# EUROPEAN CHOLANGIOCARCINOMA (EU-CCA) REGISTRY

*An international cohort study on cholangiocarcinoma at basic, translational and clinical levels*

## STUDY COORDINATORS

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## STEERING COMMITTEE AND PARTICIPANTS

European Network for the Study of Cholangiocarcinoma (ENS-CCA) members (http://www.enscca.org/ or http://www.cholangiocarcinoma.eu)

# RATIONALE AND AIMS

The **European Cholangiocarcinoma Registry (EU-CCA Registry)** is an international collaborative project which will include a large cohort of patients, who will provide detailed knowledge about the geographical distribution and the natural course of cholangiocarcinoma (CCA). Our primary aim is to investigate the progression of the disease (i.e. signs, symptoms and outcomes) over the lifespan of individuals with CCA to improve healthcare. Secondary, we aim to update the classification of CCA subtypes and provide novel insights about genetics, epigenetics, pathogenesis, signaling pathways, and test new emerging therapies on future clinical trials. Finally, from this registry will be derived new and interesting data that can be used to create specific guidelines for patients and physicians for the standard care of CCA.

**Primary aim**

Follow-up the natural history of CCA in European countries

**Secondary aims**

- Broaden the current CCA classification by introducing information about morphological, immunohistochemical, genetic and molecular parameters
- Elucidate the cargo of environmental factors in the development and progression of this type of cancer
- Determine new early biochemical tumor markers for screening, prognosis and diagnosis of the disease
- Ascertain the role of molecular mechanisms (i.e. signaling pathways) involved in the interplay between neoplastic cells and the tumor microenvironment
- Compare effectiveness of different therapies
- Select patients for clinical trials

# METHODS

## PARTICIPATION ON THE STUDY

Patients will be recruited from European referral centers on the study of CCA. Centers could be contacted by the Coordinators of this registry or centers could send a request on their own initiative to join this effort.

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All collaborators will participate in the main tasks of the project, including: general advisory role, evaluation of the progress of the registry and review of manuscripts.

## POPULATION AND INCLUSION CRITERIA

Inclusion criteria:

- Patients diagnosed with any subtype of CCA (i.e. iCCA, pCCA or dCCA)
- Radiological imaging and/or histological analysis needs to be performed in order to meet the criteria mentioned above.

Exclusion criteria:

- Patients with unclear diagnosis

## RESEARCH DESIGN

The CCA registry is an international, multicenter and observational registry. Data will be collected retrospectively from 2010 and prospectively. All centers participating in the project will select the patients according to the in- and exclusion criteria. Ethical approval will be obtained in every country. Electronic medical records of each patient will be examined in detail, and data will be retrospectively introduced into the database. Among the features to be included in the database, it should be noted the following: general information about the patient (i.e. gender, age, demographics, etc.), disease characteristics and risk factors, medical history, clinical parameters and therapeutic strategy. After inclusion in the database, patient data will have a prospective follow-up in the outpatient clinic and will be treated according to standard of care of that particular center. Beyond a clinical data record, this initiative is also a repository of biological samples in which information on the availability of samples from each participating group can be collected (without central biobanking). During medical visits, blood, saliva, urine and stool samples could be collected and registered into the database according to standard of care, and not in favor of this registry. Nevertheless, to ensure the homogeneity of the study, every center receives a standardized protocol of biological sample collection.

## DATA MANAGEMENT

The European Cholangiocarcinoma Regitry is hosted by the online REDCap™ (Research Electronic Data Capture) platform (http://project-redcap.org/) and coordinated by Dr. Jesús M. Banales (San Sebastian, Spain) and Dr. Domenico Alvaro (Rome, Italy). Each participating center is responsible only for their cohort of CCA

patients. We aim to systematically capture covariates on epidemiology, incidence, prevalence, family history and natural history of CCA, type of CCA, histological subtypes, risk factors, chronic liver or biliary diseases, imaging correlates, survival, diagnosis and laboratory results. We have developed a data quality plan that accounts for data completeness, handling of missing data, data accuracy and data analysis, according to the Gliklich RE et al. guidelines.[1]

REDCap™ is a secure web application (https://redcap.aegastro.es/?s=eXrnXxDccK) for building and managing online surveys and databases that are geared, mainly, to support data capture for research studies.[2] Every new user of participating centers will receive a login code and their autonomy and rights (i.e. view, modify, export data) which can be adjusted as needed by the study coordinator. A very remarkable function of REDCap™ is the possibility to export the procedures in an automated way for seamless data downloads to Excel, PDF, and common statistical packages (SPSS, SAS, Stata, R) which facilitates analysis of data.[8] Participants may benefit from this function when their cohort is concerned.

