

BIORESOURCE PAPER

# Parelinoer Institute Biobank Hereditary Colorectal Cancer: A Joint Infrastructure for Patient Data and Biomaterial on Hereditary Colorectal Cancer in the Netherlands

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Each year approximately 15,000 patients are diagnosed with colorectal cancer (CRC) in the Netherlands, of whom 5–10% are associated with a hereditary syndrome. To enable future research into hereditary CRC, we established a collaborative biobank for hereditary CRC in all eight University Medical Centers (UMCs) in the Netherlands in 2009. This Biobank Hereditary CRC is part of the Parelinoer Institute (PSI), which is funded by the Dutch Federation of UMCs and the Dutch Government. Besides the multicenter collaboration, the multidisciplinary nature of this biobank – involving Gastroenterology, Genetics and Surgery – is essential for its functionality and value.

Patients at increased risk of hereditary CRC and/or Polyposis, or with a proven germline mutation causing CRC and/or Polyposis are included. Both clinical data (demographic data, details on medical and family history, information on surveillance, endoscopy and surgery, results of microsatellite instability and molecular genetic tests) and biomaterial (DNA, plasma, serum and tissue) are collected in a standardized manner.

**Keywords:** Clinical biobanking; Parelinoer Institute; hereditary colorectal cancer; harmonized standards; research standards

## (1) Bioresource Overview

### Project description

The Biobank Hereditary colorectal cancer (CRC) was established in 2009 with the aim to enable researchers to gain a better insight into the genetic factors contributing to the development of CRC, and ultimately, disease prevention. In addition, future research will improve the quality and efficiency of care of individuals with hereditary CRC.

Participants are 1) diagnosed with a germline mutation that causes CRC and/or Polyposis (e.g. *APC*, *MLH1*, *MSH2*,

*MSH6* or *MUTYH*) ('affected') or 2) are at an increased risk of hereditary CRC and/or Polyposis ('unaffected'). Patients diagnosed with CRC before the age of 70 years, diagnosed with an adenoma before the age of 40 years, diagnosed with cumulative more than 10 adenomas, diagnosed with polyposis or diagnosed with CRC and/or adenoma with a germline mutation present in the family for hereditary CRC and/or Polyposis are considered to have an increased risk of hereditary CRC and/or Polyposis. Both clinical data (demographic data, details on medical and family history plus endoscopy and surgery, results of microsatellite

instability and molecular genetic tests) and biomaterial (DNA, plasma and serum plus both unaffected colorectal tissue and affected colorectal tissue, i.e. adenoma or carcinoma) are collected in a standardized way.

The Biobank Hereditary CRC is part of the Parelinoer Institute (PSI; [1]), which is a unique nationally representative biobanking partnership between the eight University Medical Centers (UMCs) in the Netherlands. As such the Biobank Hereditary CRC is embedded in a mature national infrastructure for biobanks.

### Classification (1)

Human.

### Species

*Homo sapiens*.

### Classification (2)

Clinical biobank: biological samples and associated data, clinical data.

### Context

#### *Spatial coverage*

All eight University Medical Centers across the Netherlands: Academic Medical Center (Amsterdam), Erasmus Medical Center (Rotterdam), Leiden University Medical Center, Maastricht University Medical Center, Radboud University Medical Center (Nijmegen), University Medical Center Groningen, University Medical Center Utrecht, VU University Medical Center (Amsterdam).

Northern boundary: +53.4647366.

Southern boundary: +50.757197.

Eastern boundary: +7.222824.

Western boundary: +3.364563.

#### *Temporal coverage*

Start data: 2009. End date: not applicable. The intention is to include patients as long as possible, which implies that biomaterial and associated data will be stored without time limitations.

#### *Temporal coverage for accessibility*

N/A.

The Biobank Hereditary CRC has not indicated a date when it has to be destroyed.

