



Update on the Metformin in adults with Li Fraumeni Syndrome (MLI) trial

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LFS 2024 14.09.2024

Talk Overview



Overview on MILI




Trial Update



Public and Patient Involvement
in MILI

Overview on MILI

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Metformin in adults with Li-Fraumeni Syndrome

- **Precision-Prevention Trial** – preventing cancer in individuals who are at higher risk
- Does metformin prevent the development of cancer?
- What **scientific questions** can we answer about how cancers develop in individuals with LFS?
- How can we develop a trial **with** the LFS community?



[Home](#) > [News](#) > Oxford to launch UK's first trials unit dedicated to precision-prevention and early detection studies

Oxford to launch UK's first trials unit dedicated to precision-prevention and early detection studies

[CANCER](#) [FUNDING](#) [HEALTH](#) [MEDICAL SCIENCES](#) [RESEARCH](#)

Oxford researchers have been given a £1 million boost to support their strategy for developing new cancer prevention treatments and early diagnostic tools for people at high risk of cancer.

The UK's MILI team

Chief Investigator

Prof Sarah Blagden
Medical Oncologist,
University of Oxford.

Translational Leads

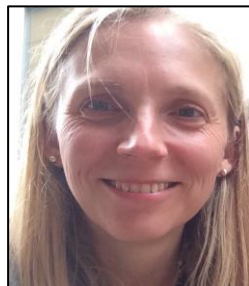
Dr Simon Lord,
Consultant Medical
Oncologist,
University of Oxford.

Prof Gareth Bond,
Genetics and Genomics
University of Birmingham

Prof Xin Lu
Ludwig Institute
University of Oxford

Radiology Lead

Dr Jamie Franklin
Consultant Radiologist
Bournemouth
University



Principal Investigator Oxford

Dr Lara Hawkes
Consultant Cancer
Geneticist, University
of Oxford. BRCA risk
stratification



Principal Investigator Manchester

Dr Emma Woodward
Consultant Cancer
Geneticist, University
of Manchester.



Principal Investigator London

Dr Angela George
Consultant Cancer
Geneticist, Royal
Marsden Hospital,
London



Principal Investigator Cambridge

Prof Marc Tischkowitz
Consultant Cancer
Geneticist, University
of Cambridge



Statistician

Prof John Norrie
Statistics, University of
Edinburgh

Coordinating Principal Investigator



Dr Helen Hanson
Consultant Cancer
Geneticist, St Georges
Hospital, London

Sponsor:



Funders:



Integrated PPI representatives



Dr Pan Pantziarka



Elizabeth Sam



Verity Easton



**The George Pantziarka
TP53 Trust**

Helping families with Li Fraumeni Syndrome
and related conditions

What questions is MLI asking?

- Does metformin prevent or delay the emergence of cancer in people with LFS – **provide evidence for licencing decision**
- Why does cancer happen in LFS? – **insights into tumorigenesis from serial blood sampling, measurement of mitochondrial activity etc.**
- Are some P53 mutations more cancer-forming than others? – **sequencing correlation with outcome to provide prognostic information**
- What is the impact of yearly prevention and/or surveillance on quality of life? – **QOL data (fear of cancer scale)**

