DISCOVER

ISSUE ONE

CANCER RESEARCH IN MANCHESTER

Contents

Contributors

Robert Bristow is Director of the Manchester Cancer Research Centre (MCRC). His research at the Cancer Research UK Manchester Institute aims to understand how genetic changes affect prostate cancer progression and response to treatment.

Sharzad Harrap is the MCRC Biobank Coordinator at The Christie. She has been in this role since 2016, managing new Biobank applications and supporting the set up and delivery of studies.

Sara Cabral is an EPSRC funded third year PhD student jointly supported by the MCRC and The Henry Royce Institute studying breast cancer bone metastasis. Her project is titled *"Developing preclinical peptide hydrogel models of breast cancer metastasis to bone using patient-derived tumour cells and xenografts".*

Kathy Morse is a 57 year old woman from Salford who was diagnosed with a rare gynaecological cancer in 2020. She now shares her story to raise awareness and encourages others to get checked, urging people not to 'die of embarrassment'.

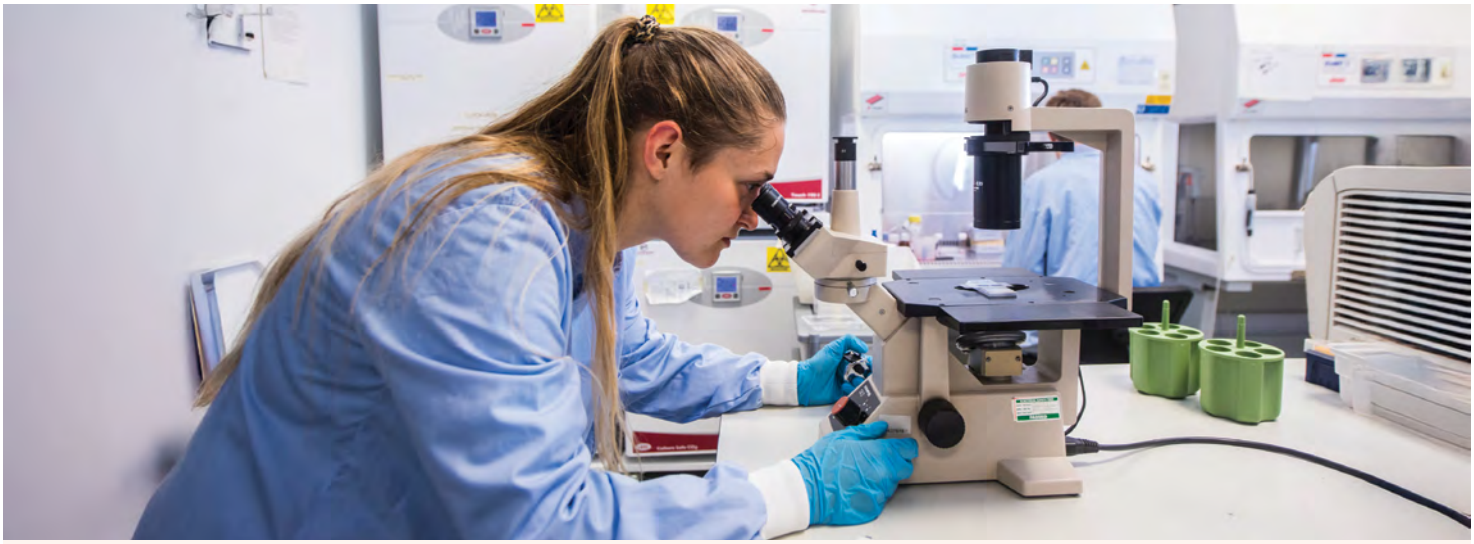
Alicia-Marie Conway is an Academic Clinical Lecturer at the CRUK National Biomarker Centre and Medical Oncology trainee. Her research aims to improve the outcomes for patients with difficult to treat cancers.

Alex Clipson is Deputy Team Lead of the Nucleic Acids Biomarkers Team at the CRUK National Biomarker Centre. Her research develops cutting-edge technologies to understand more about a patient's tumour from donated blood samples.

Emma Woodward is a Consultant Clinical Geneticist at Manchester University NHS Foundation Trust and Honorary Senior Lecturer at the University of Manchester. Her research is aimed at improving the understanding of hereditary cancers.

Stepan Romanov is an MRC funded final year PhD student studying breast cancer risk prediction in the Breast Imaging lab. His project is titled *"Using Artificial Intelligence to quantify cancer risk from breast images using full resolution screening mammograms".*

Mia Nuckhir completed her PhD studying breast cancer lung metastasis in December 2024. She was awarded the Medical Research Council Doctoral Training Partnerships Pathways to Impact award in September 2024 to author this patient focused magazine in collaboration with the MCRC communications team.



Team Science at the Manchester Cancer Research Centre

Behind every discovery is a team of dedicated scientists working together to achieve a common goal. Long gone is the idea of a lone scientist working in a single lab making headway against a disease as complex as cancer.

This transformative approach, known as Team Science, is re-defining how we tackle the biggest challenges in cancer research, driving discoveries from the lab into the clinics for patients.

At the Manchester Cancer Research Centre (MCRC), Director, Professor Robert Bristow champions this way of working, ensuring collaboration is at the centre of every stage of the research process.

Cancer Team Science

"Team Science can be implemented in multiple ways, but its guiding principles are rather simple, it relies on goal alignment and scientific altruism".

"Team Science starts by defining an important problem: what global cancer challenge needs to be tackled with a group effort? Next, it is about approaching the problem as a team to find a solution. Open communication, diverse idea generation and innovative collaboration is key at this stage to build a team with complementary and multidisciplinary expertise suited to solve the problem at pace and scale".

The MCRC embodies this approach to Team Science. Formed in 2006 by The University of Manchester, Cancer Research UK and The Christie NHS Foundation Trust, the MCRC works to achieve what one organisation alone could not, making research, innovations and progress possible.