## (2) Methods

### Steps

Eligible individuals for the Biobank Hereditary CRC are included at three different departments: the departments of Human Genetics, Surgery or Gastroenterology. Individuals are considered to be eligible when they have been diagnosed with a germline mutation that causes CRC and/or Polyposis, diagnosed with CRC before the age of 70 years or with an adenoma before the age of 40 years, diagnosed with cumulative more than 10 adenomas, diagnosed with polyposis, diagnosed with CRC and/or adenoma with a germline mutation present in the family for hereditary CRC and/or Polyposis. Patients are recruited

and consented in one of the participating UMC's by a clinician or a research nurse. Standard operating procedures (SOPs) are in place to cover the consent and withdrawal process.

Each department collects biomaterials in a uniform way and in a routine clinical care setting.

Tissue from a surgical procedure or colonoscopy will be stored as frozen or Formalin-Fixed Paraffin-Embedded (FFPE) material. Tissue samples are processed by trained and certified staff through the UMC histology departments and only surplus material is passed to the Biobank Hereditary CRC. Some participants will visit the UMC more often, e.g. for endoscopy surveillance. For these participants, follow-up data will be collected and samples of plasma, serum and tissue will be stored with a maximum of twice a year in order to reduce the burden. This will be the first two visits in a year because it is not possible to determine in advance which event is important.

Sample handling and storage are based on SOPs. These procedures were established by PSI to ensure standardized sample collection and handling, and to guarantee a collection of samples of high and reproducible quality [1]. Deviations from the SOPs are recorded using predefined categories which include: issues with haemolytic, lipemic, icteric, wrong tube, incorrect volume collected, storage temperature deviation, longer storage time, incorrect mixing/homogenization, different centrifugation process, storage problem or other deviation as free text. **Figure 1** shows the schematic workflow of the Biobank Hereditary CRC. The biomaterial is stored at each participating UMC. Note: this is a general workflow that can deviate in the different participating UMCs, depending on the local workflows.

### Stabilization/preservation

**Table 1** gives an overview of procedures for collecting, processing and storing of samples defined in the Biobank Hereditary CRC's biomaterial protocol.

### Type of long-term preservation

See **Table 1**.

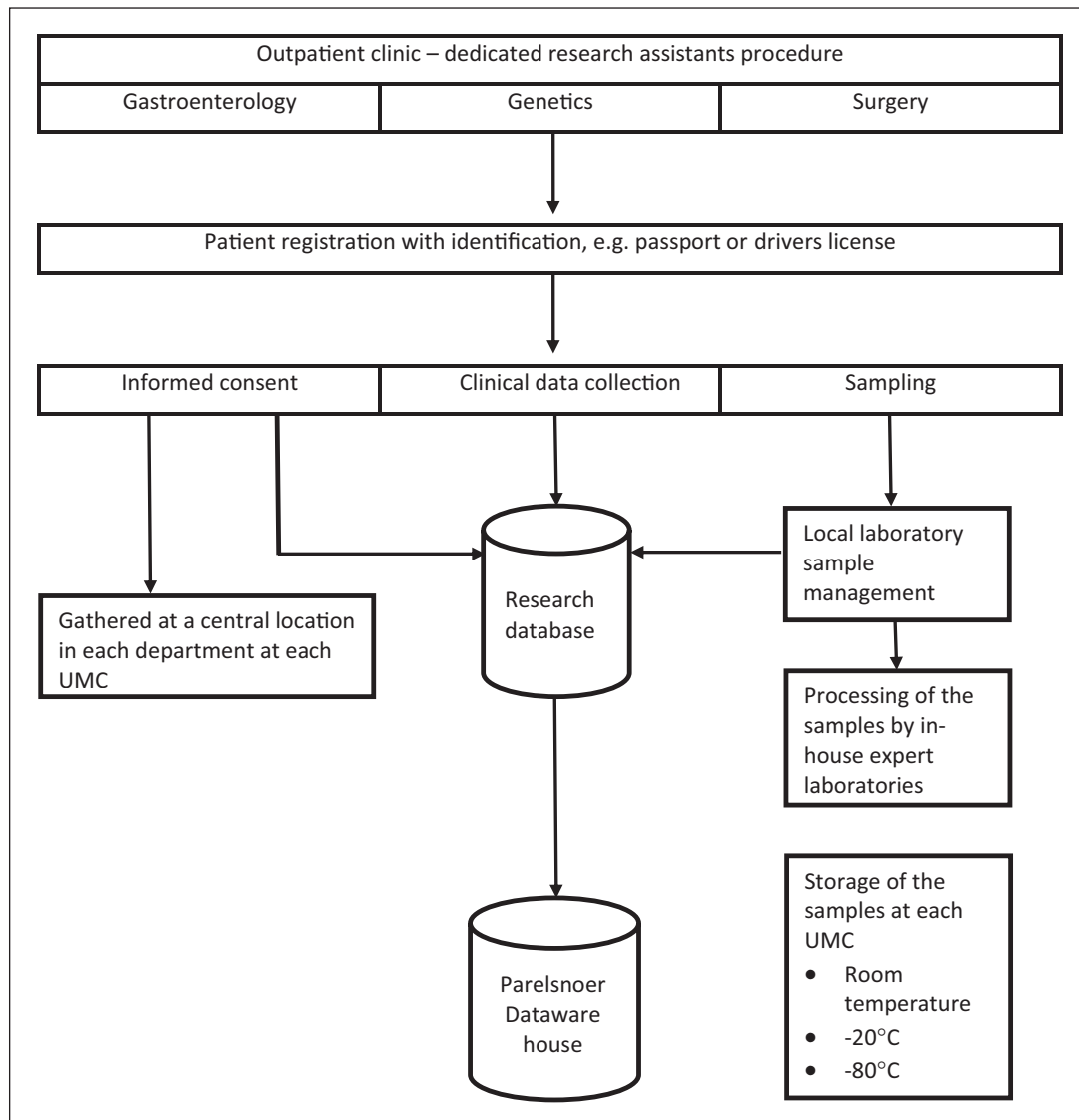
### Storage temperature

See **Table 1**.

### Shipping temperature from patient/source to preservation or research use

Body fluids (DNA, plasma, serum) from the clinical departments are transferred by the internal clinical transport service of each UMC to the Front Office of the laboratory that is responsible for the sample handling.

Fresh frozen and FFPE tissue are directly transferred from the operating rooms to the Department of Pathology by the internal clinical transport service of each UMC. The tissue should be sent in a good leak-proof, unadorned container with formalin. The volume of formalin should be at least twice as large as the tissue fragment. Until transport, tissue can best be stored at 4°C (refrigerator) or briefly at room temperature and not in (melting) ice.



**Figure 1:** The flow of biomaterial and associated clinical data of the Biobank Hereditary CRC.

**Table 1:** Overview of procedures on collection, processing and storage of samples defined in the Biobank Hereditary CRC's biomaterial protocol.

Sample	Volume/number	Processing	Time between sampling and storage	Aliquoting	Storage
DNA (blood)	6 ml EDTA blood	Standard DNA isolation from EDTA in clinical routine of the Department of Human Genetics	Within 4 weeks (4°C) or 3 months (<-20°C)	Stock solution, after first issuance: normalized fraction 100 ng/μL	-20°C
Serum	10 ml, addition of a clot activator	2,000 × g at room temperature for 10 minutes	Within 2–4 hours	Maximum of six aliquots (0.5 ml)	-80°C
EDTA plasma	10 ml	2,000 × g at room temperature for 10 minutes	Within 2–4 hours	Maximum of six aliquots (0.5 ml)	-80°C
Fresh frozen tissue	Sample of affected and unaffected tissue	Immediately frozen after collecting the sample	Immediate	0.5 cm <sup>3</sup> samples	-80°C
FFPE tissue <sup>1</sup>	Sample of affected and unaffected tissue	Immediately stored in formalin after collecting the sample (0.5 cm <sup>3</sup> ), afterwards embedded in paraffin	Immediate fixation	0.5 cm <sup>3</sup> samples	Room temperature

<sup>1</sup> FFPE = Formalin-Fixed Paraffin-Embedded.

**Shipping temperature from storage to research use**

Body fluids, or materials and fresh frozen tissue samples are shipped on an excess of dry ice ( $-80^{\circ}\text{C}$ ) and FFPE samples at room temperature. Shipment is carried out by various certified courier services. At the moment, data loggers are not used. However, each confirmation of receipt of a shipment attests that sufficient dry ice was still present in the package.

