LiFTS

Li-Fraumeni over Time Study

UK LFS 2025

Saturday 13th September 2025

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Wellcome Sanger Institute & University of Cambridge

Acknowledgments

Thank you to all the Participants!

NHS Cambridge University Hospitals NHS Foundation Trust

NHS Great Ormond Street Hospital for Children NHS Foundation Trust

NHS Royal Devon University Healthcare NHS Foundation Trust

NHS Guy's and St Thomas' NHS Foundation Trust

George Pantziarka TP53 Trust

NHS Birmingham Women's and Children's NHS Foundation Trust

NHS Grampian

UKRI Medical Research Council

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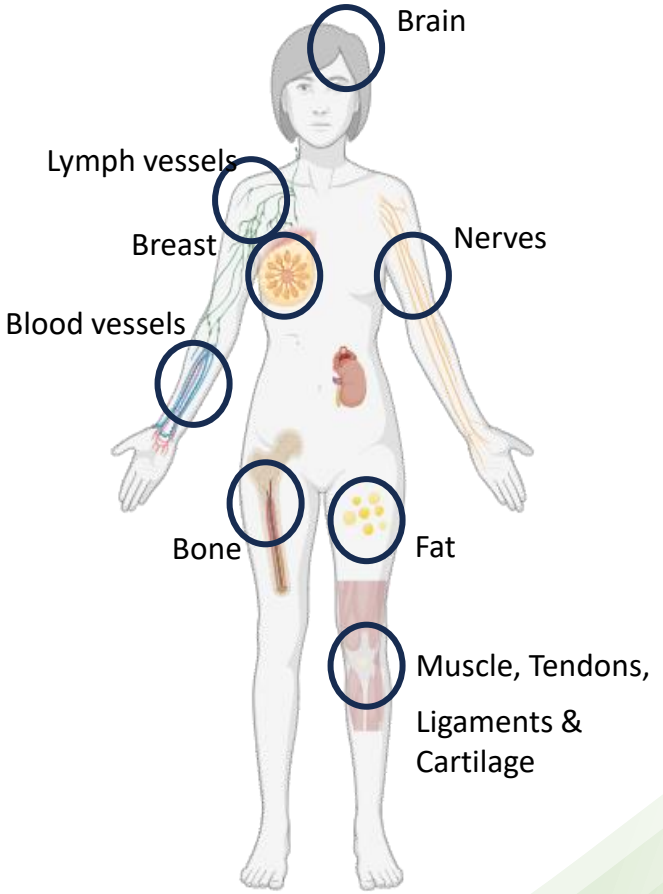
CANCER RESEARCH UK

Understanding cancer risk in Li-Fraumeni syndrome

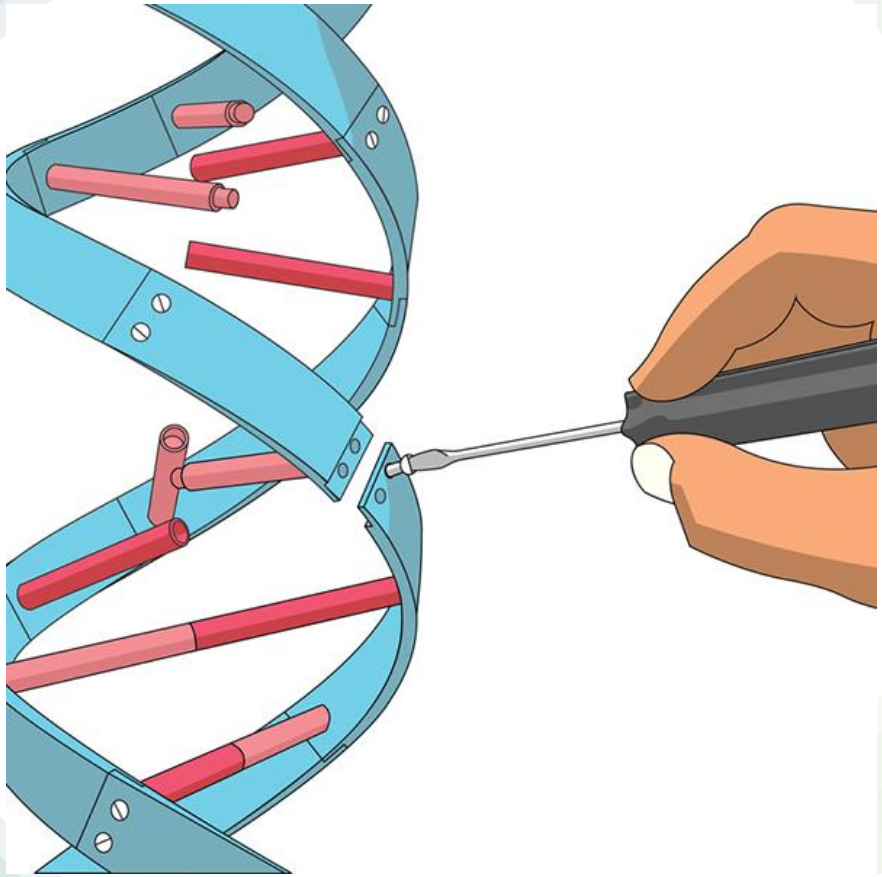
- People with LFS have a higher lifetime chance of developing cancer.
- The condition can be passed on from a parent to a child.
- Risk varies: even in the same family, some people may develop cancer while others may not.
- Cancers often start earlier in life than in the general population.
- Certain genetic changes may influence the type of cancer or level of risk.



Why TP53 is so important

- *TP53 is a protective gene. Its job is to act like a guardian, helping to stop cells from turning cancerous. This is why it is sometimes called the 'guardian of the genome.*

- *When TP53 is not working properly, it can increase the chance of cancer developing. In fact, changes in TP53 are found in about half of all cancers.*



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Yet … there's still so much we don't fully understand:

- Why some cancers are more common in people with LFS than in the general population.
- Why cancer risk varies so much between individuals and even within the same family.
- How changes in the *TP53* gene affect different parts of the body.
- How we can better predict cancer risk to guide personalised care and monitoring for people with LFS.

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What determines cancer risk in different organs?

