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The European registry of familial pancreatic cancer and hereditary pancreatitis

Submission date 23/01/2025	**Recruitment status** Recruiting	[_] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 24/01/2025	**Overall study status** Ongoing	
Last Edited 04/04/2025	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims

Pancreatic cancer is the tenth most common cancer in the UK with around 10,000 people diagnosed each year. Pancreatic cancer has the lowest survival of all common cancers, with less than 1 in 4 surviving more than 1 year after diagnosis and less than 1 in 14 surviving beyond 5 years. In most cases, we do not know why pancreatic cancer develops, but we do know of risk factors that increase the likelihood of developing the condition. These factors include age, tobacco use, obesity and genetic factors. Having any one, or a combination of these does not mean you will definitely develop cancer.

Pancreatic cancer is a difficult cancer to diagnose, with less than 1 in 5 people being diagnosed at an early stage when treatment is most likely to be successful. Unfortunately, only 1 in every 10 people with pancreatic cancer will receive potentially curative surgery, only 2 in 10 will receive chemotherapy and 7 in 10 will not receive any active treatment. Nearly half of pancreatic cancer cases are diagnosed through an emergency presentation, where the one-year survival rate is only 12% which is three times lower than people diagnosed through a GP referral.

Most cases of pancreatic cancer appear out of the blue, with no previous family history of the condition. There are, however, families where there is more than one case of pancreatic cancer. This could be entirely coincidental but, in some cases, pancreatic cancer develops in these families because of a faulty gene that is inherited by affected individuals (familial pancreatic cancer).

Every organ in your body is made up of millions of cells. The growth of these cells is normally very carefully controlled; cancer develops when these cells grow out of control, forming a lump. Cell growth is controlled by the genes within each cell and damage to these genes can result in loss of control of how your cells divide. In many cancers, we know which genes have been damaged to cause that specific cancer, but in the majority of families with a history of pancreatic cancer, we do not yet know the causative gene.

Through years of dedicated research into pancreatic cancer, we now know some of the genes that cause pancreatic cancer to develop, however, we are still a long way from fully understanding the genetic cause of inherited pancreatic cancer.

We want to further our understanding of the genetic cause of pancreatic cancer. We want to understand the role of known genes in the development of pancreatic cancer and also want to search for other genetic causes of pancreatic cancer that have not yet been discovered.

Who can participate?
Registry:
1. Two first-degree relatives with pancreatic adenocarcinoma.
2. A family with three or more relatives with pancreatic ductal adenocarcinoma.
3. Families with pancreatic cancer and other cancers (e.g. bowel, breast/ovarian, melanoma, gastric) that suggest a known cancer predisposition syndrome.
4. Families with a known inherited cancer syndrome (e.g. Hereditary Non-Polyposis Colorectal Cancer (HNPCC), familial atypical multiple mole melanoma (FAMMM), Lynch syndrome) with one individual affected by pancreatic cancer
5. Peutz-Jeghers syndrome
6. Families with a causative gene linked to pancreatic cancer (e.g. BRCA2 or yet undiscovered genes) and at least one case of pancreatic cancer in the family
7. Families with two or more relatives with idiopathic pancreatitis
8. Families with at least one case of pancreatitis and a confirmed causative mutation in the PRSS1 gene

Screening:
1. Individuals over 40 years of age from an established pancreatic cancer family. Inheritance of predisposition consistent with high penetrant autosomal dominant inheritance. For example, at least two first-degree relatives with pancreatic ductal adenocarcinoma, where no non-penetrant carriers have to be assumed over the age of 75 years
2. Unaffected member of a family with an associated cancer syndrome and at least one case of pancreatic cancer, who has been shown to carry the relevant genetic alteration
3. Any member of a hereditary pancreatitis family who has been confirmed to carry a causative PRSS1 mutation
4. An affected member of a family consistent with HP who has tested negative for known causative PRSS1 mutations
5. Individuals incidentally found to have cystic lesions or other clinical features that indicate an increased risk of pancreatic cancer may also be included
6. There will be adaptation to risk models as the study progresses to fit the needs of the study outcomes as the study progresses

What does the study involve?
Registry:
Should you wish to register your family details with EUROPAC, we need you to complete a questionnaire that will give us all the information we require to enter your family into our database. The questionnaire is all about you, your lifestyle and relevant medical history and asks about all of your relatives, whether they are alive or not, any relevant medical history and the cause of death of any deceased relatives.
We want the information we put in our database and any advice that we give to you and your family, to be as accurate as it possibly can. We will not proceed with your registration unless we have all the necessary information that we need to do so. The most important part of this process is to confirm the information you are giving us about your affected relatives. We require confirmation of diagnosis for any relative who has been affected by pancreatic cancer or who has a relevant genetic syndrome. We can only accept confirmation in the form of:
1. A letter from a pancreatic specialist, clinical geneticist or GP with all of your relative's details stating the diagnosis of pancreatic cancer or a relevant genetic syndrome.
2. A death certificate stating pancreatic cancer as the cause of death