**Quality assurance measures**

The sample handling is embedded in the quality management system of all cooperating UMC's [1]. Process control is based on SOPs that cover all phases of biobanking: collection, pre-analysis, registration, processing and storage of the samples.

**Source of associated data**

For the Biobank Hereditary CRC a minimal dataset was defined. This dataset comprises patient information collected in the context of routine daily clinical practice (**Table 2**). At baseline clinical data is collected on demographic data, details on medical and family history plus endoscopy and surgery, results of microsatellite instability and molecular genetic tests. During the follow-up, data is obtained on the treatment of the patient. Furthermore, in order to facilitate complete follow-up information on all included patients, connections to existing medical registries are actively sought (e.g. links to registries for vital status, cause of death, cancer diagnoses and pathology records).

The Biobank Hereditary CRC guarantees the privacy of the participants, because both biomaterial and the associated clinical data are stored using unique codes.

As described by Manniën et al., the information supplied by each UMC is periodically uploaded, after validation, to the central database of PSI for storage on a national level [1]. During the upload of data to central database, a Trusted Third Party encrypts identifiers of each UMC.

**Ethics Statement**

In 2009, the local Research Ethics Committees (RECs) of all UMCs have approved the initiation of the Biobank Hereditary CRC. Each research proposal that includes the use of biomaterial and/or clinical data of the Biobank Hereditary CRC must be submitted to the scientific review committee of the Biobank Hereditary CRC. This committee will decide whether a protocol is relevant and valid. As a next step, the research proposal has to be approved by the REC or a formal Institutional Review Board (IRB). These committees will assess whether the study objective fits the scope of the Biobank Hereditary CRC and its informed consent procedure.

Eligible patients are invited to participate in the Biobank Hereditary CRC, and sign the informed consent after understanding the goals of the biobank. SOPs are in place to cover the consent and withdrawal process.

**Constraints**

Geographical: the Biobank Hereditary CRC collects biomaterial primarily collected at UMCs, tertiary care hospitals. Only patients who provided written informed consent are included. Participants may withdraw their consent at all times.

**(3) Bioresource description****Object name**

The Biobank Hereditary CRC.

**Bioresource name**

The Biobank Hereditary CRC.

**Bioresource location**

All eight UMCs across the Netherlands participate in PSI:

- Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
- Erasmus Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands
- Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands
- Maastricht University Medical Center, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands
- Radboud university medical center, Geert Grootplein-Zuid 10, 6525 GA Nijmegen, The Netherlands
- University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands
- University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
- VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

**Bioresource contact**

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**Bioresource URL**

[http://www.parelsnoer.org/page/en/Parels?mod\[Parelsnoer\\_Module\\_Pearl\]\[n\]=25](http://www.parelsnoer.org/page/en/Parels?mod[Parelsnoer_Module_Pearl][n]=25)

**Identifier used**

N/A

**Bioresource type**

The Biobank Hereditary CRC Radboud Biobank is a collaborative clinical biobank. It stores biomaterials (see **Table 1**) and clinical data (**Table 2**) of individuals with an increased risk of hereditary CRC and/or Polyposis or diagnosed with a gene mutation which causes CRC and/or Polyposis and achieves almost total population coverage because the larger part is seen in a UMC.

**Type of sampling**

The Biobank Hereditary CRC is a biobank that combines both 'affected' individuals diagnosed with a gene mutation that predisposes to CRC and/or Polyposis (e.g. APC, MLH1, MSH2, MSH6 or MUTYH) and 'unaffected' individuals at increased risk of hereditary CRC and/or Polyposis (i.e. diagnosed with a CRC or adenoma at a relatively young age).

**Anatomical site**

See **Table 3**.

**Disease status of patients/source**

See **Table 3**.