The software can run on a number of different operating systems (Linux, Unix, Windows, Mac) and currently has several language translations already compiled (e.g. English, French and German).[8]

## DATA COLLECTION AND VALIDATION

Creation and administration of the database as well as control of the CCA patient data included by every center will be managed from the headquarters of the registry at the Biodonostia Research Health Institute (Spain), albeit each center shall have a trained researcher responsible for collecting and introducing the data of its own patient cohort. Every researcher will receive training in REDCap™ and the process of entering data. This training gives a step-by-step explanation of all the variables included in the CCA database that can be supplemented with brief explanatory videos (training resources page) provided by the REDCap™ software.

Patient data will be anonymized and each patient in the registry will receive an anonymous individual code based on the acronym of the city and number of the patient. Each participating center may only view and manage those cases included in its data access group, and only the registry coordinator and manager may have unlimited access to the included cases.

## COLLABORATING ENTITITES

Drs. Jesus M. Banales from Biodonostia Research Health Institute – Donostia University Hospital (San Sebastian, Spain) and Domenico Alvaro from the Sapienza University (Rome, Italy) are the Coordinators of this registry.

Currently, the following centers are actively participating in the registry:

- Biodonostia Research Health Institute – Donostia University Hospital (San Sebastian, Spain)
- Sapienza University of Rome (Rome, Italy)
- Kaiser Franz Josef Hospital (Vienna, Austria)
- Hôpitaux Universitaires Pitié Salpêtrière - Sorbonne Université (Paris, France)
- Hôpitaux Universitaires Henri Mondor (Paris, France)
- Saarland University Medical Center (Homburg, Germany)
- Institute for Pathology - University of Regensburg (Regensburg, Germany)
- Medical School Hannover (Hannover, Germany)
- University Hospital Heidelberg (Heidelberg, Germany)
- Marche Polytechnic University - Ospedali Riuniti University Hospital (Ancona, Italy)
- University of Padua (Padua, Italy)
- University of Sassari (Sassari, Italy)
- Humanitas Clinical and Research Center (Milan, Italy)
- Milan University Hospital (Milan, Italy)
- Lithuanian University of Health Sciences (Kaunas, Lithuania)
- Erasmus MC Hospital (Rotterdam, Netherlands)
- Norwegian PSC Research Center (Oslo, Norway)
- University of Warsaw (Warsaw, Poland)
- Teaching Hospital No 1 (Rzeszów, Poland)
- Regional Institute of Oncology Iasi (Iasi, Romania)
- Octavian Fodor Regional Institute of Gastroenterology and Hepatology (Cluj Napoca, Romania)
- University of Salamanca (Salamanca, Spain)
- “12 de Octubre” University Hospital (Madrid, Spain)
- Clinic Hospital of Barcelona (Barcelona, Spain)
- University of Navarra Clinic (Pamplona, Spain)

- Hospital of Navarra (Pamplona, Spain)
- The Royal Marsden NHS Trust (London, United Kingdom)
- Greater Glasgow and Clyde NHS Trust (Glasgow, United Kingdom)
- The Christie NHS Foundation Trust (Manchester, United Kingdom)

## REFERENCES

1. Gliklich RE, Dreyer NA, editors. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. Rockville (MD); 2010.
2. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics. 2009 Apr;**42**(2):377-81.

## LIST OF ABBREVIATIONS

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| **CCA** | Cholangiocarcinoma |
| **dCCA** | Distal Cholangiocarcinoma |
| **ENS-CCA** | European Network for the Study of Cholangiocarcinoma |
| **EU** | European Union |
| **iCCA** | Intrahepatic Cholangiocarcinoma |
| **MTA** | Material Transfer Agreement |
| **pCCA** | Perihilar Cholangiocarcinoma |
| **REDCap** | Research Electronic Data Capture |