



The UK metformin in Li Fraumeni (MILI) Study

Sarah Blagden

Funded by NIHR & CRUK

The UK's MILI team

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Translational Leads

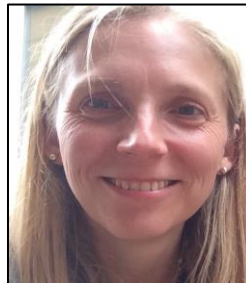
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Sponsor:



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)

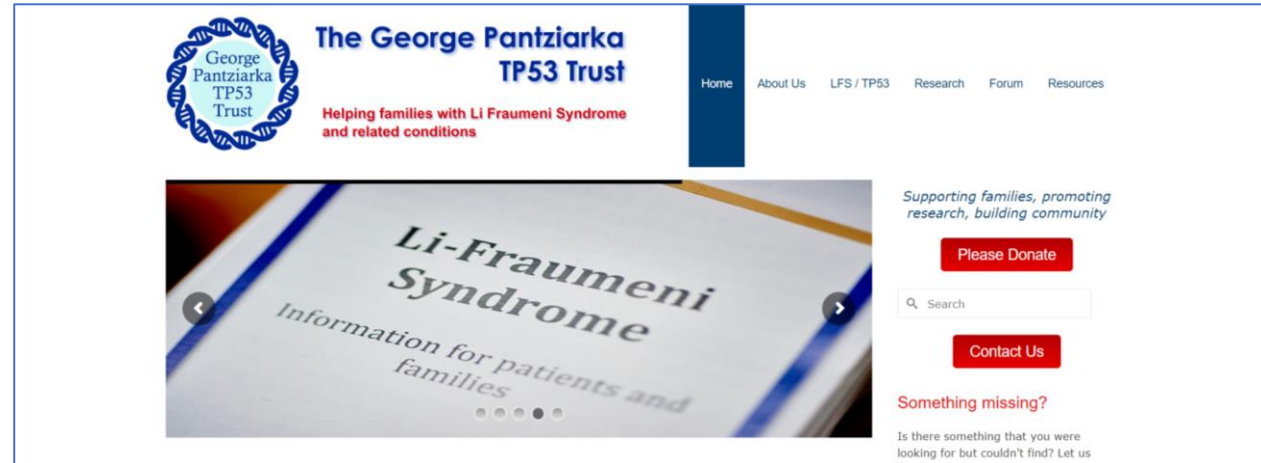
Study Design and Recruitment

- 224 people aged ≥ 16 y with LFS in UK, recruitment commences January 2023
- **Randomised 1:1 to cancer surveillance and metformin versus cancer surveillance alone**
- Precision-Prevention Design
- Those randomised to metformin will receive it by post, have telephone side effect assessment
- Surveillance will comprise annual whole body and brain MRI and dermatological examination
- Four centres: Oxford, London (RMH), Cambridge and Manchester will act as Trial Centres for consenting and scanning with regional genetics units acting as research sites
- Recruit over 2 years and on metformin for 5 years
- Data pooled into a single international meta-analysis.

How are participants identified?