"Team Science expands beyond organisational and even national boundaries. Cancer is a global challenge, impacting everyone in some manner, so why should our response not be equally international?"

"Take early detection as an example. A 'traditional' approach might see laboratory scientists identifying biomarkers in a lab to detect cancer earlier, while separately a clinician leads work to implement screening and local governments work to improve healthcare services".

"But why not bring all these people together?"

"This is what we are doing in Manchester. Focusing on Early Detection, Manchester are founding partners in the International Alliance for Cancer Early Detection, a £50m alliance between centres in the US, UK and Europe. Initiatives like this bring international experts in laboratory, clinical and population science together with patients, public, and policymakers across the globe to solve major problems".

Robert Bristow
Director of the MCRC

BRAINatomy: leveraging the cancer team science approach

Expert biologists, physicists, doctors, patients and patient advocates were brought together on BRAINatomy, an innovative data-driven study aimed at improving the long term outcomes for children diagnosed with brain tumours, jointly-funded through a collaboration between Stand Up To Cancer® in the US and Cancer Research UK's Stand Up To Cancer® (SU2C) campaign.

Children with brain tumours are often treated with radiotherapy, a type of cancer treatment that uses x-rays or protons. Whilst effective, radiotherapy can lead to damage to certain parts of the brain causing issues with memory, hormone regulation and overall quality of life. In BRAINatomy 1, researchers used image-based data mining methods- a way of comparing radiation dose to specific regions of the brain with patient outcomes- to identify areas of the brain that are sensitive to radiation treatment.

Researchers studied MRI scans from patients before and after radiotherapy and identified features on pre-treatment scans that were associated with later learning difficulties and parts of the brain where receiving radiotherapy was linked to changes in brain function.

These changes were associated with the development of learning difficulties and hormone regulation issues later on in childhood.

Identifying these sensitive regions of the brain means that researchers can create a map of areas to avoid during radiotherapy treatment. For example, they discovered that radiation dose to an area of the brain that includes the hypothalamus, which is responsible for controlling the release of hormones, water retention and appetite among many other things, was associated with later learning difficulties.

Further funding has been secured from Stand Up To Cancer® and Cancer Research UK to extend the project into BRAINatomy 2. This stage of the project will assess the effects of proton beam therapy, a type of high-precision radiotherapy treatment that uses high dose protons, comparing it to traditional radiotherapy. It will also test whether giving replacement hormones or drugs to reduce inflammation- a common side effect of radiotherapy treatment- could counteract its damaging effects, and whether advanced scanning of children who have finished their treatment could be used to predict others that are most at risk of damage.

The goal is to improve quality of life, allowing a child to live as normal a life as possible after successful treatment for their cancer.

To find out more about this groundbreaking research, visit the CRUK and brainstrust websites.

Clinical Trials: The 5W's

How do doctors know that a new drug is safe and effective to give to patients?

The answer lies not only in research, but in clinical trials. These trials involve real patients testing new treatments, but how exactly do they work?

When?

The first clinical trial conducted by a physician took place in 1747 by Dr James Lind aboard a Naval ship called the Sailsbury. His trial, involving just 12 sailors aimed to find a cure for scurvy, a disease that plagued many long-distance sailors caused by low levels of vitamin C.

Fast forward to the 1950s, the first clinical trial focusing on a treatment for cancer took place. The trial tested a chemotherapy agent called mechlorethamine on a small group of patients with lymphoma, a type of blood cancer affecting white blood cells in the immune system.

Fast forward again to 2023 and, according to the World Health Organisation, 2,254 clinical trials enrolled their first trial participant in the UK. 20% of these - 378 trials - were focused on cancer. These modern trials differ in many ways from the early physician-led clinical trials- today's are far more rigorous, result from years of preclinical research, follow well-structured phases and involve thousands of patients.

What?

0 — PRECLINICAL

Lab-based research to tell if a treatment is useful and safe.

1 — SAFETY

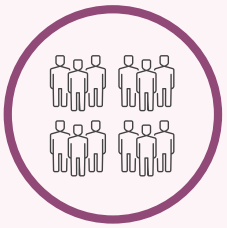
20-80 participants to assess the treatment's safety and side effects.

2 — SAFETY & DOSING

100-300 participants to assess the treatment's safety and effectiveness.

3 — SAFETY & EFFICACY

1000-3000 participants to compare the treatment to existing treatments.



4 — POST-APPROVAL

Surveillance in the general population to evaluate the long-term effects.

A clinical trial is divided into four defined phases. The drug or treatment must meet the objectives of the study in order to progress from one phase to the next. For example, the drug must be shown to be beneficial compared to standard treatments to move from phase 3 and be approved at phase 4.

If this doesn't happen, the drug or treatment is likely discontinued. Although, in some cases, the drug or treatment can be modified and repurposed if there is an indication that it may have promise for other conditions.

800

clinical studies including observational and phase 1-4 studies are currently active at The Christie

Why?

Clinical trials are essential to ensure that new treatments are safe and effective.

It may seem risky to test a drug in people, but it is absolutely necessary and only happens after years of what researchers call preclinical research.

Preclinical research typically involves two stages. The first is *in vitro* testing, where the drug or treatment is studied in cells or tissues outside of the body, in the laboratory.

The second stage is *in vivo* testing, where the drug or treatment is tested in a whole, living organism- in cancer research, this is usually an animal. This is to understand how the drug or treatment will work in the body and whether it has any unwanted side effects.

Preclinical research also involves pharmacological testing to understand how it interacts with the body and how the body processes the drug to make sure that it works and remains stable. This is required by regulatory bodies before a drug can be tested in a clinical trial, but is separate from the early preclinical research that is done at the Manchester Cancer Research Centre (MCRC).

Even after extensive preclinical testing, a clinical trial is essential to confirm that the drug or treatment is safe for humans. Research in cells and animals provide valuable insights, but factors like dosage and side effects must also be confirmed in people, as results from in vitro and in vivo work do not always directly translate to humans.