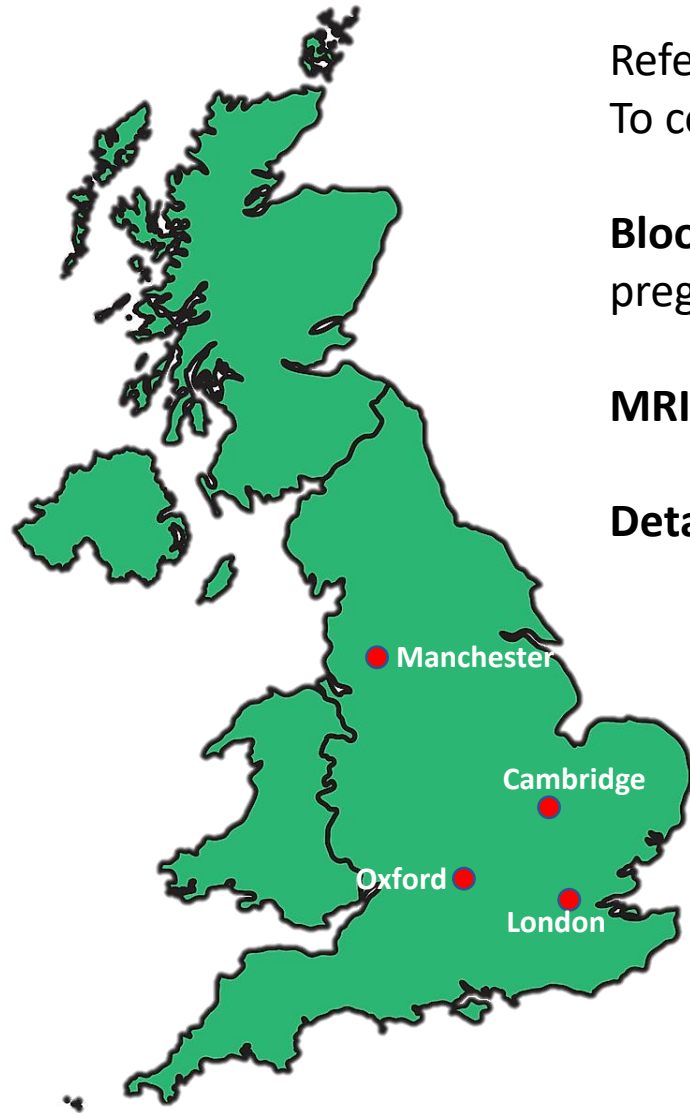


Recruitment

UK Cancer Genetics network and integrated into the surveillance pathways for adults with LFS: comprised of 24 UK centres.

Eligibility: Eligible participants are **aged >16 years old with confirmed form of LFS**

What happens then?



Referred to nearest of four Major Genetics Centres
To consent and undergo blood tests and MRI

Blood tests: full blood count, liver and kidney tests,
pregnancy test

MRI: Whole body (and brain)

Detailed questionnaire: family history, diet etc.