We know that changes in the *TP53* gene can behave differently depending on the organ. This may explain why, in Li-Fraumeni syndrome, some organs (like the breast, brain, or soft tissue) are more likely to develop cancer than others.

What we don’t yet fully understand is why these differences happen.

Because of this, it is still challenging to:

- Predict each person’s exact cancer risk,
- Design the most effective early detection programmes,
- Develop treatments tailored specifically for people with LFS.

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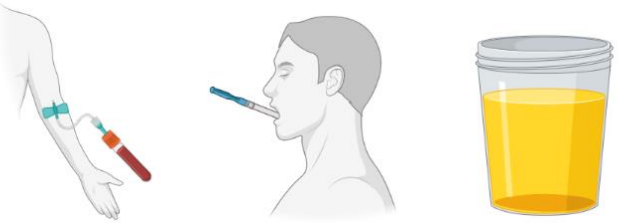
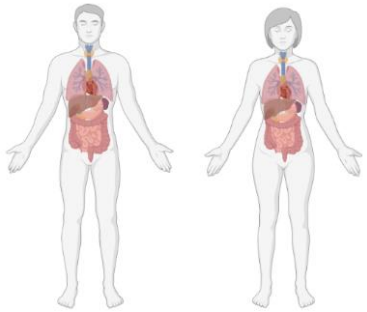
Three ways we can learn from samples in LiFTS

1. Regular samples
We can collect blood, saliva/cheek swabs, urine, or semen every 6–12 months.
This helps us see how things change over time.



2. Samples from medical procedures
If someone already has a biopsy (for example, from the colon, skin, or a tumour that needs to be removed), small pieces of those samples can be saved for research.
No extra procedures are needed.

3. Organ donation (optional)
Some people may choose to donate tissue or organs for research.
These donations can give us insights we could not get in any other way.



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Recurrence risk

- Sometimes, a TP53 mutation happens in a child for the very first time in a family.
  This is called a *de novo* mutation.
- In these families, it is difficult to know how likely it is that future children will also inherit the mutation.
  This uncertainty is called recurrence risk.
- By using new, ultra-accurate methods (like NanoSeq) on sperm samples from fathers of children with *de novo* mutations, we hope to create a more reliable test.
  This could help families get clearer answers about their future risks.

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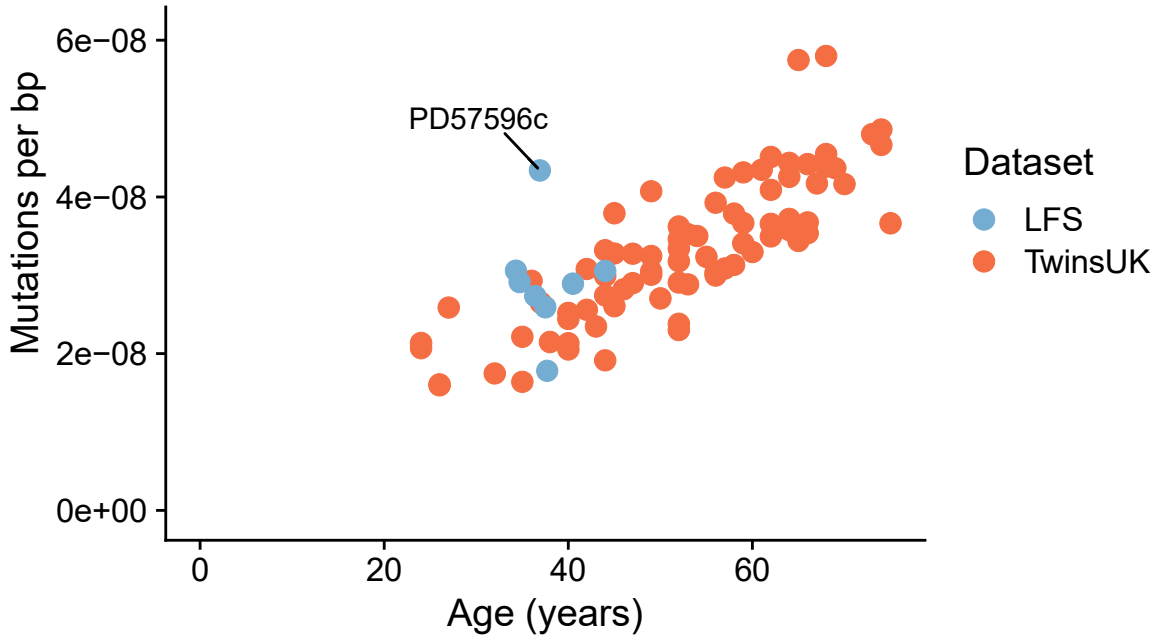
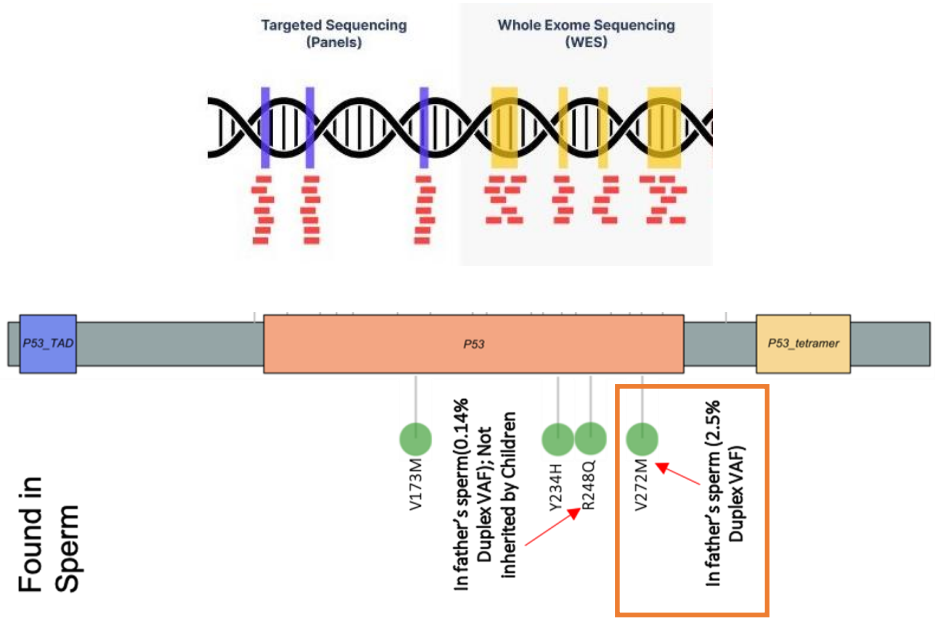
Looking for TP53 mutations in sperm to understand recurrence risk

Whole genome survey of sperm



Most fathers of children with LFS had the usual number of mutations in their sperm for their age. But one father had a much higher number than expected.