Animals in research

Scientific research involving animals is crucial for improving our understanding of health and disease as well as for developing new drugs and treatments for patients. **It only takes place when there is no alternative.**

All research involving animals is carried out under strict ethical guidelines and the animal's welfare is balanced against the scientific need of the study at every step. The animal's health is monitored daily, and any problems are immediately addressed. The animals are usually housed in groups, in cages that have environmental enrichment for their comfort.

At the Cancer Research UK Manchester Institute facility, the only animals used in research are mice. Mice are a good model for research as their genes are very similar to humans.

The facility supports researchers based within the MCRC partnership with **17** different cancer research areas each comprising several projects that involve the use of animals. On average, these projects use between **200 to 600** mice per year.

All research projects involving an animal are carefully considered by the Institute's Animal Welfare and Ethical Review Body before being sent to the Home Office for approval. The **3Rs of replacement, reduction and refinement** guide the use of animals in scientific research. This means that ways to reduce the number of animals involved, the refinement of methods to improve animal welfare, or the use of replacement methods without animals all have to be considered before a project can be approved.

Who?

Each clinical trial has a list of criteria a patient has to meet in order to take part. Mostly, the criteria relates to the type and stage of a person's cancer, and any previous treatments they may have had. This is because trials tend to focus on only one type, or related types of cancer, and because different drugs may interact with one another, producing harmful side effects or reducing their effectiveness.

A person's general health and medical history is also important, particularly if they have a health condition that may be made worse by a potential side effect of the drug or treatment being tested.

It's a careful balance, as trials need clear criteria, but they must also be as inclusive as possible, representing people from diverse backgrounds so that the approved treatment works for everyone, regardless of race or ethnicity.

Unfortunately, not everyone will be eligible to take part in a clinical trial. People who want to get involved can discuss their options with their GP or healthcare provider- they will be able to help patients make sense of the trial process and guide them through their options.

Lists of clinical trials are published on the Cancer Research UK and ClinicalTrials.gov websites.

Where?

Clinical trials take place across the country, commonly in multiple hospitals at the same time. Trials open in different locations for different reasons, often due to the hospital's expertise, the facilities available and the number of patients the trial needs to recruit.

The Christie is one of the largest single site cancer hospitals in Europe, treating more than **64,000** patients each year.

More than 500 phase 1-4 clinical trials are active at The Christie.

Trial Spotlight:

A trial looking at a drug called UCB4594 for cancer that has spread

Cancer cells evolve clever ways to avoid being detected and destroyed by the body's immune system. One of these ways is to express a protein called human leukocyte antigen G, or HLA-G. Normally, HLA-G is only found in parts in the body that need protecting from inflammation caused by the immune system.

For example, it is found in cells that make up the cornea and retina in our eyes, and in cells called trophoblasts that form the placenta during pregnancy to prevent the growing foetus from being seen as foreign and attacked by the mother's immune system.

By expressing HLA-G, cancer cells can evade attack by the body's immune system, making it a promising anti-cancer target. UCB4594 is a new immunotherapy- a type of drug that stimulates the body's immune system, designed to target HLA-G. In preclinical testing, it was shown that UCB4594 helped the immune system to identify cancer cells that express HLA-G.

Phase 1 of this trial aims to find a safe and effective dose of UCB4594 in patients that does not cause too many unwanted side effects. Phase 2 will look to see whether UCB4594 works well alone or in combination with other common cancer treatments. HLA-G is expressed in many different cancer types, so this trial is not initially aimed at patients with a specific type of cancer but is open to patients with 1 of 9 different types of solid cancers that have spread.

To find out more about clinical trials, visit the CRUK and the National Cancer Institute websites.

Scan here to access further information

Inside the Biobank

The Manchester Cancer Research Centre (MCRC) Biobank is a vital resource that supports cancer researchers and patients in Manchester. Based at The Christie, the Biobank collects and stores samples from patients across the region for researchers to use in their cancer research projects.

Sharzad Harrap, MCRC Biobank Coordinator at The Christie explains how the MCRC Biobank works and the critical role it plays in advancing cancer research.

29,150

patients consented to the MCRC Biobank

The MCRC Biobank collects a range of samples for use in research, these include:

- Tumour samples
- Matched normal samples- taken from a normal part of the same tissue as the tumour for comparison
- FFPE tissue- tissue fixed in a preservative and embedded in wax
- All different blood types
- Urine samples
- Ascitic and pleural fluids- fluid build-up in the abdomen and around the lungs
- Stool samples
- Saliva samples

"This is tissue that would likely have been disposed of anyway and they're such useful samples for research!"
Sharzad Harrap

232,400

samples collected from patients

Here's how it works:

1 Patient consent
Patients interested in donation consent by signing a MCRC Biobank consent form, accompanied by a detailed patient information sheet.

2 Sample collection
Samples are collected from patients, mostly this is done during their routine appointments and procedures.

3 Sample processing
Samples are barcoded and linked to the patient's assigned Biobank number to ensure anonymity.

4 Sample storage
Samples are stored in line with set guidelines until needed.

5 Sample request
Samples are requested based on the needs of the research.

6 Sample use
Samples are used in a cancer research project.

Collection models

Collections have changed a lot since the first sample was banked in 2008, Sharzad explains. "We now do bespoke collections- we adapt to what the research needs and let that drive our collections".

The MCRC Biobank works differently to many other facilities as they can collect samples and send them out straight away, meaning the samples are in the hands of researchers as soon as possible.

This is called a prospective collection, and it is made possible by collaborations with the surgeons and pathologists who take the samples from patients.

106,800

samples provided directly to researchers

As part of their routine collections, where samples are collected and stored for future use, the MCRC Biobank also obtains rare tumour samples.

"Patients are coming to The Christie from across the UK to receive specialist care for rare tumour types that might not be seen in other locations. By banking these samples, it give us access to rare tumours before we start the research" Sharzad explains.