Screening:
Everyone who is offered the opportunity to take part in the screening will be seen in our EUROPAC clinic at the Royal Liverpool Hospital or offered a telephone appointment. At this

appointment, we will discuss your personal and family history again and talk through the rationale and process of screening. You will have the opportunity to ask any questions and we will confirm your intention to take part and sign a consent form.
We work with a number of collaborators across the UK who can facilitate screening. If appropriate, we can refer you to a local screening centre who will offer you an appointment to meet them before screening.
After your clinic appointment, we will start the screening process. This will involve blood tests and scans of your pancreas that will be performed either: every 6 months, annually, or every other year, depending on your risk. A set of baseline investigations will be arranged. Analysis of your pancreatic juice may be available. You can choose to take up any or all the options. Once the results of your investigations are available, we will write to you with the outcome and inform you of any further action that may be required.
You will either be seen in clinic, or contacted every year. At this annual check-in, we will check for any changes in your medical history, or if there have been any new developments in your family. We will talk through the results of your screening investigations and confirm with you your willingness to continue the screening process.
The blood tests and imaging can all be described as the best medical management for high-risk patients. The collection of pancreatic juice for molecular analysis is a research investigation. The findings are convincing within a laboratory setting but the molecular analysis has not been proven in living subjects in an ongoing trial.
No aspect of normal medical treatment will be withheld as part of this trial and at the end of the trial, it is expected that the results will be published in the scientific literature. You would not be identifiable to others as a result of any publications.

What are the possible benefits and risks of participating?
Registration:
We recognise that this can be a worrying process to go through. Hearing that you or members of your family are at increased risk of developing illnesses like pancreatic cancer can be worrying. If you or any of your family members are struggling to process the information provided as a result of registering with us, please contact the EUROPAC office and we can arrange to talk through this with you. However, as we are not able to formally provide specific genetic counselling, we may also suggest talking to your GP or a clinical geneticist for further information.
Taking a blood sample from you should be a straightforward process and not affect you in any way. Occasionally, superficial bruising can occur around the area where the sample has been obtained. If an attempt to take blood from you is unsuccessful, this will not impact your registration with EUROPAC.
Genetic testing can reveal altered genes that can predict your susceptibility to certain illnesses in the future. We will only disclose the results of genetic tests that may be relevant to the family to participants who request us to do so.
Although every effort is made to preserve your confidentiality and protect your anonymity, it is theoretically possible for collaborators to identify you from information shared with them.

Screening:
All the screening methods have advantages and disadvantages.
The blood tests are very low risk, and a serious complication would be very rare. All the equipment used will be sterile, single-use equipment in common use within the NHS. A bruise would be a relatively common complication.
The CT scan builds up an image by passing radiation through the body. It is known that moderate and high doses of radiation are damaging and, at worst, could even cause cancer. The risk of cancer from each CT scan is described as low and calculated at somewhere between a one in a thousand and one in ten thousand chance. A single CT scan of the abdomen has been calculated to be the equivalent of a few years of normal background radiation. For this reason, we only

conduct one baseline CT scan.
The MRI scan uses strong magnets to generate the images. If you have any metallic implants in your body (such as coils in the blood vessels around your brain or a pacemaker), it is very unlikely that you will be able to have an MRI. We will talk about this in the clinic. You will lie on a bed and pass through a tunnel during the scan, if you have claustrophobia or become anxious in enclosed spaces you may not tolerate the MRI.
The EUS involves the insertion of a scope through the mouth, down your food pipe (oesophagus) and into the stomach, where images of the pancreas are obtained by a very high-definition ultrasound. The throat is numbed with local anaesthetic and you are sedated during the procedure so it is normally well tolerated. There is a risk of causing damage to the gullet or stomach during the procedure. This is a rare complication (and can very rarely be fatal) that occurs at a rate of between one in a thousand and one in ten thousand procedures. If this were to occur, it can be treated and may (but doesn't always) require an operation to repair it.
The OGD and collection of the duodenal juice aspirate carries a similar risk of puncturing an organ as the EUS described above and is otherwise a similar procedure.
You may find that having screening investigations makes you more anxious about your health and your cancer risk. This is difficult to predict. Other people find having the investigations reassuring as it helps to put their minds at rest.
Any of the blood and imaging methods could detect a problem that is unrelated to pancreatic cancer. CT scans are very effective at detecting problems within the body and there is always the possibility of finding something unexpected. If this falls within the expertise of the clinician who would oversee the screening process for you, they would deal with this. If appropriate, you would be referred to another specialist. Conversely, all the investigations performed are targeted towards your pancreas so there is a small chance that conditions developing outside of your pancreas may not be detected as this is beyond the scope of the imaging being performed.
It is possible that the screening investigations could detect a problem with the pancreas. Growths can be "benign", (for example, inflammation or scarring) or could be a cancer. It is difficult to tell the difference between the two without performing further investigations. This may include further scans or biopsies of an area of concern. If a growth is found and it is possible to remove it, your consultant would discuss your options with you in the clinic and an operation may be offered.