The Randomisation Process



Randomised

1:1

Cancer Surveillance



Cancer Surveillance + metformin



Updates by phone from
Oxford-based study nursing
team

Metformin arm of the study



6 month's supply of metformin delivered by post

One in the morning for 2 weeks



6 monthly calls

One in morning, one in evening for 2 weeks



Two in morning, one in evening for 2 weeks



Two in morning, two in evening



500mg

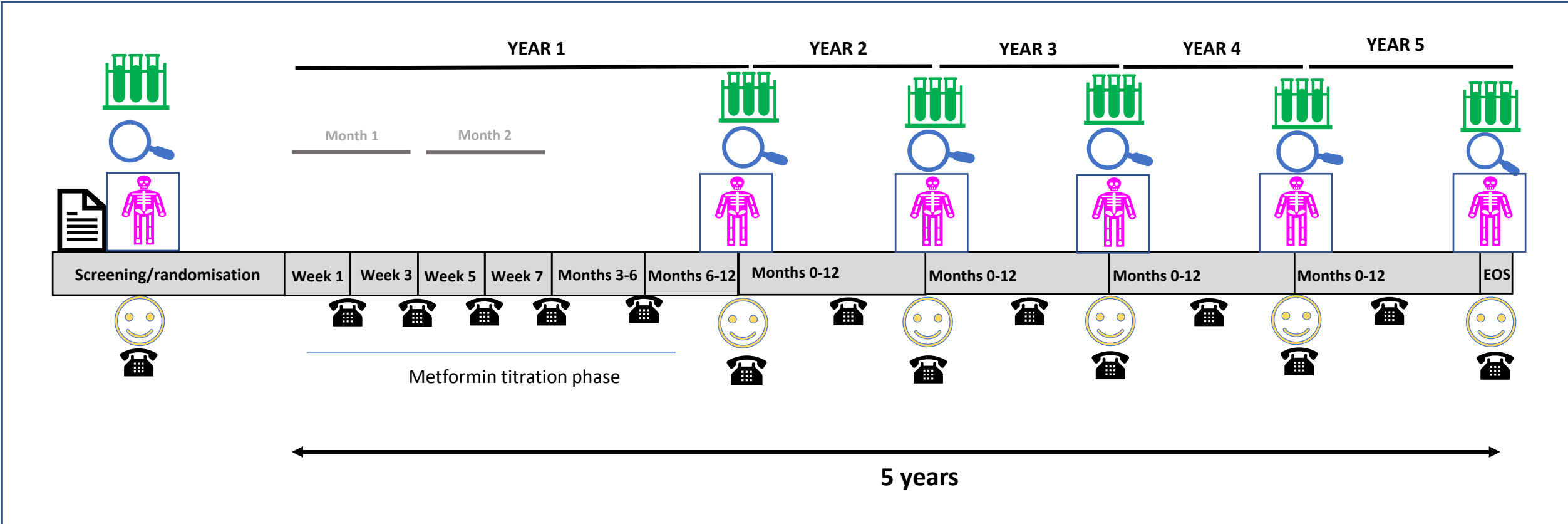
1000mg

1500mg

2000mg

Dose Titration Phase

MILI EVENTS



PROCEDURES



Patient information and consent form



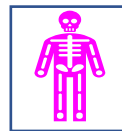
Safety review with haematology & biochemistry blood tests



Telemed Safety and symptom review. Metformin delivered directly to patients.



Examination and Dermatological Assessment



Whole Body & Brain MRI scan



Quality of Life Questionnaires

What questions is MRI asking?

- Does metformin prevent or delay the emergence of cancer in people with LFS – **provide evidence for licencing decision**
- Why does cancer happen in LFS? – **insights into tumorigenesis from serial blood sampling, measurement of mitochondrial activity etc.**
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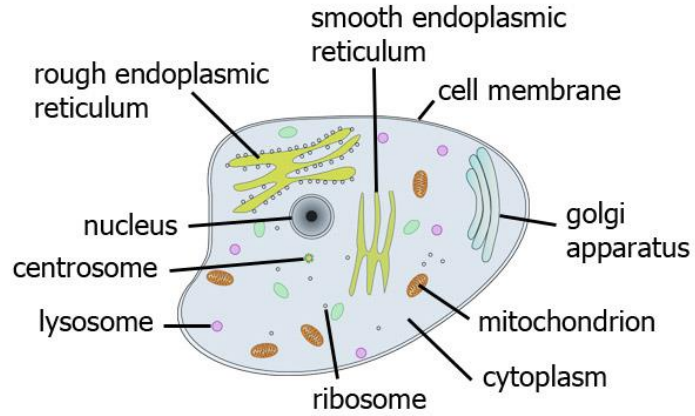
What are the scientific questions?

- Does metformin prevent or delay the emergence of cancer in people with LFS – **provide evidence for licencing decision**
- Why does cancer happen in LFS? – **insights into tumorigenesis from serial blood sampling, measurement of mitochondrial activity etc.**
- Are some P53 mutations more cancer-forming than others? – **sequencing correlation with outcome to provide prognostic information**
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How does metformin work – direct or indirect?