**Table 2:** Overview of patient information collected in the context of the Biobank Hereditary CRC.

<b>Data category<sup>1</sup></b>	<b>Items<sup>1</sup></b>
General information of the patient	Identifier Date of birth Gender Date of inclusion Patient category Ethnicity/race Date of death Autopsy has been performed Cause of death
Information on medical history of the patient	Date of consult No previous surgery or admission to a hospital CRC CRC – date of diagnosis Diagnosis of CRC – based on complaints Diagnosis of CRC – based on surveillance CRC Year of start surveillance CRC Type of surveillance used at diagnosis of CRC Date of penultimate surveillance Additional remarks regarding CRC in general Adenomas Adenomas – date of diagnosis Colitis Ulcerosa/M. Crohn Colitis Ulcerosa/M. Crohn – date of diagnosis Date of first visit to a hospital Above 10 adenomas (cumulative) Date of diagnosis of 10th adenoma Above 10 polyps unlike adenoma Date of diagnosis of 10th polyp unlike adenoma Cancer unlike CRC Cancer unlike CRC – date of diagnosis Additional remarks regarding medical history
<b>Intoxication</b>	Smoker's category Type of tobacco Amount of cigarettes per day Year of start smoking Last year of stop smoking Passive smoker
<b>Physical examination</b>	Height (cm) Current weight (kg) Weight at endoscopy (kg) Weight at surgery (kg) Highest weight (excl. pregnancy – kg) Year of highest weight
<b>Information on first degree family members of the patient</b>	Relationship between first degree family member and patient Year of birth of first degree family member Date of inquiry of medical history of first degree family member Medical history of first degree family member Age at diagnosis of first degree family member Date of death of first degree family member First degree family member participant of biobank
<b>Genetic testing</b>	Genetic testing started in family Year of start genetic testing Genetics center Germline mutation present (patient or family) Gene with germline mutation Name of germline mutation Is the patient a mutation carrier Year of diagnosis germline mutation – patient Molecular diagnostics on colorectal related material Microsatellite instability present

(Contd.)

<b>Data category<sup>1</sup></b>	<b>Items<sup>1</sup></b>
	IHC MLH1 IHC MSH2 IHC MSH6 IHC PMS2 Hypermethylation Additional remarks regarding molecular diagnostics – other
<b>Endoscopic examination</b>	Endoscopy Date of endoscopy Type of endoscopy Indication for endoscopy Total number of polyps (endoscopy) Location of endoscopy Number of polyps per location (endoscopy)
<b>Lesion – endoscopy (&gt;10 polyps, registration of additional information)</b>	Polyp number Location of lesion Distance between lesion and anus (cm – stretched endoscope) Size of lesion (mm – endoscopy) Form of lesion Type of lesion (macroscopic – endoscopy) Radically removed (macroscopic – endoscopy) Treatment of lesion (endoscopy)
<b>Surgery</b>	Surgery Date of surgery Type of surgery Location of the tumor Location of distant metastasis Stoma Stoma – temporary or permanent Preoperative radiotherapy Date of start preoperative radiotherapy Total dose of preoperative radiotherapy (gray – cumulative) Total of preoperative radiotherapy fractions Preoperative chemotherapy Type of preoperative chemotherapy Date of start preoperative chemotherapy Total of preoperative chemotherapy cycles
<b>Pathology</b>	Histology Histological grade Tumor size (pT) Number of removed lymph nodes – surgery Number of positive lymph nodes – surgery Number of removed polyps/adenomas – surgery Location of regional metastasis Lymphocytic infiltration Adenoma (surgery) Location per adenoma (surgery) Number of adenomas (surgery) Size of largest adenoma (mm – surgery) Location largest adenoma (surgery) Hyperplastic polyps (surgery) Number of hyperplastic polyps (surgery) Additional remarks regarding tissues removed at surgery Type of removed material – endoscopy Type of lesion Type of adenoma Type of dysplasia (adenoma)
<b>Data on biomaterial</b>	Collecting time Specimen type Sample code Storage type

(Contd.)

Data category <sup>1</sup>	Items <sup>1</sup>
	Tissue status
	Biopsy location
	Carcinoma location
	Collection method
	Amount of tissue
	DNA concentration
	DNA quality
	SOP respected?
	SOP deviation
	Other SOP deviation

CRC = colorectal cancer.

<sup>1</sup> Not all data is available for all patients.