Where is the study run from?
The University of Liverpool (UK)

When is the study starting and how long is it expected to run for?
July 2019 to July 2039

Who is funding the study?
1. NHS England
2. Pancreatic Cancer UK
3. Cheshire and Merseyside Cancer Alliance

Who is the main contact?
Study Coordinator, europac@liverpool.ac.uk

Contact information

Type(s)
Principal investigator

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Additional identifiers

Integrated Research Application System (IRAS)
248099

Central Portfolio Management System (CPMS)
42827

Study information

Scientific Title
Primary and secondary screening in individuals with inherited pancreatic disease syndromes for pancreatic ductal adenocarcinoma and complications of other pancreatic diseases

Acronym
EUROPAC

Study objectives
The EUROPAC study has been productive, producing 19 publications in the last 5 years alone. However, some of our principal objectives have not yet been met. Most importantly we have not yet identified an effective modality for early detection of pancreatic cancer. One reason for this is ongoing technological developments; the tools available to us now were not available when EUROPAC started (in the 1990s). The other reason is simply the lack of outcomes to date. Validating methods for detecting early pancreatic cancer requires prospective events. We observe 5 cancer cases per year in the familial pancreatic cancer (FPC) cohort of families and one case of pancreatic cancer in the hereditary pancreatitis (HP) group every 2 years. Unfortunately, these have mostly been in individuals who were not on our screening programme or indeed registered with EUROPAC.

The rationale for continuing the EUROPAC study is that we can now improve our recruitment practices to enrich for incident cases within our group of registered individuals. The epidemiological and demographic data we have already acquired and (in some cases) published will be used for stratification of cancer risk. We will also benefit from improved methods of pancreatic imaging including advances in end luminal ultrasound, computed tomography and magnetic resonance imaging. There are also new biomarkers available, which we will be able to test and, following validation, could be used to phase subsequent screening.

Continuing the study will also allow us to further develop our study of disease progression. There is no limitation of cases for this aim and recruitment of further patients will allow models to be refined and improved. We therefore wish to continue recruitment to this registry and to continue to pilot secondary screening for pancreatic cancer in the individuals registered. The registry has also proved an invaluable resource for studying pancreatic diseases in general, including diabetes, acute and chronic pancreatitis as well as cancer. We also wish to continue this analysis, monitoring disease progression from acute pancreatitis to chronic pancreatitis with endocrine and exocrine failure.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 30/09/2019, Yorkshire & The Humber - South Yorkshire Research Ethics Committee (NHSBT Newcastle Blood Donor Centre Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 (0)207 104 8079; southyorks.rec@hra.nhs.uk), ref: 19/YH/0250

Primary study design
Observational

Study design
Observational registry

Study type(s)
Prevention, Screening, Efficacy

Health condition(s) or problem(s) studied
Pancreatic ductal adenocarcinoma (PDAC)

Interventions
EUROPAC, although having international reach is described in relation to the UK. This national prospective observational study has been running for several decades but has been modified into the current trial in 2019, which aims to recruit and screen 10,000 individuals with either familial pancreatic cancer (FPC) or hereditary pancreatitis (HP). Applicants are assessed for eligibility by generating an individual pedigree and by attributing a family risk score (FS). Those with an FS >30 are offered baseline imaging and then 3-yearly triplets of endoscopic ultrasound (EUS) yearly, and a magnetic resonance scan (MRI) (in the third year). Those with an FR >60 are offered both EUS and MRI yearly. Biospecimens are collected at registration to support future biomarker development and detect pancreatic cancer early.