The MCRC Biobank currently has **70** active projects, **23** of which focus on rare cancers such as penile cancer, salivary cancer and cancer of unknown primary (CUP).

PhD student Sara Cabral talks about how she used the Biobank in her work on bone metastasis in breast cancer.

"My project is looking at a protein called osteomodulin which is found in the extracellular matrix- the supportive network that surrounds cells in breast tissue. We've found a link between expression of osteomodulin and increased risk of bone metastasis, and we're trying to understand this better by developing new models", Sara explains.

The Biobank helped Sara set up a bespoke, prospective collection for bone products so that she could create an accurate model of the bone using advanced 3D printing technology.

"We use bone donated by women undergoing a total hip replacement at Wythenshawe Hospital. It's a waste product, so using it for research is a win-win!"

Sara's work aims to see if osteomodulin could act as a biomarker- a biological indicator - to predict whether a woman with breast cancer is likely to develop bone metastasis.

"If we could identify women early on, it could help guide their treatment. For example, they could be started on an anti-absorptive therapy like Zoledronic acid which has been shown to reduce the chance of metastasis" Sara says.

Sara Cabral
PhD student

Kathy's story: My Rare Cancer Diagnosis

Chances are you know something about breast and lung cancers, but an estimated 1 in 4 people in the UK (or 24% of people with cancer) are diagnosed with a cancer that most people have probably never heard of.

These are known as rare cancers, and include cancers of the penis, tongue, appendix, and vagina, among others.

A cancer is considered rare if fewer than 6 cases are diagnosed per 100,000 people each year.

Kathy Morse

Kathy was diagnosed with a rare cancer in 2020 after noticing she was dizzy when she sat down. Initial tests came back as normal; however, Kathy later discovered a lump in her vagina that turned out to be a rare vaginal cancer.

Just 252 people are diagnosed with vaginal cancer each year in the UK.

"Having a rare cancer makes you feel extra isolated, and it needs more explanation to others... not one person I've spoken to in four years knows about my type of cancer." Kathy says.

Kathy was referred to The Christie for treatment where tests showed that her cancer was stage 3, meaning that it had also spread to nearby lymph nodes. In early 2021, Kathy's 2.5 cm tumour was removed, and her vagina was reconstructed during a long 7-hour surgery. She then started a gruelling 5-week course of chemotherapy and radiotherapy.

Vaginal cancer is extremely rare in younger women - most cases are in women over the age of 75. Kathy was only 53 years old when she was diagnosed, meaning she was not at high risk of getting vaginal cancer.

She is now determined to raise awareness of rare and gynaecological cancers, *"I'm hopeful to raise the profile and understanding of rare cancers and maybe even advocate for a rare cancer specialist nurse"* Kathy explains.

"I share my story to help others and remove the stigma around rare cancers"

To anyone with a recent diagnosis of a rare cancer, Kathy says *"my advice is to take one day at a time and don't feel stigmatised, get as much information as you can!"*

Rare cancers receive less funding, meaning there are often fewer new treatments than there are for more common cancers. This is why it is so important we hear from people like Kathy. If you would like more information on vaginal cancer, or Kathy's story, you can visit: CRUK and the eve appeal.

Scan here to access further information

SPACE FOR

expert cancer support

Our cancer support specialists, psychologists and benefits advisors run workshops and 1-2-1 support if you or someone you love has cancer.

Find us at The Robert Parfett Building,
The Christie Hospital, NHS Foundation Trust,
15 Kinnaird Road, Manchester, M20 4QL.
You don't need an appointment and all our support is free – just come in.

0161 641 4848
maggies.org/manchester

MAGGIE'S
Everyone's home of cancer care

The Hidden Cancer: CUP

A cancer of unknown primary, also called CUP, is a type of rare cancer that affects around 8,100 people in the UK each year.

In patients with CUP, cancer cells are found, but doctors cannot tell where in the body the cancer started. Even after performing scans and other tests like biopsies, the source of the cancer remains unknown. Detailed analysis of the biopsied cancer cells looking for a telltale appearance or markers confirm that they are metastatic, meaning they have come from another part of the body, however the site of the original cancer remains unknown.

Because doctors cannot tell where the cancer started (the primary cancer) CUP are particularly hard to treat.

In April 2024, researchers at the Cancer Research UK National Biomarker Centre including Drs Alicia-Marie Conway, Alexandra Clipson and Steven Hill published research on a new tool called **CUPiD**, which leverages biomarkers to help identify the primary site of a CUP.

A cfDNA methylation-based tissue-of-origin classifier for cancers of unknown primary

Instead of relying on tissue from invasive biopsies to detect the primary cancer, the National Biomarker Centre team use a liquid biopsy, a specific kind of blood test that can detect signs of cancer, such as cancer cell DNA.

All cells in our body release DNA into our blood as they grow and die, and cancer cells are no exception. This creates a mixture of normal and cancer cell DNA known as circulating-free DNA, or cfDNA in our blood.

The researchers at the National Biomarker Centre were specifically interested in a type of alteration that happens in normal and cancer cell DNA called methylation, which is where chemical tags called methyl groups are added to DNA, instructing the body to either ignore or listen to certain genes.

The addition of these methyl groups, called methylation patterns, are consistent within the same cancer type, but vary between different types of cancer. They are like unique postcodes for each type of cancer that can pinpoint where that piece of DNA has come from, making them very useful to identify CUP.

CUPiD is a machine learning tool- a form of artificial intelligence, called a classifier that analyses data and classifies it into categories. The team trained CUPiD using existing methylation datasets of various cancers to teach it how to identify and classify different cancers. By comparing its predictions to known cancer types in the database, the model gets more and more accurate, and with repeated training, CUPiD is able to predict the cancer type of previously unseen samples.

When CUPiD was tested on liquid biopsies from patients with CUP, it correctly predicted the type of primary tumour in 88.5% of cases.

What's next?

Although further testing and refinement of the tool on larger CUP datasets is needed, CUPiD's approach to classify CUP is promising.