Direct

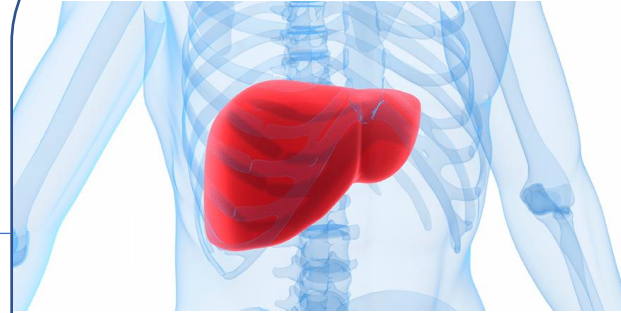


Measure by genetic signature from blood



Computational comparison

Indirect

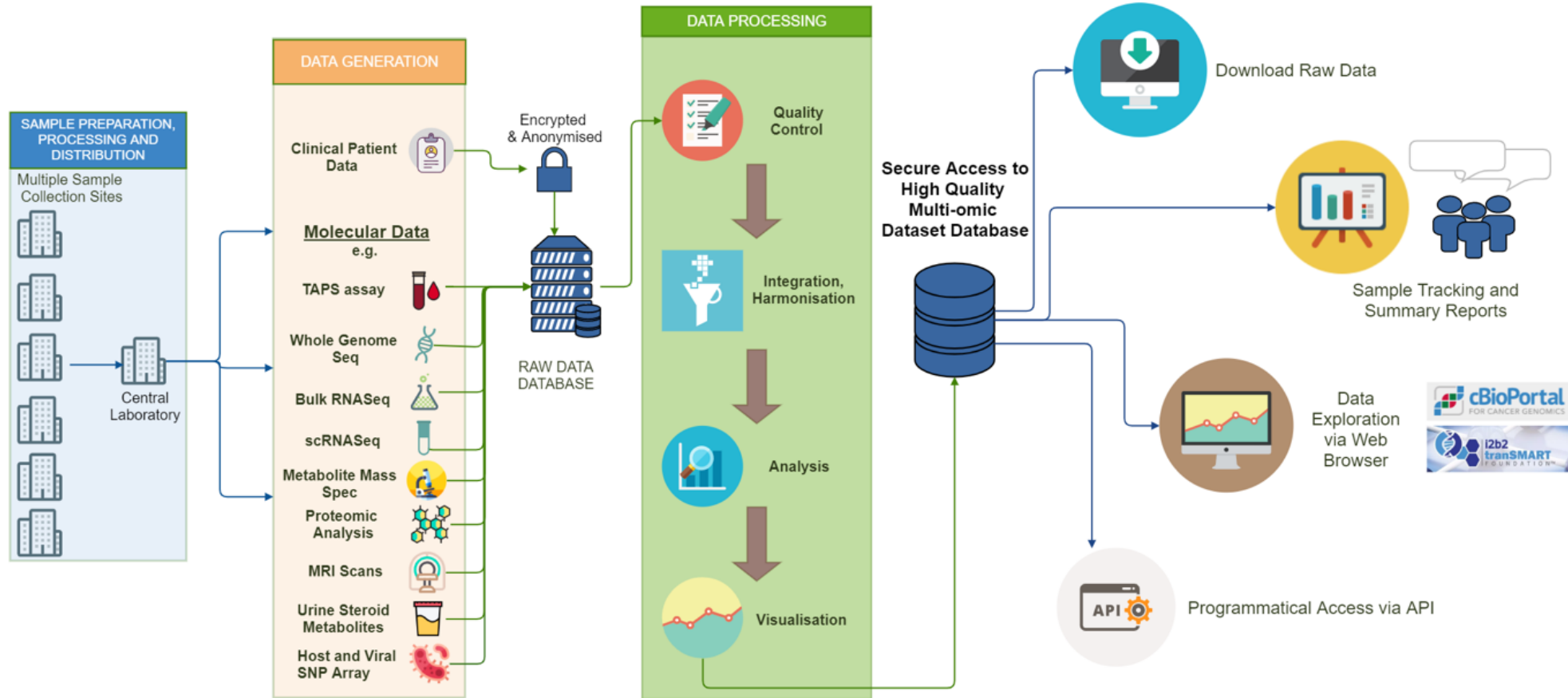


Lower levels of insulin, sugar and growth factors

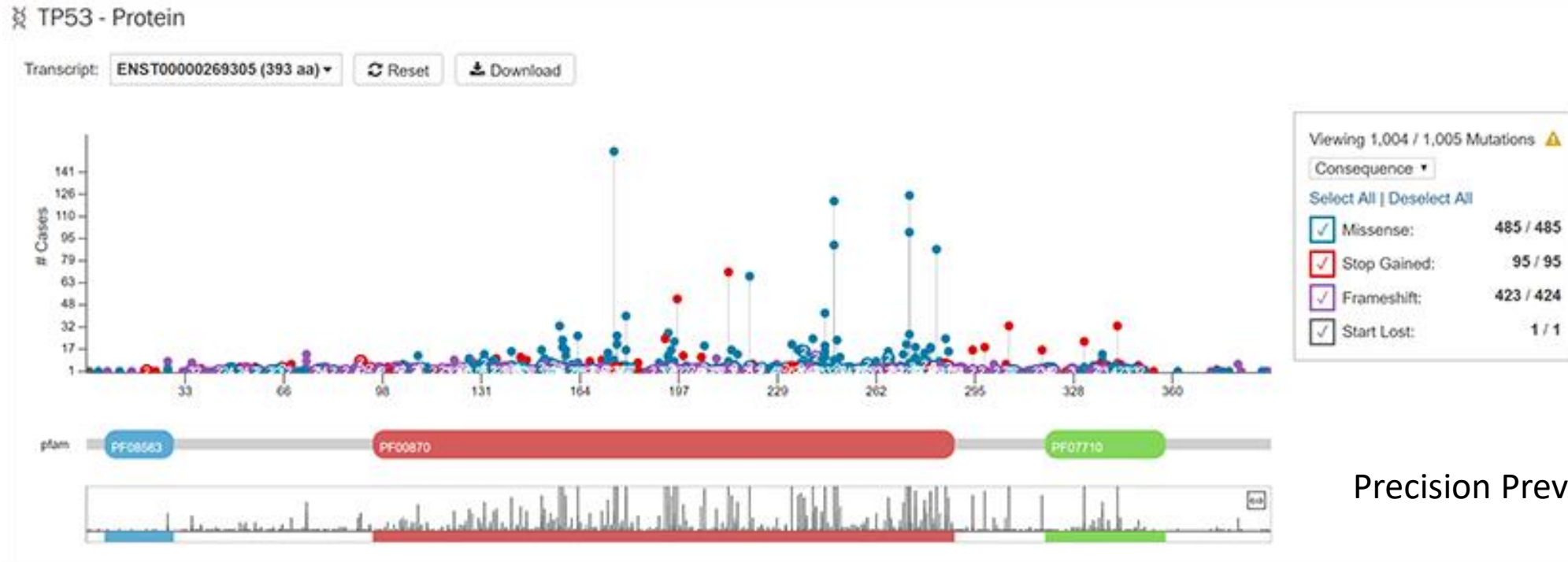
Better health – lower cancers

Measure by levels of insulin, IGF1, glucose, PI3K pathway from blood tests

Our Translational Data Platform