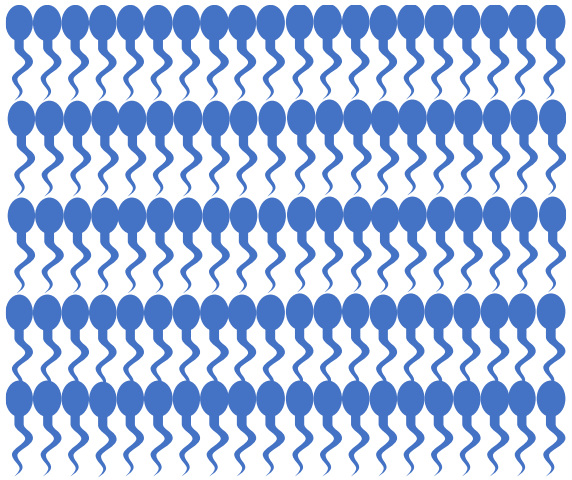
Targeted sequencing confirmed the exact mutation in sperm



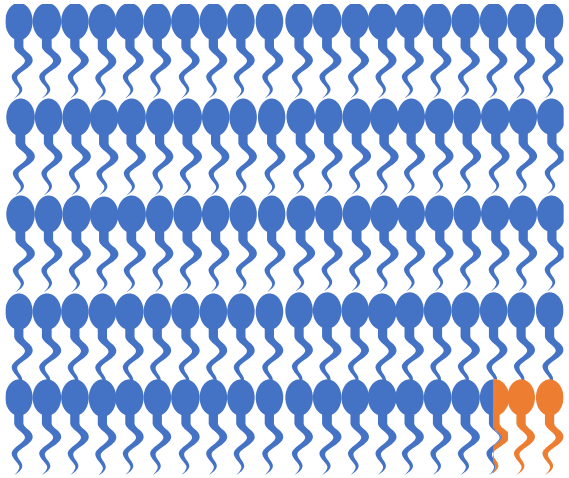
About 1 in 40 of his sperm carried the same TP53 mutation seen in his child.

Recurrence risk in fathers of children with LFS

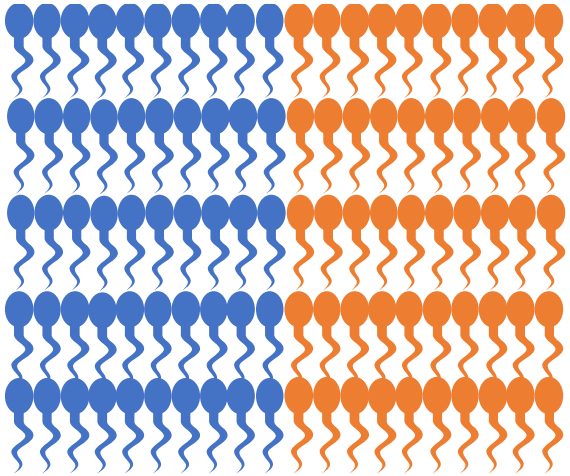
Fathers with no *LFS*
no *TP53* mutation
Recurrence risk = ~0%



Fathers with no LFS
de novo TP53 mutation expansion
Recurrence risk = ~2.5%



Fathers with LFS
50% of sperm carry *TP53* mutation
Recurrence risk = 50%



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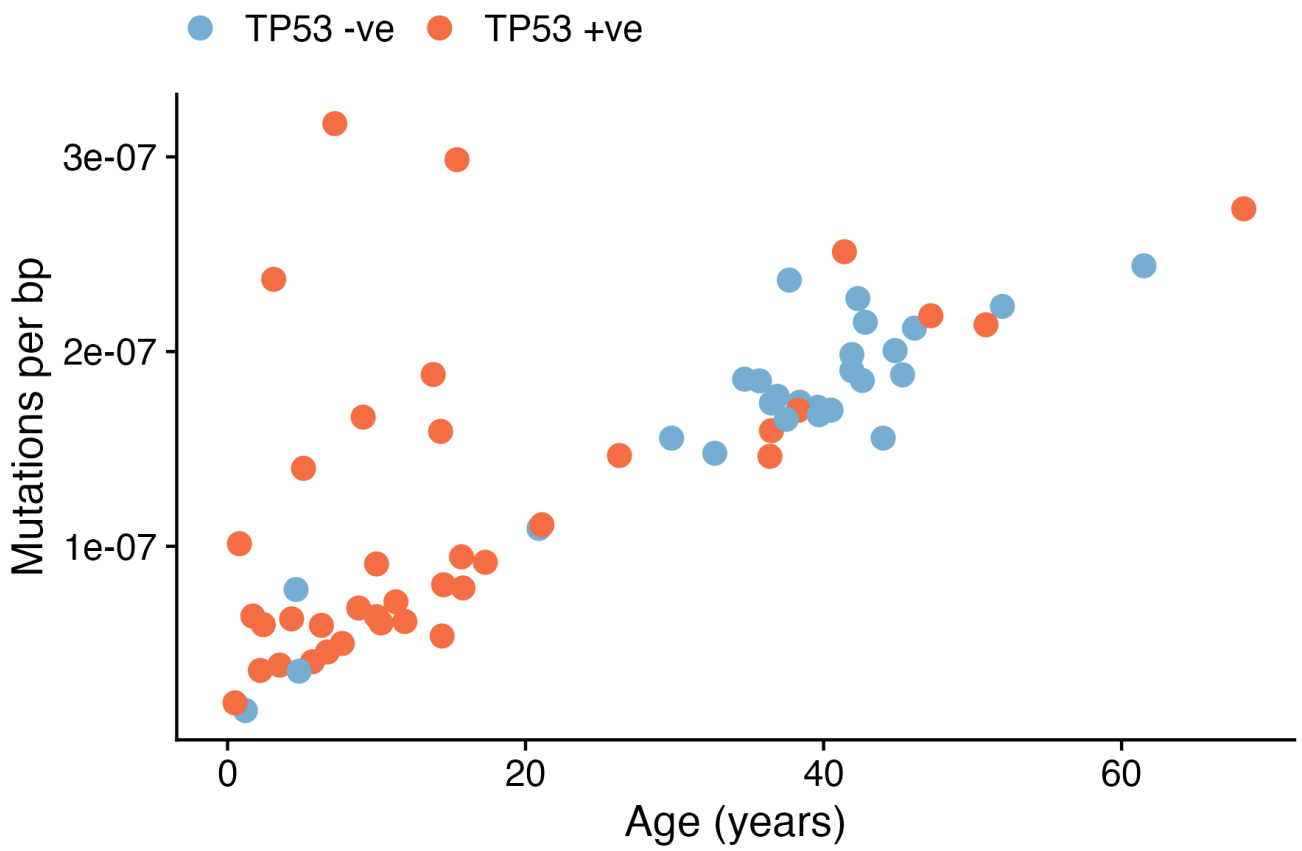
Chemotherapy effect on the accumulation of mutations in blood of LFS