"The next steps are to test CUPiD in a larger number of samples from patients. This will enable us to assess how well the test works and who might benefit most before designing a trial where we use the test to make treatment decisions. Being sure the test is robust and accurate is an important step before it can reach patients."
Dr Conway explains.

"We have secured funding from a Cancer Research UK Biomarker Project Award supported by Stand Up To Cancer® to do this, we will refine the tool and then test it on over 500 samples from patients where we know where the cancer started."
Dr Clipson says.

The hope is that the liquid biopsy approach would be introduced for all patients with CUP at the beginning of their diagnostic journey, so that their cancer can be compared to known samples to identify the primary cancer as early as possible. The team has also recently secured funding to adapt CUPiD to identify different types of biliary tract cancer (BTC). Diagnosing BTC often requires an endoscopic biopsy, but a limited amount of tissue can be obtained. So, the thought is that similar to its use in CUP, CUPiD could help detect unique methylation patterns in BTCs and differentiate the subtypes, enabling patients to be diagnosed earlier without the need for repeat invasive biopsies.

How could this impact patients?

Normally, a lab technique called immunohistochemistry is used to identify a CUP, where biopsied patient tissue is stained to try to identify proteins specific to a particular type of cancer. But, as there are so many different types of cancer, patients often have to undergo multiple, invasive biopsies to collect tissue for testing. These biopsies are an additional, unnecessary strain on patients and the testing is time consuming.

Also, as doctors cannot identify a patient's primary cancer, they end up being treated with chemotherapy which often does not work well. This is because the newer, more tailored therapies like immunotherapies are not currently available without knowing what the primary tumour is.

If widely adopted, this liquid biopsy method could reduce the need for invasive procedures, shorten the time it takes to diagnose patients, and increase the chances that patients receive a more targeted, effective treatment.

To find out more about CUP, you can visit the National Cancer Institute and Macmillan websites.

Scan here to access further information

It's in Our Genes: Hereditary Cancer Syndromes

Cancer is a genetic disease that's caused by changes in our DNA.

Most of the time, alterations in our DNA do no real damage. But sometimes, they happen in important genes allowing cells to grow out of control and turn into cancer. Generally these cancer causing changes happen by chance. However, environmental may have an impact, for example, we know that smoking and UV from the sun or artificial sources like sun beds can lead to cancer through by causing changes in our DNA.

12% of all cancers are linked to an inherited gene change.

A small proportion of people are at increased cancer risk because of changes in DNA that are in particularly important genes, and are part of a person's genetic makeup and so can be inherited. Here individuals and at-risk family members have a higher than average risk of developing certain types of cancer compared to the general population.

Individuals with these hereditary cancer syndromes are often diagnosed with multiple cancers over their lifetime and, depending on the gene involved, may develop their first cancer in childhood. So, it is really important that we are able to identify individuals with these hereditary cancer predisposing gene alterations as early as possible when there is the opportunity to implement age appropriate strategies for cancer prevention and early detection.

There are more than 20 different hereditary cancer syndromes.

Not all hereditary cancer syndromes are routinely tested for in the clinic. However, genetic testing would be recommended for people diagnosed with specific cancers in childhood or those with a strong family history of certain cancers.

Here are two examples of some of the more common hereditary cancer syndromes:

Hereditary breast and ovarian cancer syndrome is the most common hereditary cancer syndrome. It is caused by alterations in the BRCA1 and BRCA2 genes and increases the risk of developing breast cancer by up to 70% and ovarian cancer by up to 45%.

Lynch syndrome is a hereditary cancer syndrome caused by alterations in one of four genes that are responsible for finding and correcting errors in DNA. Mutations causing Lynch syndrome increase the risk of getting bowel cancer at a young age, as well as womb, ovarian, stomach, prostate and other cancers.

Research led by Professor Emma Crosbie, Professor of Gynaecological Oncology at the University of Manchester, led to a change in national policy in 2023 meaning that all women with womb cancer are now screened for Lynch syndrome- helping to identify women who may then also be at increased risk of developing bowel cancer, earlier.

Dr Emma Woodward, a Consultant Clinical Geneticist at Manchester University NHS Foundation Trust and Honorary Senior Lecturer at The University of Manchester is doing pioneering research to improve risk prediction and early detection for people that have, or are at risk of developing, hereditary cancer syndromes.

She is involved in several groundbreaking studies, including the CanCYP, ATLAS and DONATION projects.

CanCYP:

Patients with hereditary cancer syndromes often come to their doctors with pressing questions about their diagnosis, such as, ***"How likely is it that I will develop another cancer?"***. CanCYP is an innovative, data-driven project aiming to provide more accurate and personalized answers to these common patient questions.

The CanCYP project will make use of existing clinical data from NHS patients about their genetics and medical history from sources such as the National Cancer Registration and Analysis Service (NCRAS) database.

In this initial study, the focus is on children and young people with known hereditary alterations in the RB1 and TP53 genes who have developed cancers and undergone treatment, as well as any family members with confirmed alterations.

RB1 and TP53 are important genes that regulate cell growth and death. When altered, these genes are known to cause retinoblastoma (a rare childhood eye cancer of the retina) and Li-Fraumeni syndrome that increases the risk of several cancers including breast cancers and sarcomas.

This data will be used to calculate personalised cancer risk predictions, which can then be used in the clinic. By providing these tailored predictions, CanCYP has the potential to transform how doctors manage a person's risk focusing on strategies for prevention and early detection.

ATLAS:

The risk of a patient with Li-Fraumeni syndrome (LFS) developing a cancer over their lifetime is extremely high, up to 90% by the age of 60. So, detecting cancers at an early stage is key.

Currently, early detection for LFS patients involves annual whole-body MRI scans, often starting in childhood. Whilst these scans are mostly effective at detecting cancers, they can be challenging for patients as they require them to travel to hospital and waiting for results can cause patients increased anxiety.

ATLAS is a cutting edge trial that aims to detect cancers earlier in patients with LFS using liquid biopsies.