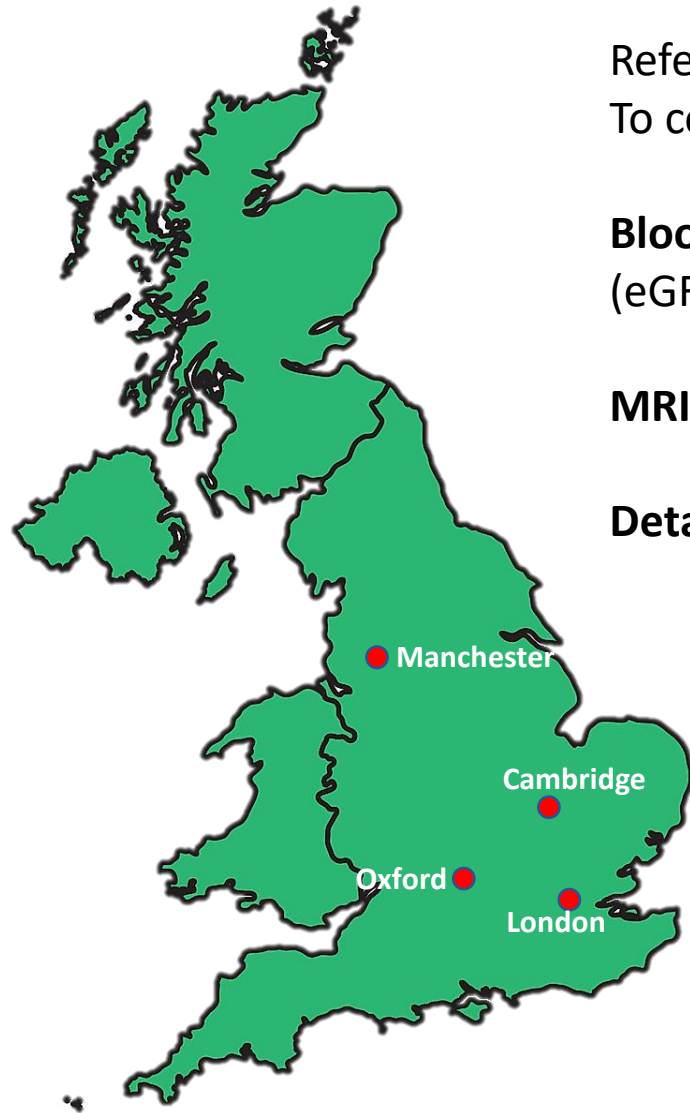
**Dr Helen
Hanson**



Eligible if:

- Confirmed pathogenic form of LFS
- Aged 16 or over
- Not currently taking metformin
- No current cancer or having chemotherapy (for last 6 months)
- Not pregnant
- No serious heart, kidney or liver problems
- Not diabetic
- Can tolerate MRI (ie no pacemaker etc)

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 (eGFR), 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

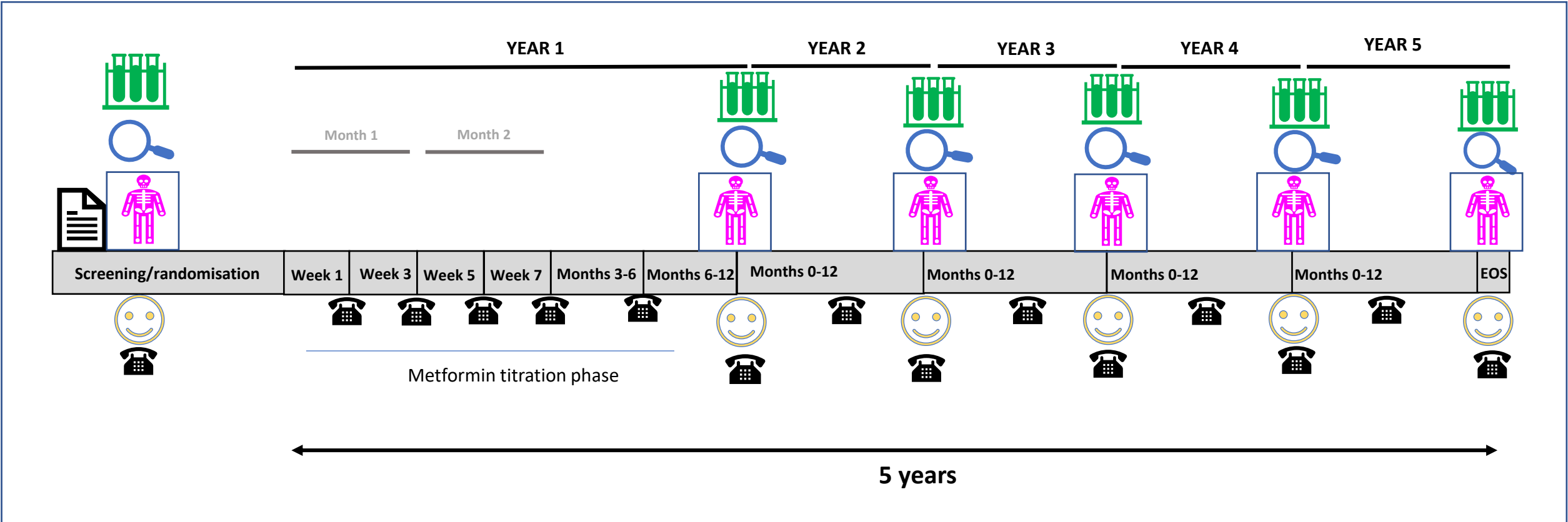
1000mg

1500mg

2000mg

Dose Titration Phase

MILI EVENTS



PROCEDURES



Patient information and consent form



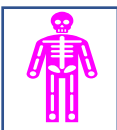
Safety review with haematology & biochemistry blood tests



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



Examination and Dermatological Assessment



Whole Body & Brain MRI scan



Quality of Life Questionnaires

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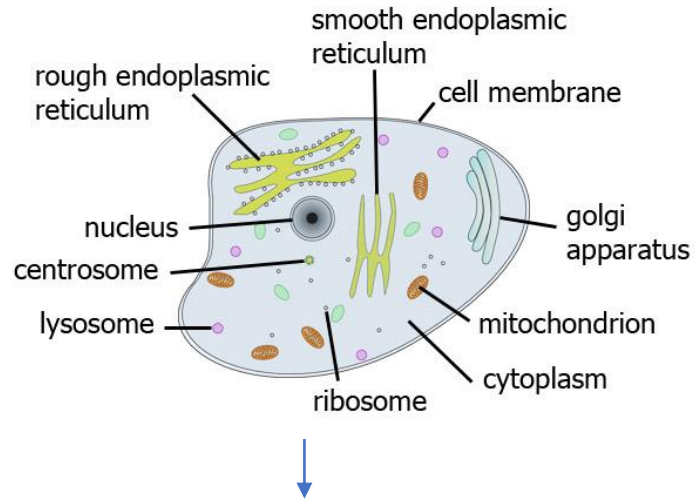
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How does metformin work – direct or indirect?

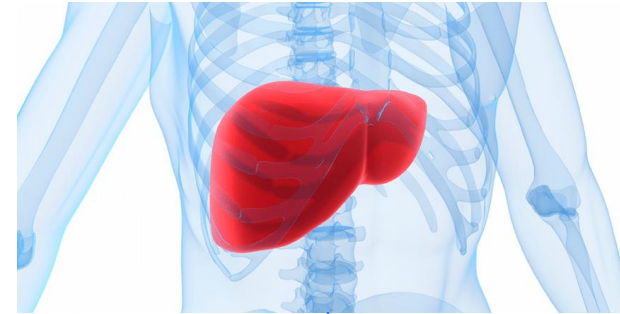


Direct



Measure by genetic signature from blood

Indirect



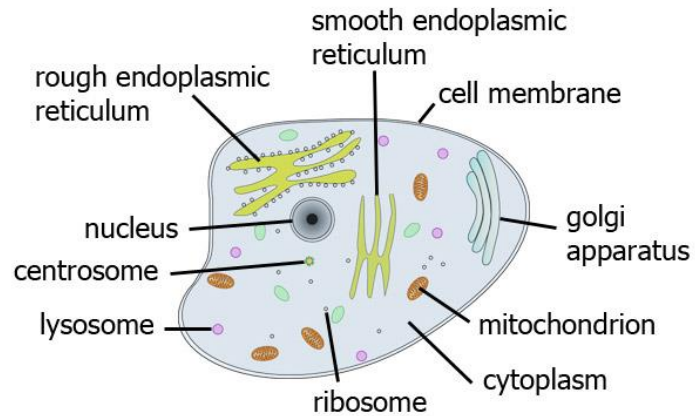
Lower levels of insulin, sugar and growth factors

Better health – lower cancers

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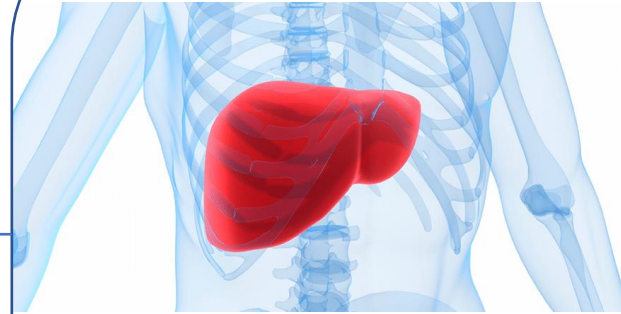


Direct



Measure by genetic signature from blood

Indirect



Lower levels of insulin, sugar and growth factors

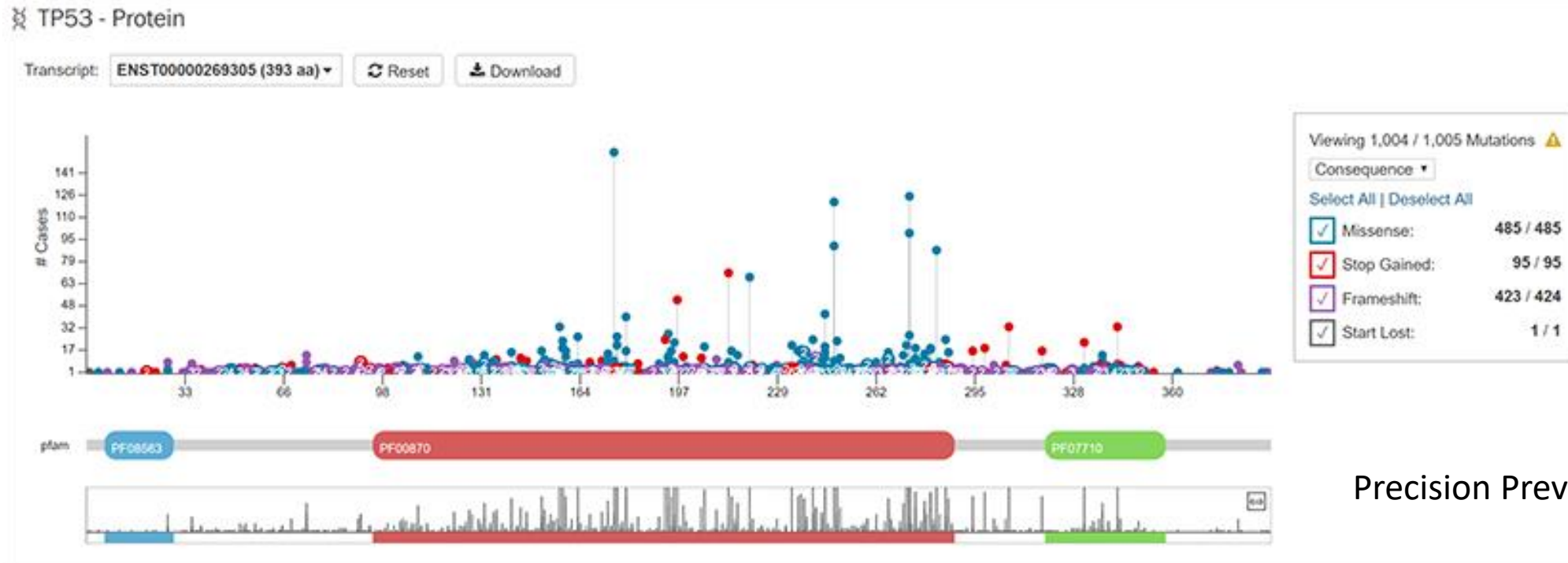
Better health – lower cancers

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



Computational comparison

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?

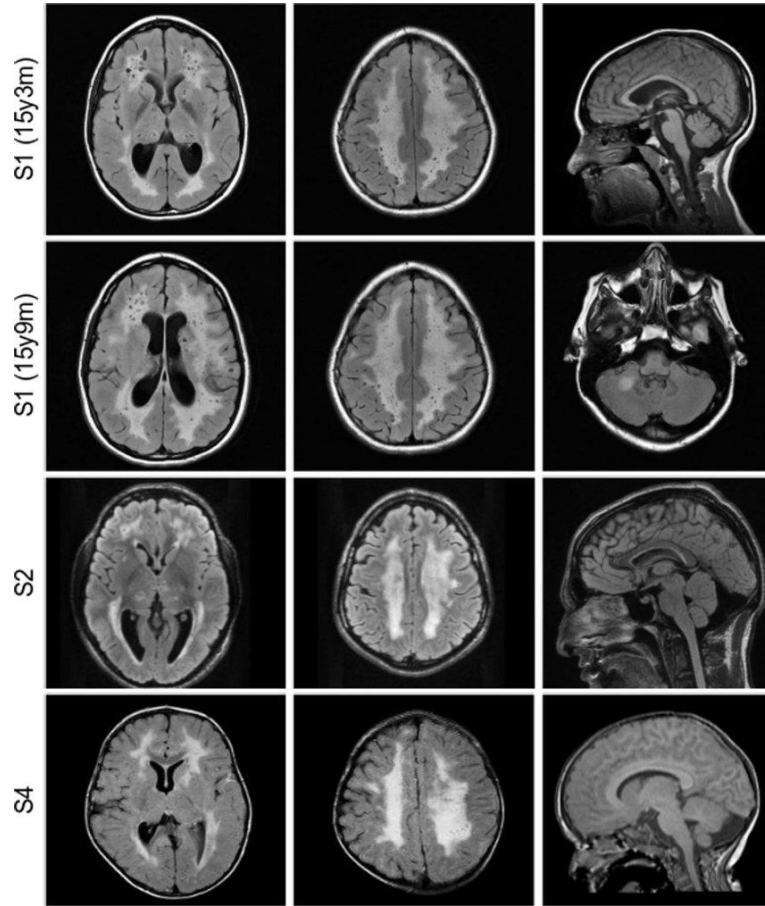
Can vaccines be developed against them?

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
 - Your feelings about screening and its impact on your mood & thoughts
 - How LFS bothers you 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



Why go into the MILI study?

- Largest study of its type in LFS 
- Designed with close involvement from LFS community
- One of the first Precision Prevention trials 
- Will tell us if metformin delays/reduces risk of cancer (endpoints may extend) 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) 



Funding approved
NIH - MILI

approx. 250 adults



Funding approved
MILI

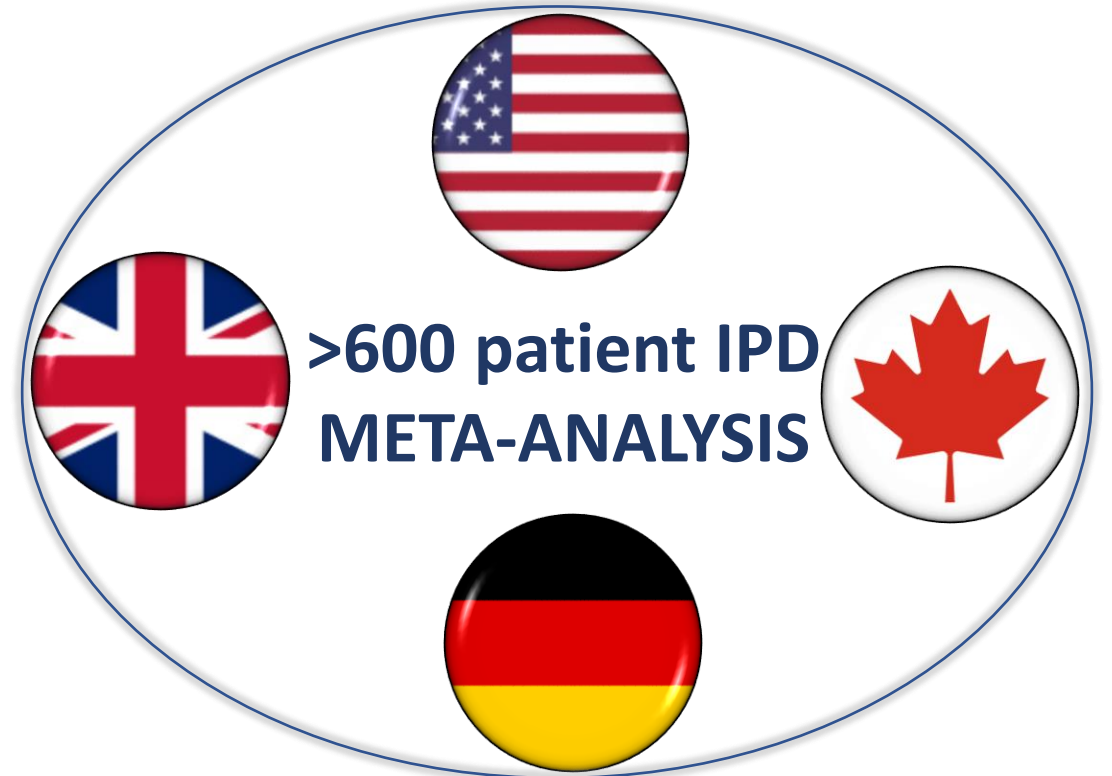
approx. 220 adults



German - MILI

adults and children
CI: Christian Kratz

SHARED PROTOCOL



Thank you!

Recruitment starts January 2023



Dr Pan Pantziarka



Elizabeth Sam



Verity Easton



**The George Pantziarka
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Are you a **BRCA** mutation carrier? Do you have Lynch or Li Fraumeni Syndromes?

Join us to share your ideas about the type of research into new treatments to prevent or delay cancer you would like us to explore



SCAN ME

Wed 21st Sept 22 | 4pm-6pm | Virtual Meeting

Register and find out more:

www.cancer.ox.ac.uk/ppm