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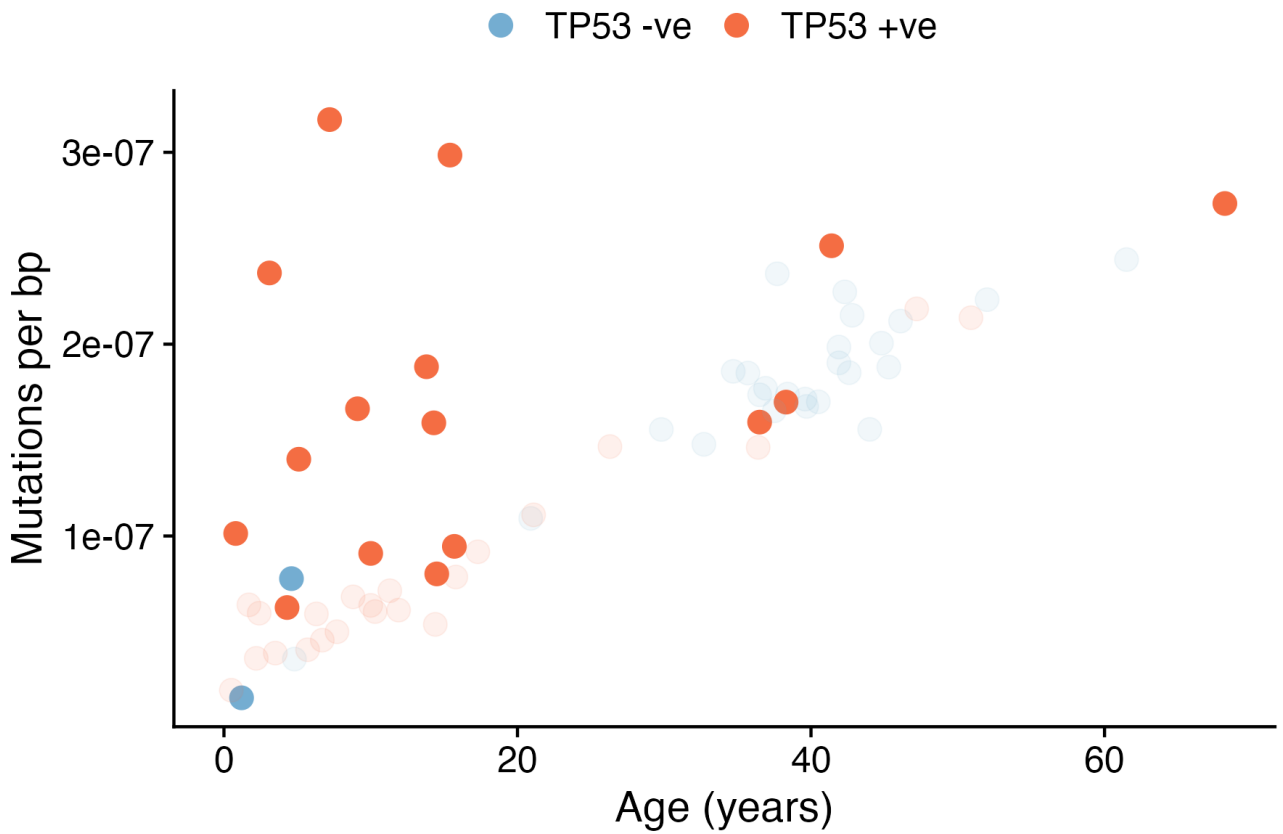
Chemotherapy effect on the accumulation of mutations in blood of LFS

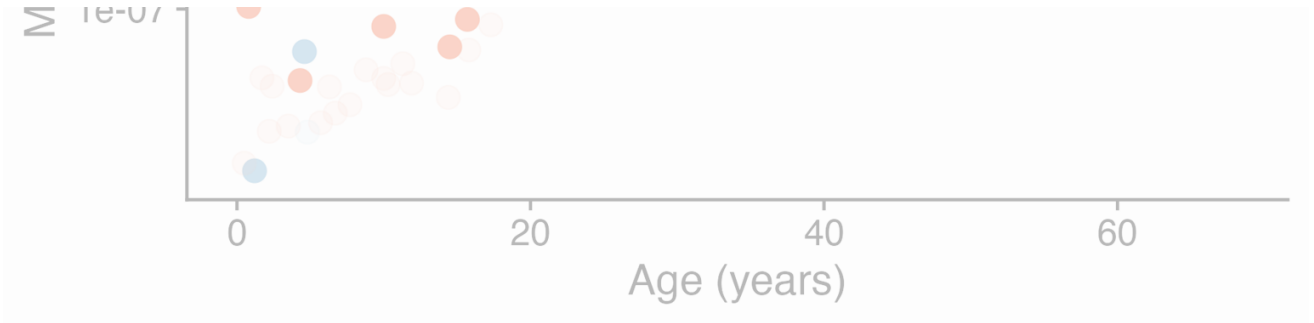


- Excess somatic mutations in **some** LFS individuals post chemotherapy
- Further investigation on how these excess mutations might affect acceleration of secondary cancer transformation is required

Chemotherapy effect on the accumulation of mutations in blood of LFS

Article | Open access | Published: 01 July 2025

The long-term effects of chemotherapy on normal blood cells



- Excess somatic mutations in **some** LFS individuals post chemotherapy
- Further investigation on how these excess mutations might affect acceleration of secondary cancer transformation is required

Benefits of taking part in LiFTS

- Your participation will help us develop better ways to monitor and treat cancer risk in people with LFS.
- For families where the *TP53* mutation happened for the first time (*de novo* mutation), we may be able to give a clearer estimate of recurrence risk using the father's sperm.
- We may be able to spot very early signs of cancer changes, which would always be shared with you and your clinical team.

