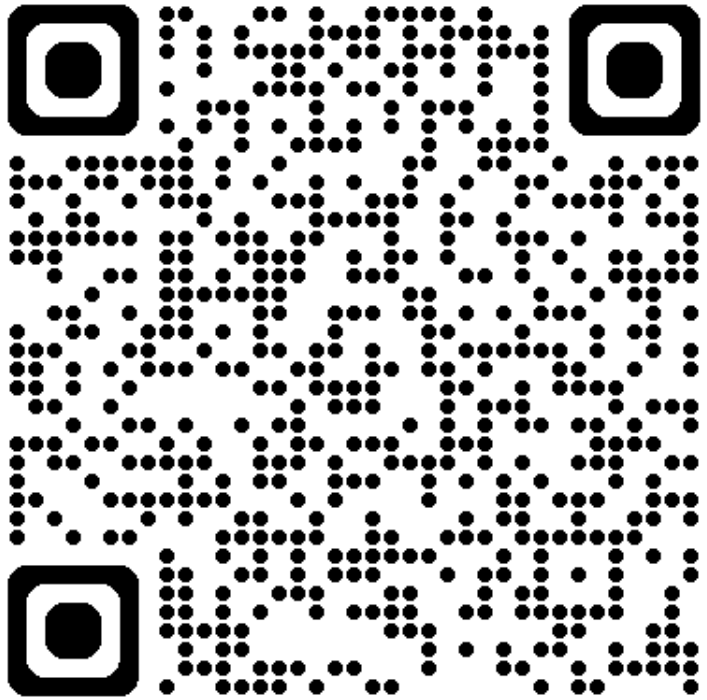
THE UNIVERSITY OF SYDNEY

Genomic Testing for Interstitial Lung Disease



International Delphi Survey and Global Mapping

Qualitative analysis – expert interviews

- Semi-structured individual interviews (n=17)
- Median duration 39 min (range 32-61)
- 100+ pages of transcripts
- Deductive qualitative analysis based on initial structure (expert perspective)
    - Experience/training
    - Infrastructure
    - Identifying cases
    - Genomic tests requested
    - Impact of care
    - Research
    - Governance

Very passionate people!

→ Key themes

Expert interviews – key themes

Training and experience

Continuing Medical Education (CME) in Genetics for ILD clinicians who want to request genomic tests is recommended

Training should cover relevant local governance and legal requirements

Experience is currently gained through observation, trial-and-error, mentoring, short Genetics courses, reading of published literature, involvement in research

Collaboration with Genetics specialists is recommended to increase skills

"I went to their centre"

"I imported the know-how"

"being able to do that in a formal structured way [training and research] helped me understand nuances that I would not have grasped by myself"

"it's not as straightforward as here is a list of tests that you do"

Expert interviews – key themes

Service infrastructure

The clinician needs dedicated time for evaluating familial ILDs

Genetic counselling is necessary, but its availability is variable

Access to Genetics expertise to interpret uncertain results is required

Access to psychological support for patients is helpful

Managing the costs of testing can be difficult

"a centralized way of dealing with VUSs."

"the ideal in my mind would be a dedicated clinic, that encompasses the ILD/respiratory physician, a clinical geneticist and a genetics counsellor, all sort of in the same clinic, working together at the same time"

"you have to start with the geneticists from the beginning and then grow together"

"I don't think in the routine clinic there's time for it"

"these conversations are difficult. They often take a lot of time"

"it took me hours to figure out the paperwork"

Expert interviews – key themes

Patients typically tested

Patients diagnosed with ILD having one or more relatives with ILD

Sporadic ILD cases with extrapulmonary features suggestive of telomeropathy

Young ILD patients (<50 years of age)

"There are a lot of people with genetic pulmonary fibrosis. It's not particularly rare, particularly when you work in an ILD clinic"

"clearly the ones that have 2, 3, 4 family members, those are the highest priority"

"you have to select the right patients"

Expert interviews – key themes

Tests requested

Genetic sequencing with standardized panel testing is generally available

Leukocyte telomere length (LTL) measurement is considered useful, but its availability is low

The testing methods, sample types and the order of tests are considered important, but recommendations are based on local availability of tests

"I only do genetic sequencing and for some specific patients I also ask for telomere length analysis but after the genetic analysis"

"I think telomere length testing should be done on everybody coming to the clinic actually, that should be part of our standard"

"the question ends up being less medical and probably more financial"

"sometimes for the same patient, or for different patients, we would order different genetic panels, because one is covered by insurance, and another is not so"

Expert interviews – key themes

Impact on care

Multidisciplinary discussion of cases including input from Genetics is recommended

Genomic testing influences clinical decisions (i.e. choice of ILD treatment)

ILD patients with genomic findings may require multidisciplinary care for complex syndromes (hematology, hepatology, pediatrics, transplant etc.)

ILD screening of relatives is recommended, but there is no guidance on its implementation

Genetic evaluation of asymptomatic relatives is useful if the index case has a confirmed pathogenic genomic finding

"what I see in my patients is that they get some sort of clarity"

"it does have an impact, mostly on the things that you wouldn't do"

"when I find variants, we discuss them in the MDD"

"be more vigilant about progression"

"You are the key person also for the family"

Expert interviews – key themes

Governance

Effective and honest communication with patients is essential

Patients should be counselled prior to testing and informed consent needs to be documented

Privacy and confidentiality need to be balanced against use of data to help other affected relatives

No consistent procedure exists to share genomic data to help in the care of relatives

Patients who are tested usually inform their relatives themselves

Consent forms for genomic testing should capture a nominated person other than the patient to receive results

"one of the biggest challenges is actually dealing with the psychological ramifications of the test"

"with the advent of AI and really advanced technologies, the question of the de-identification will eventually have to be addressed"

"you should be able to answer questions in an informed way when you are consenting a patient"

"perhaps there might be an opt out system where, if a person didn't want their results shared, they could do that"

Expert interviews – key themes

Research

The majority of patients want to take part in research

Biobanking of samples is encouraged

Prospective registries would be helpful

Collaboration (including internationally) is needed for larger studies and to standardize tests

Raising awareness and community outreach can help increase research recruitment

“how do we turn a VUS into a pathogenic result?”

“targeted treatments for particular genetic abnormalities. That'll be the game changer”

“we could be collaborating internationally a lot better”

“to include a specific paragraph for research in the consent”

What do **you** think about genomic testing for ILD?

- Not useful clinically?
- No time to do it?
- Not really available?
- Difficult to understand/interpret?
- Game changer for ILD?
- Will become a big part of practice?

Feel free to contact us:

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