Liquid biopsies are a unique type of blood test that can detect signs of cancer, such as DNA from cancer cells. The amount and genetic makeup of this cancer cell DNA, called circulating-free DNA (cfDNA) is known to change over time. So, the idea behind the ATLAS trial is that regular liquid biopsies, monitoring cfDNA levels and its makeup in the blood, could be an additional way to detect cancers early in patients with LFS.

The study is also interested in the methylation patterns of cfDNA, a modification of the DNA caused by the addition of chemical tags called methyl groups. As it is thought that distinct methylation patterns may point to a particular organ, helping to identify the origin of the cancer. This is important as it can help to indicate which organ needs to be scanned in detail.

DONATION:

Changes in certain genes are known to play a role in causing cancer. However, a single alteration alone is not enough.

Cells must go through a series of changes, gaining multiple alterations over time to go from a normal cell to a cancer causing one. This process, called mutational evolution, happens very early, and causes precursor lesions to develop into cancer.

Unfortunately, these early changes are particularly difficult for researchers to study. It is especially difficult to study cancers that have hard to spot symptoms, such as pancreatic cancer, as these patients often go to their doctor later, when the cancer has already grown or spread.

The DONATION project aims to model the early mutational evolution that leads to pancreatic cancer, a notoriously hard to treat cancer caused by inherited mutations in 5-10% of cases.

The project will make use of samples from patients enrolled in the rapid autopsy programme, where donors undergo a post-mortem examination within six hours of their death.

Rapid autopsies provide a unique opportunity to study cancer, as samples can be collected from all the different parts of the body, including where the cancer has spread and importantly, unaffected tissues too.

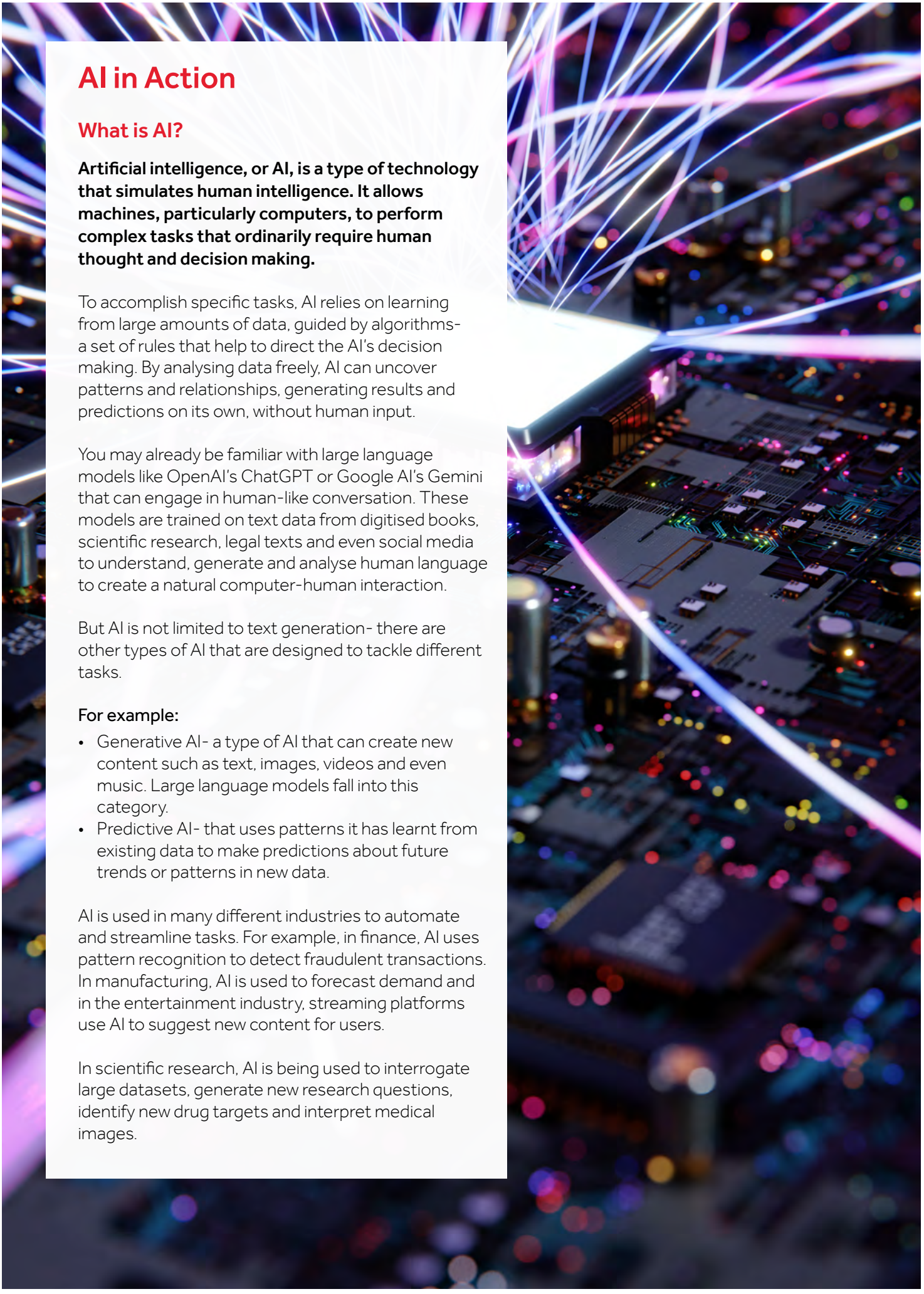
The project will compare samples from patients with known hereditary alterations in genes such as BRCA1 and BRCA2 that are responsible for repairing damaged DNA, to samples from healthy donors and those with non-cancerous precursor lesions to try to understand the early changes that lead to the development of cancer.

These changes will also be modelled in the lab using pancreatic organoids, a 3D, cell-based model that mimics the structure and function of the pancreas.

The hope is that by understanding the early changes that lead to cancer, researchers can find a way to intervene and prevent the cancer from progressing to its untreatable late stages.

To find out more about topics related to Dr Woodward's research, visit the National Cancer Institute, Macmillan and Genomics Education Programme websites.

Scan here to access further information



AI in Action

What is AI?

Artificial intelligence, or AI, is a type of technology that simulates human intelligence. It allows machines, particularly computers, to perform complex tasks that ordinarily require human thought and decision making.

To accomplish specific tasks, AI relies on learning from large amounts of data, guided by algorithms- a set of rules that help to direct the AI's decision making. By analysing data freely, AI can uncover patterns and relationships, generating results and predictions on its own, without human input.

You may already be familiar with large language models like OpenAI's ChatGPT or Google AI's Gemini that can engage in human-like conversation. These models are trained on text data from digitised books, scientific research, legal texts and even social media to understand, generate and analyse human language to create a natural computer-human interaction.

But AI is not limited to text generation- there are other types of AI that are designed to tackle different tasks.

For example:

- Generative AI- a type of AI that can create new content such as text, images, videos and even music. Large language models fall into this category.
- Predictive AI- that uses patterns it has learnt from existing data to make predictions about future trends or patterns in new data.

AI is used in many different industries to automate and streamline tasks. For example, in finance, AI uses pattern recognition to detect fraudulent transactions. In manufacturing, AI is used to forecast demand and in the entertainment industry, streaming platforms use AI to suggest new content for users.

In scientific research, AI is being used to interrogate large datasets, generate new research questions, identify new drug targets and interpret medical images.

A role for AI in predicting breast cancer risk

PhD student Stepan Romanov uses predictive AI in his work aimed at improving risk prediction for breast cancer. His focus is on breast tissue density- a measure of the amount of fatty versus glandular and fibrous tissue in the breasts.

"My project aims to better predict a women's risk of developing breast cancer by using AI to make the most of data available from mammograms from women enrolled in the NHS Breast Screening Program. Our goal is to make risk prediction more personalised, not just to detect breast cancer early, but also to predict the development of a cancer before it is even formed. Personalised risk prediction would also help us to identify women who are at low-risk who could be moved into the lower-risk program so that they are not being screened unnecessarily" Stepan explains.

Read more of Stepan's research here

The NHS Breast Screening Program.

Anyone registered with a GP as female will be automatically invited for an NHS breast screening, beginning between the ages of 50 and 53. Screening then takes place every three years, up until a person's 71st birthday.

The screening uses a type of X-ray called a mammogram to check for breast cancer and can find a cancer even before there are visible signs or symptoms. Four mammograms are taken in total to get the best images of both breasts, taking a few minutes each. Results of the mammograms are sent through the post, usually within two weeks of the screening appointment.

In 2022-23, the screening program detected cancers in **18,942 women** in England, and it is estimated to save **1,300 lives** each year.

Around 56,400 women and 390 men are diagnosed with breast cancer every year in the UK.

How AI sees what we can't

Typically, mammograms are used to detect lesions, abnormal growths within breast tissue and signs of breast cancer, and their role ends there. However, there is a wealth of information in these scans that could be useful for predicting cancer risk.

"It would be incredibly difficult for a radiologist to look through thousands of mammograms to see what features might correlate with a person's risk, but this is where AI is really good" Stepan says.

Stepan's work started by processing the mammograms into a usable format so that they could be applied to what's called a convolutional neural network or a CNN, a specialised AI tool that works specifically on images.

What is a CNN and how does it work?

A CNN is a mathematical tool that looks for broad features in an image, called the input.

Imagine you have an image of a cat. A CNN uses a filter to scan over the image in small sections like using a magnifying glass to look at a photo. Each filter is designed to extract features from the input image, like simple shapes, patterns and edges. Or, in the case of the cat, features like eyes, fur or whiskers. These are made into separate images showing the fur in one, the eyes in another etc.

As the CNN identifies more and more of these features, they are combined, and complex patterns and shapes begin to emerge, like the ears or face of the cat for example.

After processing the input image, the CNN connects all the identified features together and makes a prediction.

In the case of the cat, the CNN combines all the features it recognised, like the ears and the fur and it concludes that the image is of a cat.

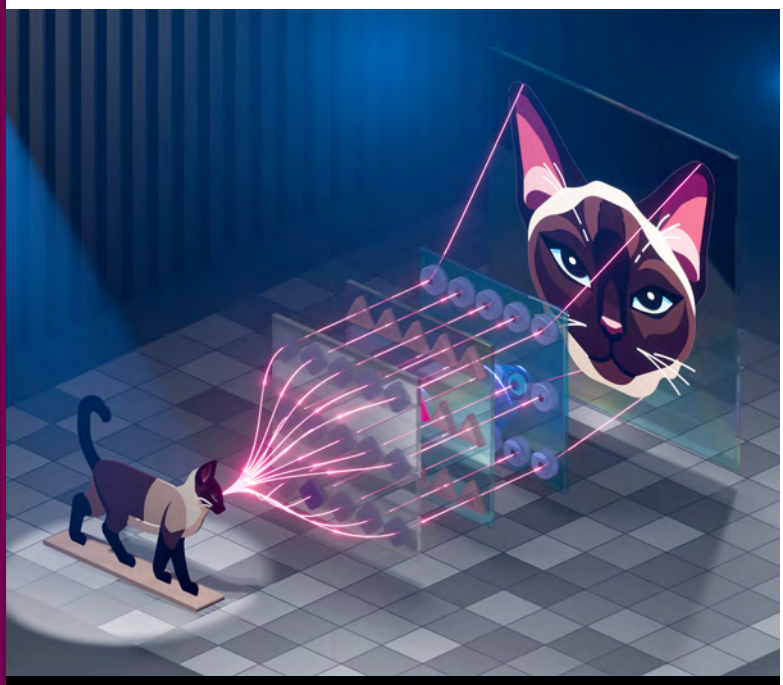
The CNN identifies features, shapes and patterns within the mammograms and based on this, the AI returns a personalised risk score.

