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Tissue and therapy assignment in cancers of unknown primary

Submission date 24/06/2026	**Recruitment status** Recruiting	[ ] Prospectively registered [ ] Protocol
Registration date 03/07/2026	**Overall study status** Ongoing	[ ] Statistical analysis plan [ ] Results
Last Edited 02/07/2026	**Condition category** Cancer	[ ] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
Doctors diagnose cancer of unknown primary (CUP) when cancer (primary) has spread to another part of the body (secondary) and doctors can't tell where it has spread from. Knowing where the cancer started means that better and more effective treatments can be given. The aim of this study is to use samples from secondary tumours from patients to identify what genetic changes have happened in their tumours and use this to work out where the primary site is. We will also use this information to find out what are likely to be the best treatments for each individual patient based on the genetic changes we find in their tumours. We hope that doing both these things will improve the effectiveness of treatments in the future.

Who can participate?
Patients aged 18 years and over who are under the care of clinicians in Sussex-based hospitals who have been diagnosed with a Cancer of Unknown Primary (CUP) or present with a Malignancy of Unknown Origin (MUO). Participants will have undergone, or will already be scheduled to undergo, a biopsy or surgery from which tumour tissue is available. Individuals with hepatitis B, hepatitis C, or HIV are excluded from participation.

What does the study involve?
Participants will provide consent for researchers to use tumour tissue obtained during routine clinical biopsy or surgery. No additional tissue samples or treatments are required. Tumour samples will undergo genetic sequencing, and the resulting data will be analysed using AI-based prediction tools.
Researchers will also access relevant information from medical records, including diagnosis, treatment, imaging findings, and outcomes. These data will be anonymised, so the research team will not be able to identify you.
Participation will not affect clinical care, as the software is still under evaluation, but the clinicians will be able to see your results. Participants can request a lay summary of the overall findings to be sent to them once the study is complete.

What are the possible benefits and risks of participating?
There are no anticipated physical risks because samples are collected as part of routine clinical care and no additional procedures are required. Participants are unlikely to receive any direct

benefit, as study findings will not be used to guide their treatment. However, the research may benefit future patients with CUP by improving diagnosis and treatment approaches.

Where is the study run from?
The study is coordinated through the University of Sussex, with patients recruited through hospital sites in the University Hospitals Sussex NHS Foundation Trust and East Sussex NHS Foundation Trust. Samples will be processed through NHS pathology services and sequenced at the Royal Marsden sequencing centre, with data analysis undertaken at the University of Sussex.

When is the study starting and how long is it expected to run for?
June 2026 to May 2028

Who is funding the study?
The study is sponsored by the University of Sussex and funded through a UK Research and Innovation (UKRI) Proof of Concept Grant and PhD studentships from the Sussex Cancer Research Centre and Sussex AI.

Who is the main contact?
Dr Frances Pearl, f.pearl@sussex.ac.uk

Contact information

Type(s)
Scientific, Principal investigator, Public

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Additional identifiers

Integrated Research Application System (IRAS)
357702

Central Portfolio Management System (CPMS)
68013

Study information

Scientific Title
Developing a pipeline for primary tissue assignment and individualised targeted therapy recommendations for cancers of unknown primary

Study objectives
Cancer of Unknown Primary (CUP) is when cancer cells are found in the body, but the place the cancer began is not known. It is the 6th leading cause of cancer death in the UK and the prognosis is poor, with a median survival of 6-9 months.
Precision medicine has transformed treatment strategies in known tumour types; however, in CUP there remains an urgent need to better understand CUP molecular characteristics to establish potential roles for novel therapeutic strategies. Treatment options remain limited due to difficulties in determining the primary site of the tumour and the lack of access to validated biomarkers.

The objective of this trial is to investigate whether a translational pipeline utilising AI-based genomic analysis could support improved diagnosis and treatment guidance for patients presenting with radiology findings suggestive of a Malignancy of Unknown Origin (MUO) and/or biopsy findings suggestive of a Cancer of Unknown Primary (CUP).

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 23/01/2026, London - Fulham Research Ethics Committee (2 Redman Place Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8000; fulham.rec@hra.nhs.uk), ref: 25/LO/0918

Primary study design
Observational

Secondary study design
Proof-of-concept trial

Study type(s)

Health condition(s) or problem(s) studied
Cancers of unknown primary (CUP)

Interventions
CUP patients will be identified as eligible for the trial by the Sussex Hospitals MDT and will be invited to participate in the study. Following recruitment and full consenting of the patient, the research team will collect anonymised patient data. The eCRF will contain details of the tumour characteristics (including histological and molecular features), treatment (including extent of surgery, radiotherapy schedule, chemotherapy schedule, and treatment dates), response to treatment, and survival data.