Intervention Type
Other

Primary outcome(s)
Number of early-stage (stage 0, 1 or 2) pancreatic cancers found, measured at baseline CT scan and at subsequent screening investigations (yearly)

Key secondary outcome(s)
1. Number of late-stage (stage 3 or 4) pancreatic cancers found, measured at baseline CT scan and at subsequent screening investigations (yearly)
2. Number of actionable lesions found, measured at baseline CT scan and at subsequent screening investigations (yearly)

Completion date
01/07/2039

Eligibility

Key inclusion criteria
Inclusion Criteria for Registry:
1. Two first-degree relatives with pancreatic adenocarcinoma
2. A family with three or more relatives with pancreatic ductal adenocarcinoma.
3. Families with pancreatic cancer and other cancers (e.g. bowel, breast/ovarian, melanoma, gastric) that suggest a known cancer predisposition syndrome.
4. Families with a known inherited cancer syndrome (e.g. Hereditary Non-Polyposis Colorectal Cancer [HNPCC], familial atypical multiple mole melanoma [FAMMM], Lynch syndrome) with one individual affected by pancreatic cancer
5. Peutz-Jeghers syndrome
6. Families with a causative gene linked to pancreatic cancer (e.g. BRCA2 or yet undiscovered

genes) and at least one case of pancreatic cancer in the family.
7. Families with two or more relatives with idiopathic pancreatitis.
8. Families with at least one case of pancreatitis and a confirmed causative mutation in the PRSS1 gene.

Inclusion Criteria for Screening:
1. Individuals over 40 years of age from an established pancreatic cancer family. Inheritance of predisposition consistent with high penetrant autosomal dominant inheritance. For example, at least two first-degree relatives with pancreatic ductal adenocarcinoma, where no non-penetrant carriers have to be assumed over the age of 75.
2. Unaffected member of a family with an associated cancer syndrome and at least one case of pancreatic cancer, who has been shown to carry the relevant genetic alteration.
3. Any member of a hereditary pancreatitis family who has been confirmed to carry a causative PRSS1 mutation.
4. An affected member of a family consistent with HP who has tested negative for known causative PRSS1 mutations.
5. Individuals incidentally found to have cystic lesions or other clinical features that indicate an increased risk of pancreatic cancer may also be included.
6. There will be adaptation to risk models as the study progresses to fit the needs of the study outcomes as the study progresses.

Participant type(s)
Population

Healthy volunteers allowed
No

Age group
All

Lower age limit
0 Years

Upper age limit
99 Years

Sex
All

Key exclusion criteria
1. Any participant who is incapable of providing informed consent.
2. For genetic testing: Any individual who does not consent to be informed of clinically significant results. Genetic testing for a predisposition for pancreatitis will still be carried out on individuals who have expressed a wish not to be informed following detailed discussions on the limitations of a right not to know in this case; testing will be carried out only if individuals wish to have testing just for research.
3. For screening: Individuals of less than 40 years of age or 10 years younger than the youngest case in the family will be excluded.
4. For screening: Any individual deemed to have less than a 2% chance of developing PDAC in the next three years will be excluded. This will depend on the evidence supporting the models and the exclusion will only apply if the steering committee agrees on the risk assessment. A risk

assessment will be made using progressively developed models.
5. For screening: Any female participant able to bear a child but who has not taken appropriate contraceptive measures.

Date of first enrolment
01/07/2019

Date of final enrolment
01/07/2039

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

Study participating centre
Royal Liverpool and Broadgreen University Hospitals NHS Trust
Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre
Glasgow Royal Infirmary
84 Castle Street
Glasgow
United Kingdom
G4 0SF

Study participating centre
The Freeman Group of Hospitals NHS Trust
Freeman Hospital
Freeman Road
High Heaton

Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Nottingham University Hospitals NHS Trust - City Campus
Nottingham City Hospital
Hucknall Road
Nottingham
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NG5 1PB

Study participating centre
Morriston Hospital
Heol Maes Eglwys
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Swansea
United Kingdom
SA6 6NL

Study participating centre
Bristol Royal Infirmary
Marlborough Street
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United Kingdom
BS2 8HW

Study participating centre
Plymouth Hospitals NHS Trust
Derriford Hospital
Derriford Road
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United Kingdom
PL6 8DH

Study participating centre
University Hospital Southampton NHS Foundation Trust
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Tremona Road
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SO16 6YD

Study participating centre
Uclh
250 Euston Road
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NW1 2PQ

Sponsor information

Organisation
University of Liverpool

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Government

Funder Name
NHS England

Funder Name
Pancreatic Cancer UK

Alternative Name(s)

PCUK

Funding Body Type
Government organisation

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

Location
United Kingdom

Funder Name
Cheshire and Merseyside Cancer Alliance

Results and Publications

Individual participant data (IPD) sharing plan
Data available upon reasonable request from Annabelle Boughey (A.boughey@liverpool.ac.uk)

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		03/04/2025	04/04/2025	Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes