



MILI

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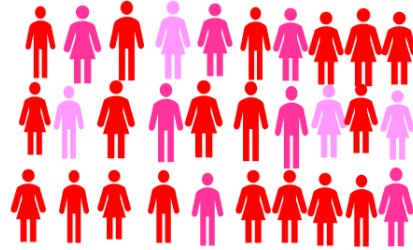
13th September 2025

Metformin in Li Fraumeni Precision Prevention trial (recruitment ongoing in UK genetics centres)

At-risk group:

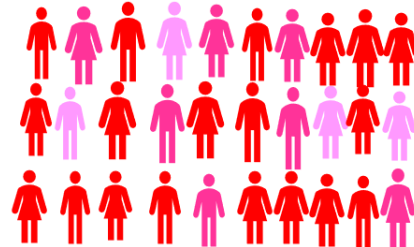
224 adults (>16y) with
confirmed diagnosis
of LFS

Randomised 1:1



Intervention (112):

Daily metformin (up to
2g/day) for up to 5 years
Plus
Annual whole body MRI
surveillance



Control (112):

No metformin
Annual whole body MRI
surveillance

Clinical Endpoints:

**Does metformin
work?**

Cancer-free and overall
survival at 5 years. QOL

Biological Endpoints:



How does metformin work?

Effect on signalling pathways: HOMA-
IR score, IGF1, PI3K cascade and
OXPHOS genomic signature.

Tumorigenesis:

Circulating biomarkers of cancer including
methylation and proteomic signatures,
cfDNA

Why does mTP53 cause cancer?

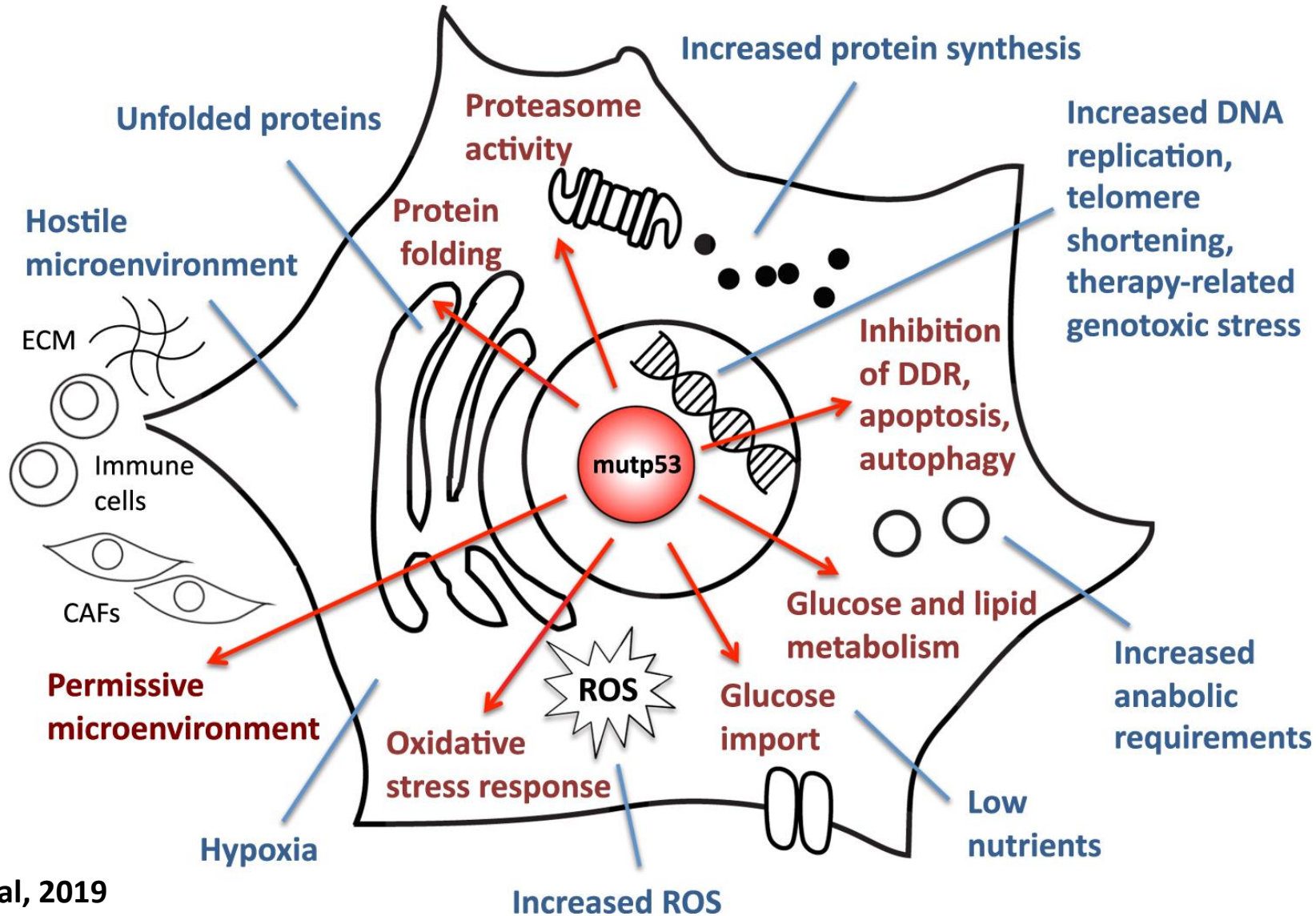


Figure: Mantovani et al, 2019

Why metformin?

The NEW ENGLAND JOURNAL OF MEDICINE

BRIEF

Increased Oxidative Stress in the Li-Fraumeni Syndrome

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Francesco S. Celi, M.D., Ross Ar



JNCI Cancer Spectrum (2020) 4(6): pkaa063

doi: 10.1093/jncics/pkaa063

First published online 18 July 2020

Article

JCI The Journal of Clinical Investigation

Inhibiting mitochondrial cancer in a mouse model of syndrome

Ping-yuan Wang, ... , Antonio Tito Fojo, Paul M. Hwang

Pilot Study Assessing Tolerability and Metabolic Effects of Metformin in Patients With Li-Fraumeni Syndrome

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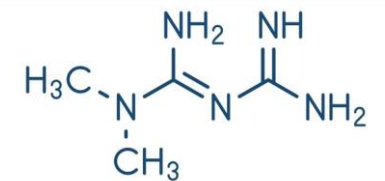
Hwang lab showed increased mitochondrial oxidative phosphorylation (OXPHOS) in LFS mice

- Seen in mice and LFS patients (*NEJM* 368(11):1027-32, 2013).
- Mouse model of LFS with mtDNA mutations (Polg^{mut}/p53^{172H/H}) – LFS mice lived 2x longer. This effect was reproduced with metformin



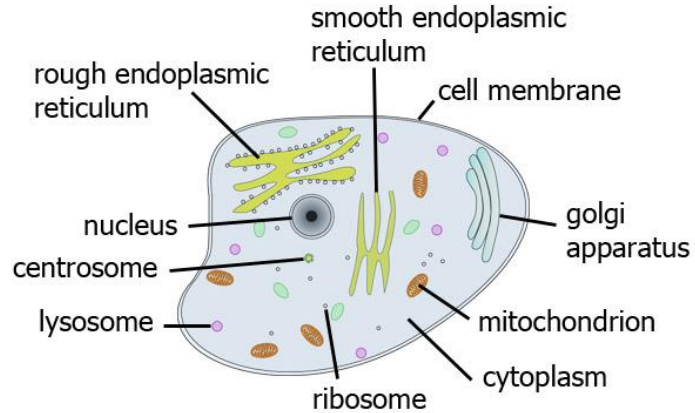
Metformin inhibits oxidative phosphorylation in mitochondria via complex 1 of the electron transport chain. Also lowers circulating glucose, insulin and IGF1.

“I’ve reached out to [my daughter’s] cancer predisposition team. One of her oncologists is not optimistic about metformin lowering the risk of cancer in LFS patients, [as it] will help obese patients in the trial lose weight, and that will lower the risk of cancer. So according to her, the results will be skewed.”



How does metformin work – directly or indirectly?