P53 mutations and cancer



Precision Prevention Trial

Are certain P53 mutations linked to certain cancers?

Are there markers in the blood that can be used to track the emergence of cancer? – methylation signature, circulating anti-P53 antibodies, cfDNA, plasma markers (mass spectroscopy).

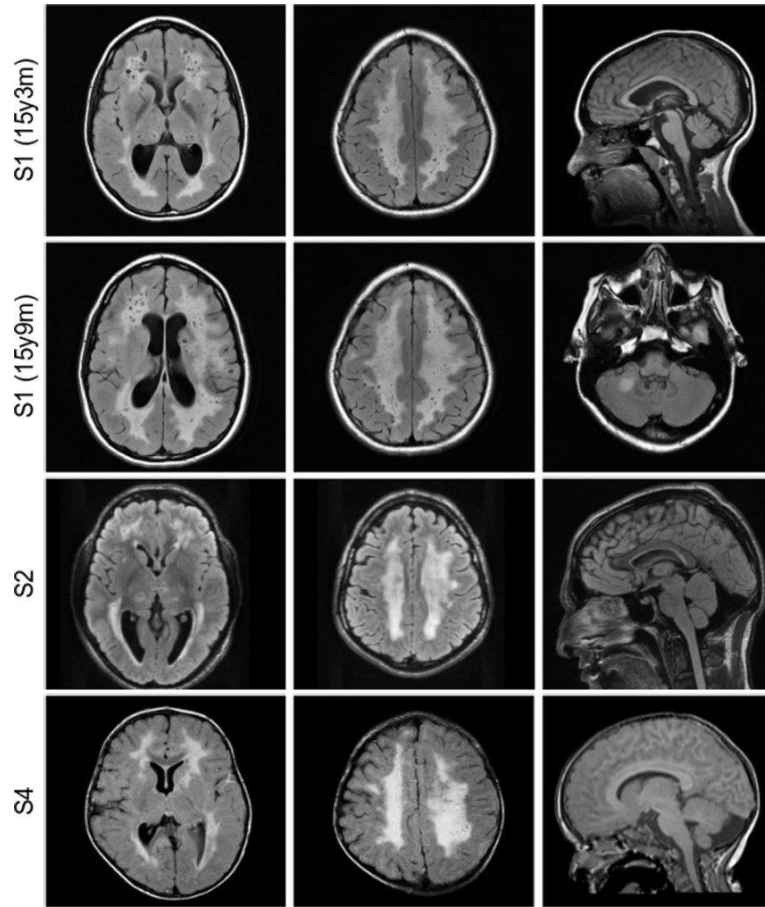
Sequencing of tumours to compare markers and P53 mutations