Excess tumour tissue from the tumour tissue samples collected during biopsy or standard of care surgical procedure will be utilised for the study, ensuring that sufficient sample is available to be sent for standard clinical pathological assessment.
FFPE samples will be prepared in the form of 5 x 10-micron curls (where tumour nuclei > 20%) indicating tumour percentage and sent for DNA and RNA sequencing (50X Whole Exome

Sequence and 100X short-read RNA sequencing). Outputs will be analysed using predictive AI programs to determine the tissue type of the tumour. The AI DependANT pipeline (UK patent No. 2500396.3) will be used to identify published actionable genes/mutations with licensed precision therapies, essential targetable genes in the tumour and potential clinical trials that the patient may be eligible for, from a molecular standpoint.

Outputs from the AI pipelines will then be combined with the anonymised patient information to allow full analysis of the data, including:
1. Turnaround time: how long from sample to AI result, given how short median survival is for CUP patients.
2. Concordance with eventual diagnosis: for patients whose primary site later becomes established, check if the AI's prediction matched.
3. Clinician qualitative feedback: ask the MDT/oncologist whether the AI output was plausible and usable.

Intervention Type
Genetic

Primary outcome(s)
1. Proportion of patients identified as eligible and invited to participate that provide written consent for AI analysis of their tumour samples, measured using study screening and consent logs as a percentage of eligible patients invited to participate, at monthly intervals from month 1 to month 12

2. Proportion of consented tumour samples containing sufficient tumour content and material to proceed to DNA and RNA sequencing, measured using pathology assessment reports and sequencing laboratory records as a percentage of consented tumour samples, at monthly intervals from month 1 to month 24

3. Proportion of sequenced samples that are fully analysed by the AI pipeline, measured using AI pipeline processing records as a percentage of sequenced tumour samples, at monthly intervals from month 1 to month 24

4. Proportion of fully analysed samples in which the AI pipeline identifies an actionable target with a licensed precision therapy, measured using AI pipeline outputs and molecular analysis reports as a percentage of fully analysed tumour samples, at monthly intervals from month 1 to month 24

5. Proportion of fully analysed samples in which the AI pipeline identifies one or more potential clinical trials for which the patient may be eligible, measured using AI pipeline clinical trial matching reports as a percentage of fully analysed tumour samples, at monthly intervals from month 1 to month 24

6. Proportion of sequenced samples that are fully analysed by the AI pipeline and a tissue type identified, measured using AI tissue-of-origin prediction reports as a percentage of sequenced tumour samples, at monthly intervals from month 1 to month 24

7. Assessment of optimisation of the diagnostic workflow for cancers of unknown primary (CUP) through incorporation of genomic sequencing and AI-derived data, measured using an end-of-study evaluation of study process metrics, genomic sequencing results, AI outputs and multidisciplinary team review, at at month 24

Key secondary outcome(s)

Completion date
31/05/2028

Eligibility

Key inclusion criteria
1. Aged 18 years or over
2. Written informed consent according to International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (ICH /GCP) and national regulations
3. ECOG Performance status 0-2
4. Suspected diagnosis of CUP as per the European Society for Medical Oncology (ESMO) guidelines, or presenting with a MOU
5. Well enough for biopsy

Patients must have:
1. The local pathology reports confirming compatibility with CUP diagnosis and the associated slides used for the diagnosis
2. Discussion at a local CUP Multidisciplinary Team (MDT) suspecting diagnosis
3. Availability of tumour histological report

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Patient with an immunohistochemistry profile that provides a definitive clinical indication of a primary cancer with a specific treatment
2. Known HIV, Hepatitis B, C positive, due to the difficulties in handling high-risk specimens
3. Patients who are unable to provide fully informed written consent

Date of first enrolment
01/06/2026

Date of final enrolment
31/05/2027

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Royal Sussex County Hospital
Eastern Road
Brighton
England
BN2 5BE

Study participating centre
Worthing Hospital
Lyndhurst Road
Worthing
England
BN11 2DH

Study participating centre
Eastbourne District General Hospital
Kings Drive
Eastbourne
England
BN21 2UD

Sponsor information

Organisation
University of Sussex

ROR
https://ror.org/00ayhx656

Funder(s)

Funder type

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Sussex Cancer Fund

Alternative Name(s)
Sussex Cancer Treatment Fund, Sussex Cancer Fund for Treatment and Research, Sussex Cancer Fund Limited, SCF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
University of Sussex

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype

Universities (academic only)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Dr Frances Pearl (f.pearl@sussex.ac.uk). Metadata from the study, and details on how to contact the data custodians, will be registered in the Health Data Research Gateway.

IPD sharing plan summary
Available on request