Accurate risk predictions rely on the model being thoroughly trained on a large and diverse data set. *"In our study, we had a training set of mammograms from about 30,000 consenting women. We are really fortunate as we have a huge amount of data to work with just because the breast screening program exists!"* Stepan says.

"To train the model, we take an image knowing the outcome of the scan, feed it through the model and compare its prediction to the known outcome. If it got it wrong, it tunes its parameters to predict the correct outcome. If you do this enough times, it will be able to correctly classify an unseen image based on what it has been previously taught".

"In our work, we've seen that AI performs on par with radiologists at predicting risk from mammographic density."

But don't worry, the aim is not to replace your doctor or radiologist with AI, its role currently is to assist them. *"AI could be used to provide a second opinion" Stepan explains. "It could look at a scan and identify features that a radiologist may have missed, and a benefit is that it is instant. After the model is trained, it is as simple as pressing a button and it would immediately tell you what the answer is".*



Visual representation of a convolutional neural network

The challenges

However, a major obstacle that stands in the way of using AI for risk prediction is what is known as the 'black box' problem. This is a fundamental problem with AI- that it works in ways that we do not fully understand, so we do not know how it works internally and how it reaches its conclusions, unlike a human that can explain their reasoning.

The problem with this, Stepan explains, is that ***"As AI makes the prediction based on your mammogram, we really can't tell a patient anything more than their risk score and this could understandably frustrate patients. Whereas current risk prediction models that consider your basic clinical features can tell you that you are high risk because you have a gene alteration, or you are using hormone replacement therapy for example".***

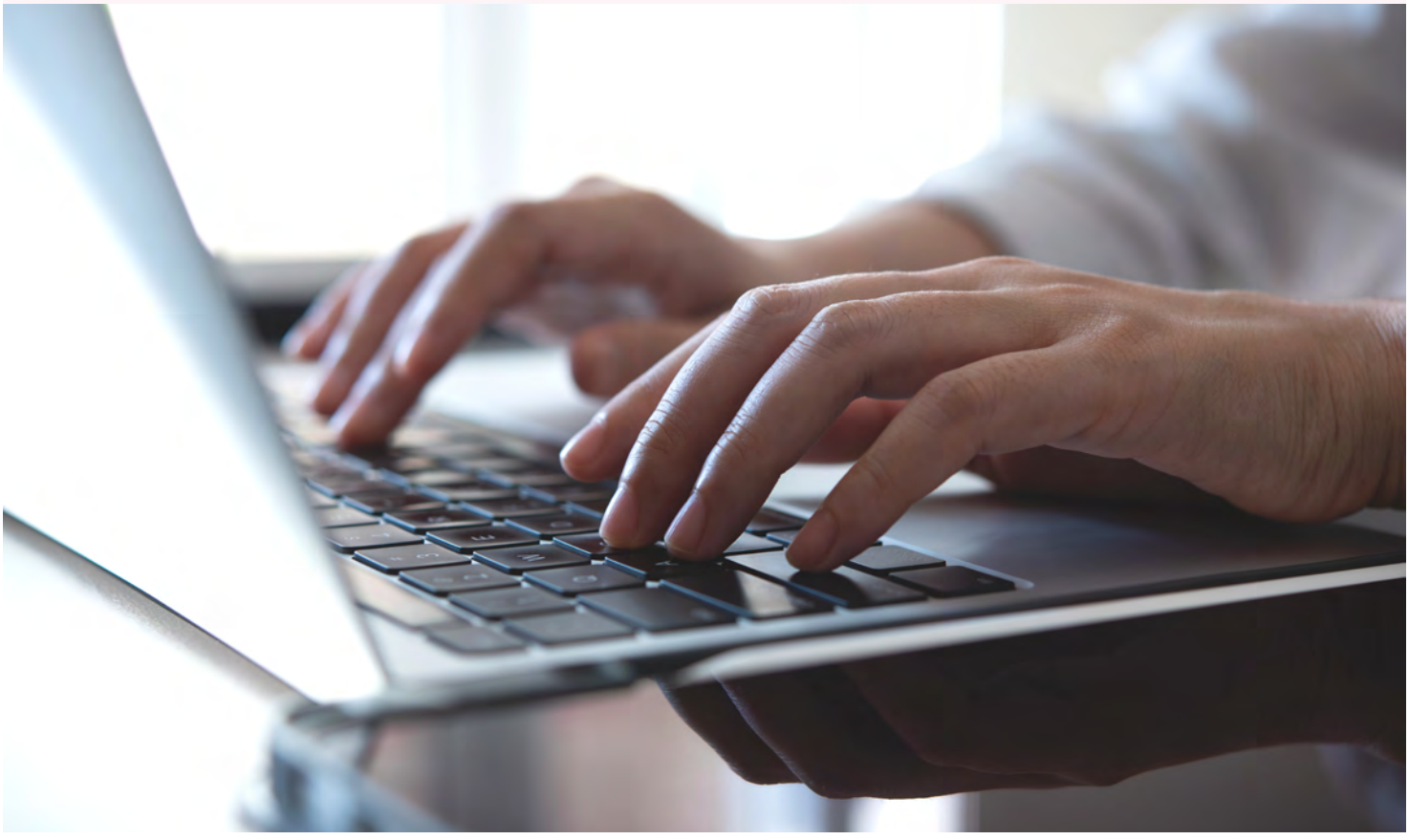
Stepan Romanov
PhD Student

Looking forward

AI has the potential to transform cancer care by offering a more informed, personalised approach to risk prediction. By analysing existing medical data, AI can help to identify patients at risk of developing cancers earlier, leading to earlier detection and patients being started on lifesaving treatments sooner, ultimately improving patient outcomes. Research like Stepan's is making important strides towards integrating AI into everyday healthcare.

To learn more about the topics covered in this article, visit the National Cancer Institute, CoppaFeel, and NHS websites.

Scan here to access further information



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