Quality of Life

- Yearly Quality of Life Questionnaires – similar to those used in SIGNIFY study – SF12v2, Cancer Worry Scale, Impact of Events scale
 - SF12 (short form) – 12 questions – quick overview of general health, energy and stress levels
 - Feelings about screening and its impact on mood & thoughts
 - How LFS impacts on a day to day basis (past 7 days)
- Metformin compliance questionnaire (metformin arm)











Educating next generation of radiologists



MRI images collected in large anonymised database to teach radiologists



Key points about the MLI study

- Designed with close involvement from LFS community 
- One of the UK's first Precision Prevention trials 
- Will tell us if metformin delays/reduces risk of cancer so that metformin could be licenced 
- Will use a Translational Data Platform to tell us how metformin works 
- Will collect blood to test biomarkers that may predict cancer early 
- Will provide coordinated MRI for people with LFS around the UK
- Will tell us whether certain mutations are more cancer-prone than other (risk-adjusted screening) 
- Will validate SIGNIFY's quality of life findings (about the benefits of MRI) in a larger patient group
- Will provide a database to teach WB+B MRI reporting 
- Will seed future prevention studies (e.g. using vaccines) 

Trial Update

20

Trial Status

- Trial started recruiting in **December 2023**
- Sites that are open: Oxford, Nottingham, Cambridge and Guys and St Thomas
- 12 patients currently enrolled



Trial Status

- Slower than hoped recruitment because we are still waiting for green light that NHS England's Specialist Commissioning will refund WB-Brain MRIs at the main study centres.