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Would you like to be involved?

Get in touch: Email us at lifts@tp53.org.uk if you'd like to know more (this doesn't commit you – it's just to show interest).
•Anyone with a diagnosis of LFS or an LFS-like syndrome is welcome.

First chat: We'll arrange an introduction and consent conversation, which can be done by phone and post.

Home packs: We can send you packs to collect cheek swabs, urine, or sperm (where relevant). You'll receive new packs every 12 months.
•Samples are collected at home and simply posted back to our Cambridge lab.

Hospital visits: You may be invited to one of our recruitment hospitals for a blood sample (currently Cambridge for adults, GOSH for children, with more centres being added).

Extra procedures: If you're already having a medical procedure (such as a colonoscopy or biopsy), let us know. We may be able to collect a small extra sample for research.

Challenges in LFS research

RARE DISEASE

GEOGRAPHICAL

PSYCHOLOGICAL

LOGISTICAL

FORMALIN!

Potential solutions

Patient registries and clinical networks

Dedicated clinical service with research embedded

Dedicated clinician / point of contact

Patient and public engagement and involvement

Tissue donation programme

Implementation in the East of England

Patient registries and clinical networks

- LFS regional registry
- PTEN national registry
- STK11 regional registry (as part of national polyposis registry)
- Hereditary renal cancer national registry
- National Inherited Cancer Predisposition Registry (NICPR)

NIHR | Cambridge Clinical Research Facility

Currently collecting buccal/ skin swabs, urine, and blood samples with optional skin biopsies

Dedicated clinical and research service

- Cambridge Research Facility dedicated research clinic for sample collection
- Hereditary Cancer Risk Management clinical service (sourcing funding for LFS, PTEN and STK11 initially)
- Clinical research working group aligned to clinical service

Dedicated clinician / point of contact

- East Anglian Clinical Genetics Service
- University Dept of Genomic Medicine

Implementation in the East of England

Patient engagement and involvement

- George Pantziarka TP53 Trust
- PTENUKI
- Dedicated East of England events including research focus groups being planned
- PPE working group embedded within the clinical service

Tissue donation programme

- All participants recruited to LiFTS will contact study team if undergoing surgery or biopsy
- Clinical team will then co-ordinate fresh frozen tissue collection through CUH tissue bank

Cambridge LFS research clinic

- Dedicated research clinic in Cambridge for individuals with LFS
- Also recruiting individuals with other genetic conditions including cancer predisposition
- Through this clinic we are able to arrange:
  - Blood sampling
  - Cheek (buccal) swabs
  - Urine sampling
  - Research skin biopsies
- If you would like to attend, please contact our team either on: lifts@tp53.org.uk or joseph.christopher1@nhs.net

NIHR | Cambridge Clinical Research Facility

What we aim to achieve?

- Better understanding: Learn how changes in the TP53 gene affect different organs and why this matters for cancer risk.
- Clarity on cancer risk: Discover how these changes can sometimes turn into cancer in people with LFS.
- Better care in the future: Find new and more effective ways to detect cancer early and develop treatments tailored to people with LFS.

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Please **contact us** by sending an email to: lifts@tp53.org.uk or joseph.christopher1@nhs.net

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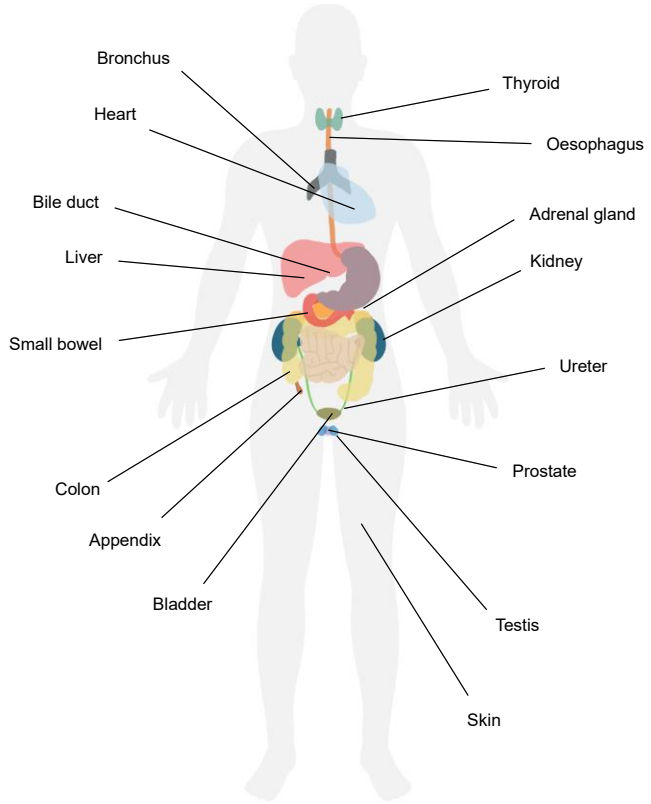
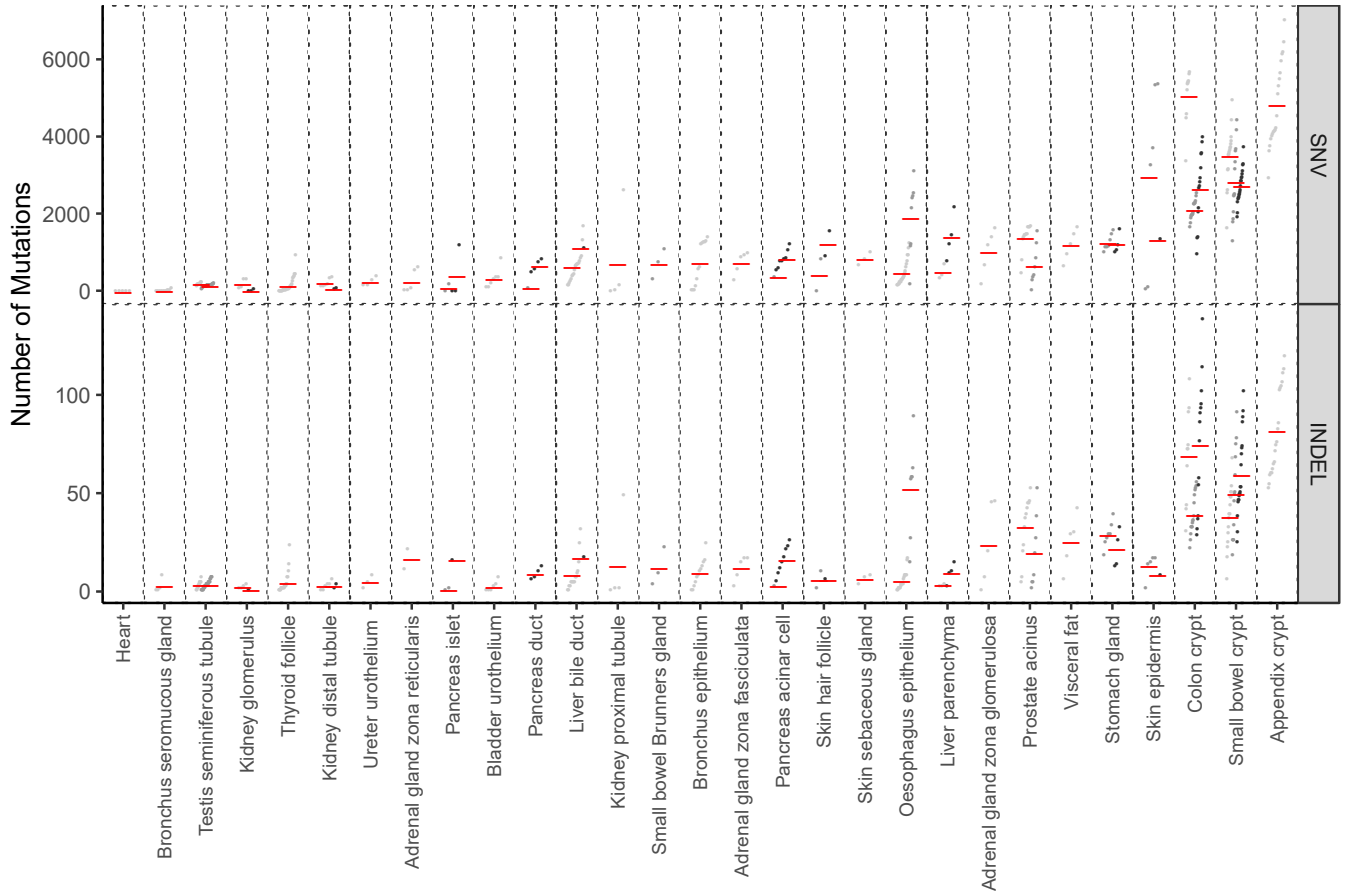
Mutant patch encyclopedia





Moore L., Cagan A., Coorens T.,…, Stratton M. & Rahbari R. Nature 2021

Coorens T., Moore L., …, Rahbari R. Stratton M. Nature 2021

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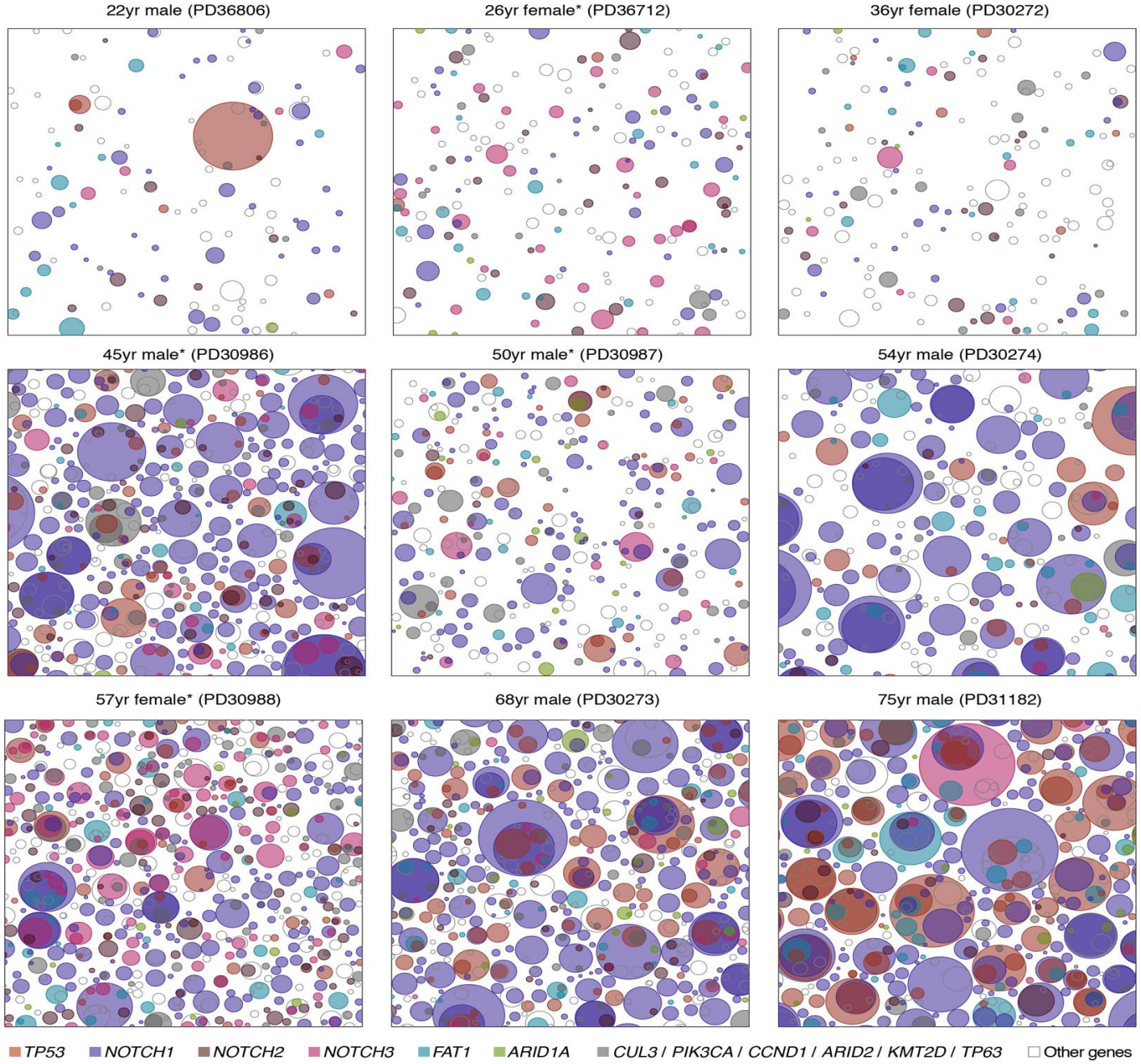