**Table 3:** Overview of the categories of participants that can be included in the Biobank Hereditary CRC.

Patient Category <sup>1</sup>	Description	Number of included participants <sup>1</sup>
1	Patient with CRC diagnosed before the age of 70 years	1,120
2	Patient with CRC with a germline mutation present in the family for hereditary CRC or polyposis	97
3	Patient with an adenoma diagnosed before the age of 40 years	167
4	Patient with an adenoma with a germline mutation present in the family for hereditary CRC or polyposis	214
5	Patient with polyposis (FAP, AFAP, MAP, juvenile polyposis)	243
6	Patient with cumulative more than 10 adenomas	178
7	Patient with other polyposis syndrome than described in category 5 (e.g. Peutz Jeghers, PTEN Hamartome Tumour Syndrome)	133
8	Patient with CRC and a germline mutation for hereditary CRC or polyposis	141
9	Healthy individual with a germline mutation for hereditary CRC or polyposis	374
10	Patient with an adenoma and a germline mutation for hereditary CRC or polyposis	211

CRC = colorectal cancer.

<sup>1</sup> A participant can appear in more than one category.

#### Clinical characteristics of patients/source

A full clinical characterization, including demographic data, details on medical and family history plus endoscopy and surgery, results of microsatellite instability and molecular genetic tests and follow-up is specified for the Biobank Hereditary CRC (Table 2).

#### Vital state of patients/source

All patients are alive at inclusion.

#### Size of the bioresource

Currently, the Biobank Hereditary CRC contains different biomaterials (e.g. DNA, plasma, serum and/or tissue) from 1,967 participants. The current number of included patients per patient category is shown in Table 3.

#### Clinical diagnosis of patients/source

See Table 3.

#### Pathology diagnosis

Colorectal carcinoma and adenoma.

#### Control samples

The Biobank Hereditary CRC does not collect control samples from individuals without a proven CRC and/or Polyposis related germline mutation or who are not at an increased risk of hereditary CRC and/or Polyposis.

#### Biospecimen type

Table 1 summarizes the variety of biomaterials that can be collected per participant of the Biobank Hereditary CRC. However, the specific collection of the biomaterials depends on the patient category, e.g. tissue will only be collected of the patients who have been diagnosed with CRC and were surgically treated in one of the participating UMCs.

#### Release date

Biomaterial and the matching clinical data are currently available.

#### Access criteria

Scientific researchers, who are not necessarily linked to the Biobank Hereditary CRC, but who are working in the field of

hereditary CRC are invited to submit their research proposals. In the catalog of PSI [1] a researcher can identify which items are collected by the latter biobank. Each new study proposal should be sent to the coordinator of the Biobank Hereditary CRC (i.e. currently dr. P. Manders; Radboudumc, The Netherlands). The coordinator will submit the proposal to the scientific review committee of the Biobank Hereditary CRC. This committee, which consists of one member of each participating UMC, will review every application on the following criteria: the anticipated significance of the research for hereditary forms of CRC and thus the patients included in the Biobank Hereditary CRC, plus scientific quality, novelty, feasibility and the suitability. The review process for rare patient groups is less strict for requests for data usage than requests for biomaterial groups, because of the finite nature of the biomaterial. The researcher will be informed in writing about the decision of the latter committee by the coordinator. As a next step, the research proposal has to be approved by the REC or a formal IRB. These committees will assess whether the study objective fits the scope of the Biobank Hereditary CRC and its informed consent procedure. The aim of the Biobank Hereditary CRC is to make the whole issuance process as simple and transparent as possible for researchers. Therefore, the coordinator of the Biobank Hereditary CRC acts as a contact for researchers throughout the *complete* issuance process.

Costs vary depending on the type and amount of samples. An economic quotation is sent covering shipping costs and partially costs for biobanking-related services (sample handling, consumables) [1].

#### (4) Reuse potential

Biomaterial and clinical data are provided to researchers on a non-exclusive basis. Therefore samples from the same participant may be used in several different projects. However, each research project must be approved by the scientific review committee of the Biobank Hereditary CRC and by the REC or a formal IRB. A prerequisite for the delivery of biomaterial and clinical data is two-way data sharing. Which implies that new information becomes available from scientific analyses, will be added to the Biobank Hereditary CRC database.

#### Competing Interests

The authors have no competing interests to declare.

#### Author Roles

Peggy Manders	coordinator of the Biobank Hereditary CRC
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