Direct



Measure by genetic
signature from blood



Simon Lord



Computational comparison

Indirect



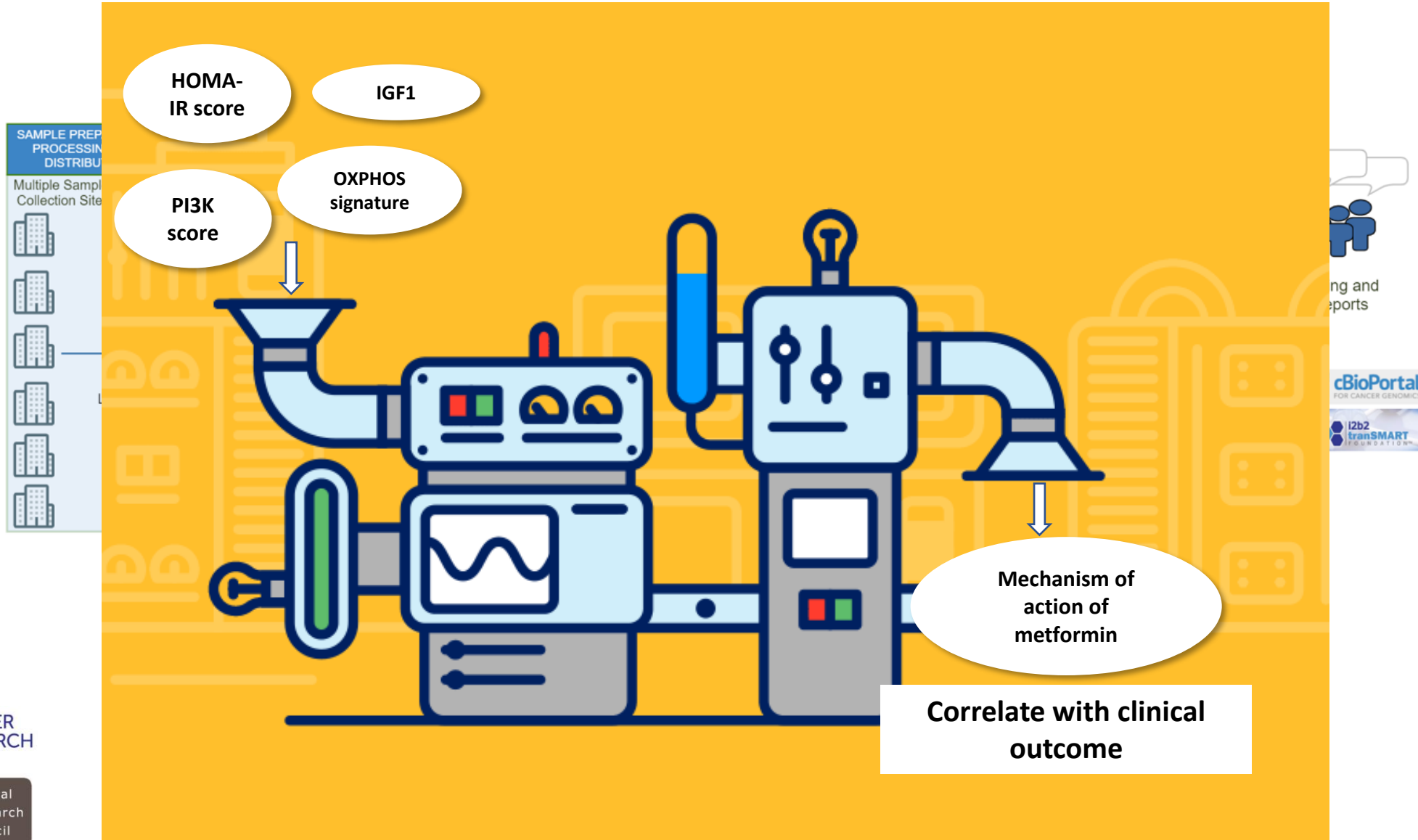
Lower levels of insulin, sugar
and growth factors

Better health – lower cancers

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

What translational questions is MILI 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)



- **40 patients** recruited so far (need to recruit 224!) at 7 sites – Oxford, Nottingham, Guys & St Thomas', Cambridge, Aberdeen, Southampton, Leicester. Sites in set up: Manchester, Royal Marsden, Edinburgh.
- Major problem with **MRI surveillance** scans
- **NHSE** → internal consultation → approved funding by Specialised Commissioning Services → Wes Streeting funding freeze → freeze lifted → new internal consultation>
- July 2025 – **Funding approved for MILI MRI scans** from NIHR's High Cost ETC panel
- Meanwhile revisiting **end date and recruitment** numbers: now require 156 participants (116 more) extended to July (?Dec) 2027

Channel 4 Documentary - October/November



MILI-Paed?