Many open questions

- Other tissues?
- Cancer risk prediction?
- Opportunities for intervention?

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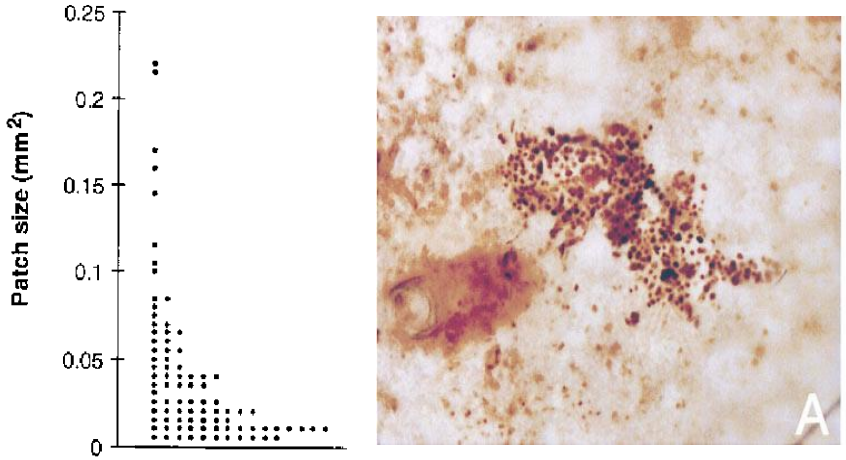
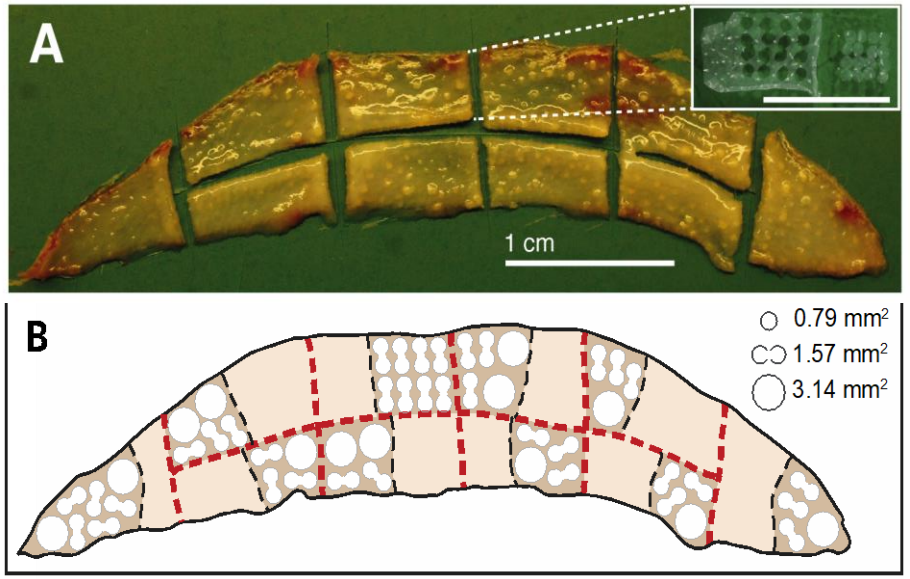
TP53 mutations in sun-exposed skin

Frequent clones of p53-mutated keratinocytes in normal human skin

(sunlight/ultraviolet/carcinogenesis/tumor promotion/clonal expansion)

ALAN S. JONASON*, SUBRAHMANYAM KUNALA*, GARY J. PRICE†, RICHARD J. RESTIFO‡, HENRY M. SPINELLI‡, JOHN A. PERSING‡, DAVID J. LEFFELL§, ROBERT E. TARONE¶, AND DOUGLAS E. BRASH*‖**††