Under Review
NIH - MILI

approx. 250 adults

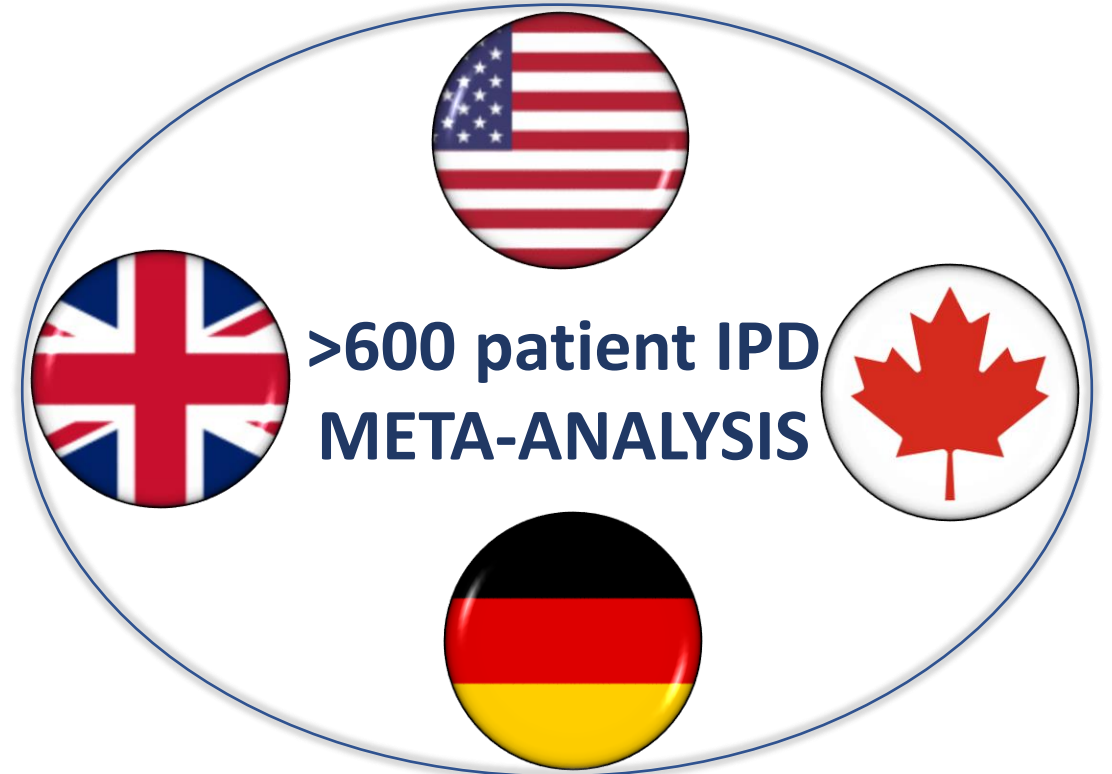


Open
MILI
approx. 220 adults



Funded
German -MILI
adults and children
CI: Christian Kratz

SHARED PROTOCOL



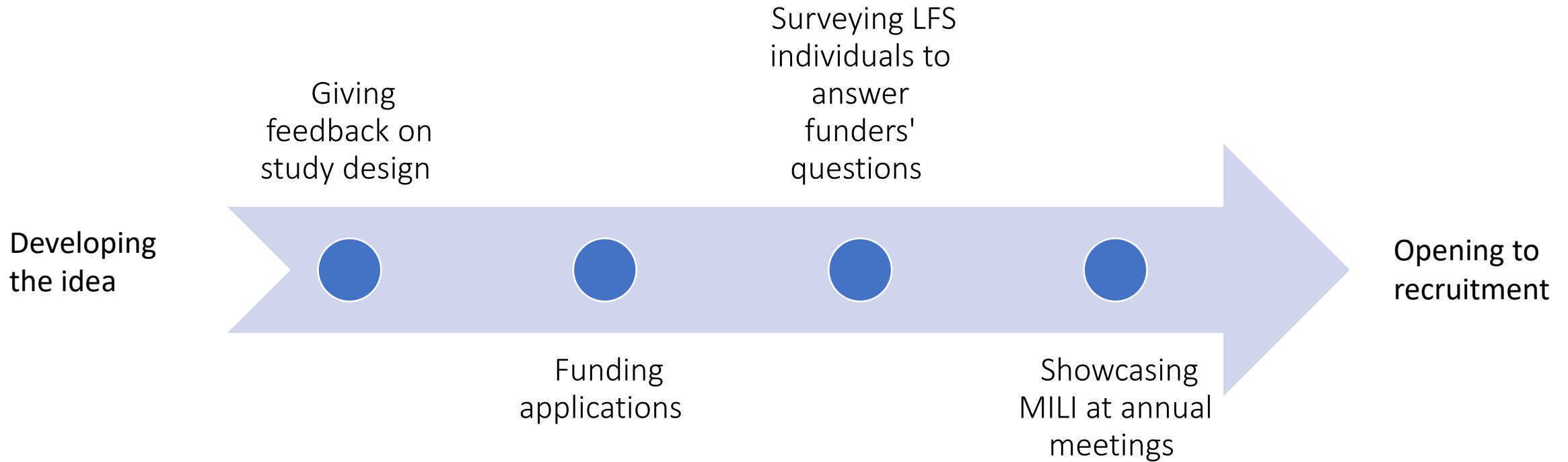
Patient and Public Involvement





The George Pantziarka TP53 Trust

Helping families with Li Fraumeni Syndrome
and related conditions

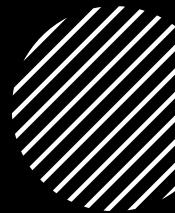


*"It has been more like a **partnership** than a formality that has to be completed."*