Martincorena *et al*, Science, 2015

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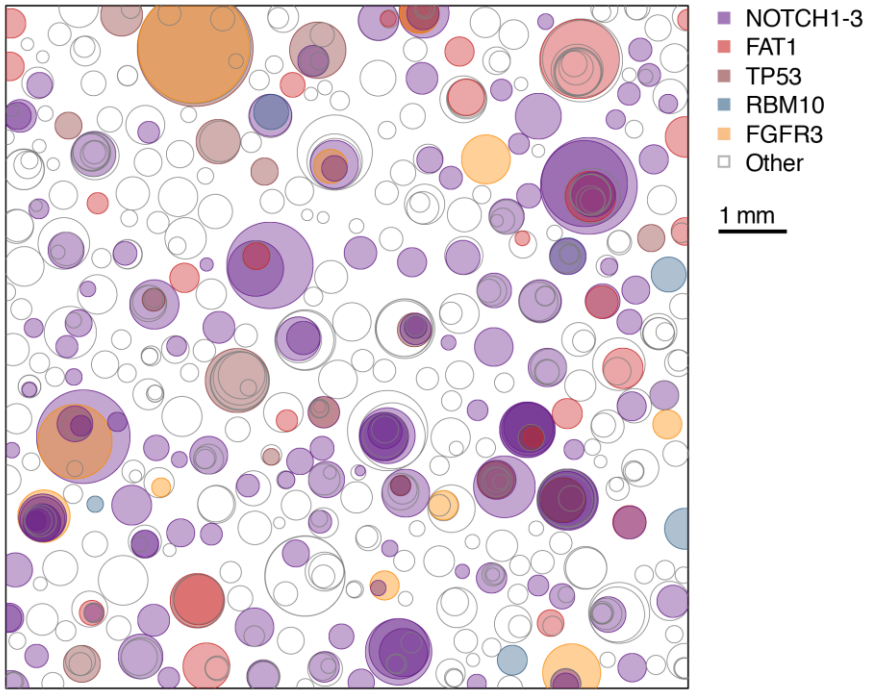
Unexpected results

- **Lots (1000s) of gene mutations in every cell,** mostly caused by sun exposure. The number of mutations are similar to that seen in cancer but these cells appear entirely normal!
- **Some of these mutations allow cells to push out their neighbours and form patches of mutant cells**
- **These mutant patches (also known as ‘clones’) can go on to form cancer**

Sun-exposed skin is a patchwork of competing mutant patches



Martincorena *et al*, Science, 2015

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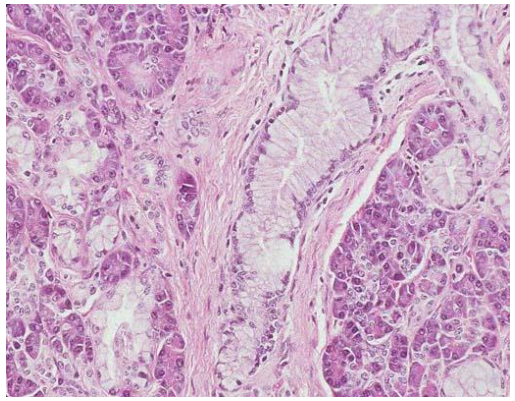
Technology (1)
Laser cutting microscope!

LCM has been a major breakthrough in studying mutant patches.

Able to use state of the art genetic technology to study these mutant patches in detail.



More ways to study these patches are being developed in our team

- DNA tags known as ‘methylation’
- Gene expression
- Studying how the different patches relate to each other (evolutionary studies) and how the DNA mutations, methylation changes, and gene expression affects this

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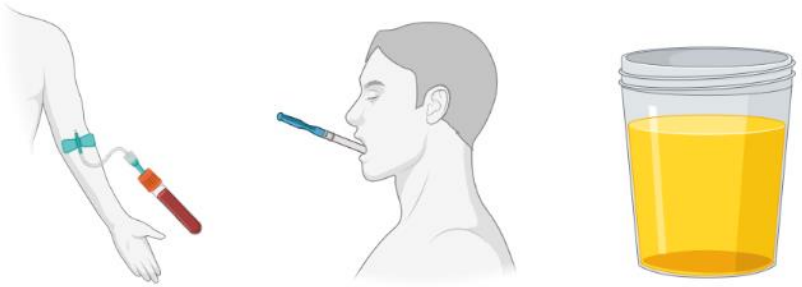
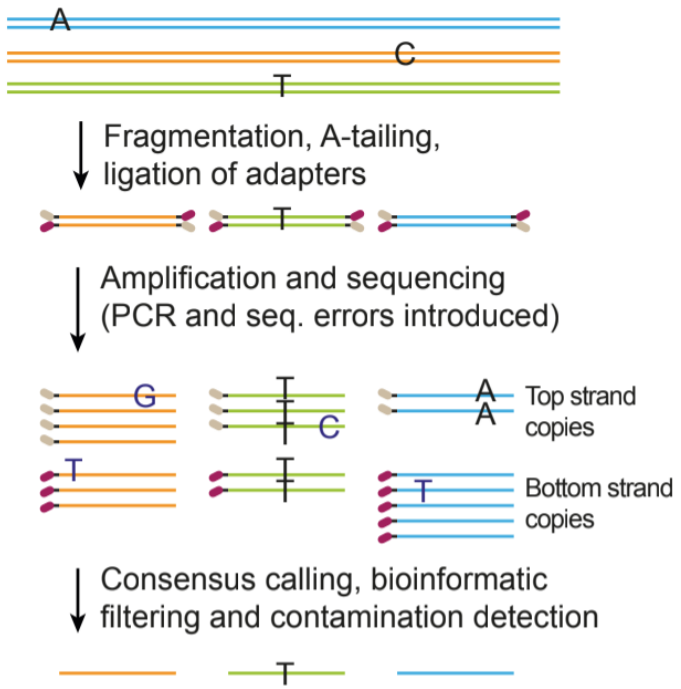
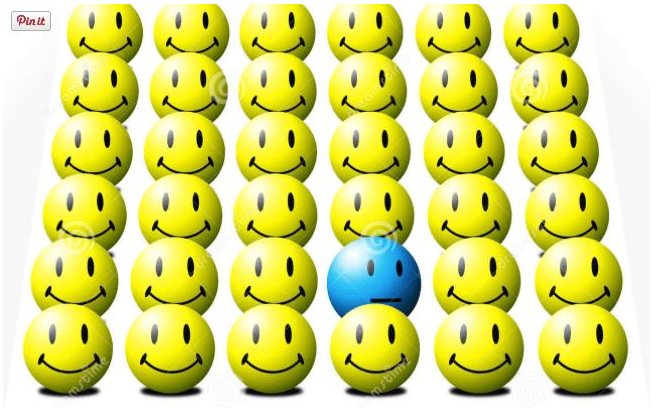
Technology (2)
Single-molecule DNA sequencing – Nano-seq

- Accurate study of patches has been restricted to those visible under a microscope
- Major breakthrough in this problem is a new DNA technology known as Nano-seq
- This now allows us to do in-depth study of patches in tissues such as blood, cheek swabs, sperm, and urine (all of which was not possible before) and see DNA mutations at unprecedented resolution







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