- Pan Pantziarka Chair of the George Pantziarka TP53 Trust



Development of a researcher- patient buddy scheme



Idea for a more innovative way to undertake PPI

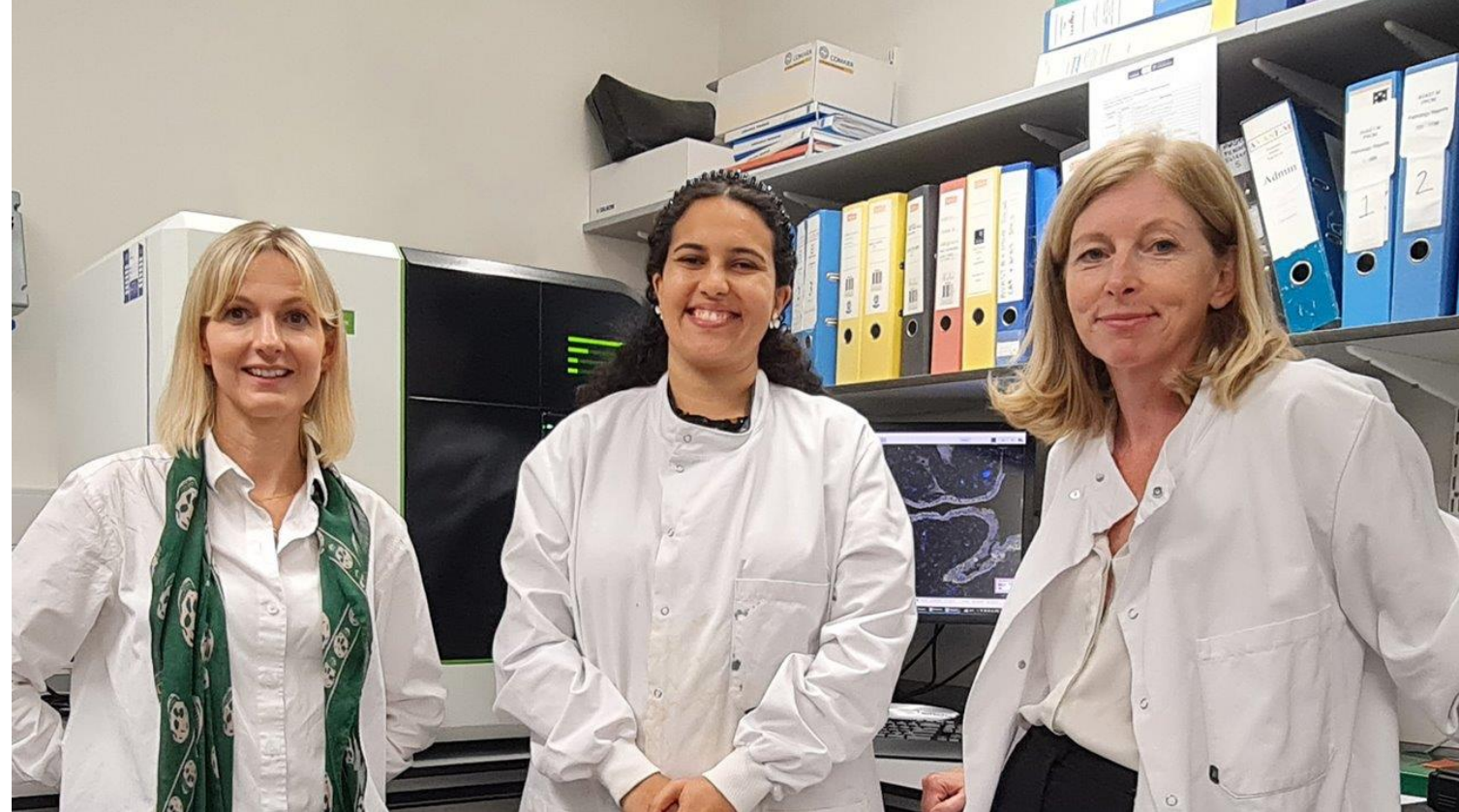


Starting with students and early career researchers so it becomes embedded in their practice



It is a simple idea to buddy a researcher with a PPI member related to their research.

Initial face-to-face meeting
Then quarterly video meetings



Buddy Scheme

- A Lab Visit in ORCRB
- Regular video calls
- Ava's day of work experience

NIHR | National Institute
for Health Research



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Thank you for listening

Thank you!



Dr Pan Pantziarka



Elizabeth Sam



Verity Easton

Also ...



David Malkin
Toronto



Payal Khincha
NCI



Christian Kratz
Hannover



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