

Brussels, 13 November 2018

COST 103/18

## DECISION

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Subject: **Memorandum of Understanding for the implementation of the COST Action “EUROPEAN CHOLANGIOCARCINOMA NETWORK” (EURO-CHOLANGIO-NET) CA18122**

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The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action EUROPEAN CHOLANGIOCARCINOMA NETWORK approved by the Committee of Senior Officials through written procedure on 13 November 2018.

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## MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

### **COST Action CA18122 EUROPEAN CHOLANGIOCARCINOMA NETWORK (EURO-CHOLANGIO-NET)**

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

- a. "Rules for Participation in and Implementation of COST Activities" (COST 132/14 REV2);
- b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14 REV);
- c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14 REV2);
- d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14 REV).

The main aim and objective of the Action is to face cholangiocarcinoma burden and heterogeneity through the creation a co-operative, interdisciplinary pan-European network harmonising clinical investigators, basic scientists, charities, European RTD Organizations, SMEs, and National and European Institutions. This will be achieved through the specific objectives detailed in the Technical Annex.

The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 84 million in 2018.

The MoU will enter into force once at least seven (7) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14 REV2.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14 REV2.

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**OVERVIEW**

**Summary**

Cholangiocarcinomas (CCAs) are an heterogeneous group of cancers of the biliary tree. CCA is considered one of the deadliest cancers and its **incidence** is increasing constantly and dramatically in Europe. Notably, CCA is the **most frequent cause of cancer metastases of unknown origin**, suggesting underestimation of the CCA problem. **CCA heterogeneity** has limited the discovery of biomarkers and novel therapeutic options, hampering the development of tools for early diagnosis and effective treatment. CCA constitutes a major challenge for researchers, clinicians, national health systems and society. Still, **coordinated multidisciplinary pan-European studies are lacking**. As such, the **EURO-CHOLANGIO-NET (European Cholangiocarcinoma Network)** aims to set up a **pan-European-wide interdisciplinary co-operative network** of stakeholders, including scientists, clinicians, regulatory authorities, small/medium enterprises (SMEs) and industry partners, to address the CCA problem. Through the creation of shared data registries inherent main relevant basic or clinic-epidemiologic aspects, conference calls, meetings, workshops, Short-Term Scientific Missions as well as training schools, **this Action will coordinate efforts aiming at advancing the understanding of CCA to translate basic research and preclinical findings into clinical practice**. For this purpose, this Action will be organized in 7 Working Groups (WGs) dealing with interrelated aspects of CCA: ***Preclinical, In-Depth Histomorphological Phenotyping, Molecular Profiling, Epidemiology, Clinical Characterization and Trials, Early Diagnostic Biomarkers, Development of Novel Therapeutic Targets and Tools, Legislation and Ethics***. These WGs will work to construct efficient connections, exchanges and promote capacity-building objectives (i.e. data registries, young researchers mobility, meetings, seminars, consensus guidelines and more).

<b>Areas of Expertise Relevant for the Action</b>	<b>Keywords</b>
<ul style="list-style-type: none"> <li>● Clinical medicine: Gastroenterology and hepatology</li> <li>● Basic medicine: Epigenetics and gene regulation</li> <li>● Clinical medicine: Oncology</li> <li>● Basic medicine: Proteomics</li> <li>● Basic medicine: Pharmacology, pharmacogenomics, drug discovery and design, drug therapy</li> </ul>	<ul style="list-style-type: none"> <li>● Translational research platforms</li> <li>● Updated characterization and classification</li> <li>● Molecular profiling</li> <li>● Early diagnosis biomarkers</li> <li>● Development of novel therapeutic tools</li> </ul>

**Specific Objectives**

To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination

- Characterisation and improvement of cellular and animal models of cholangiocarcinoma through analysis of their histomorphology, pathological background, immunology, transcriptome, proteome, metabolome, and the correlation with the human cholangiocarcinoma subtypes in order to define the experimental counterparts of specific human cholangiocarcinoma subtypes for future studies.
- Development of translational research platforms, such as patient-derived cholangiocarcinoma xenografts and three-dimensional cultures (or “organoids”) obtained from cholangiocarcinoma patients, which are amenable to the detection of genetic and/or epigenetic changes associated with cancer malignancy and drug sensitivity, thus leading the way for targeted approaches.
- Development of a common, updated characterisation and classification of cholangiocarcinomas based on the cells of origin, pathological background, etiopathogenetic determinants, relevant signalling pathways and potential druggable molecular targets.
- Molecular profiling of cholangiocarcinomas using innovative, high-throughput technologies designed to facilitate the comprehensive “omic” assessment of genomes, transcriptomes, proteomes and metabolomes of the distinct histological and clinical subtypes of cholangiocarcinoma, through mass screening of human tumours.

- Investigate the progression of cholangiocarcinomas over the lifespan for improving health care; to update the classification cholangiocarcinoma subtypes, and test new emerging therapies in future clinical trials; to validate and implement cholangiocarcinoma associated biomarkers.
- To gain insights into the determination of new sensitive and specific non-invasive biomarkers for the early diagnosis of each cholangiocarcinoma subtype, as well as to predict prognosis and treatment response, including approaches based on liquid biopsies, to enable non-invasive assessment of tumour heterogeneity and monitor tumour dynamics.
- To develop or define novel drugs and strategies to be investigated at the preclinical and clinical levels in the search of potential therapeutic tools that could result from data derived from the other activities of the network and/or the pharmaceutical industry.
- To conduct updated experimental models, such as patient derived xenografts, and translational studies based on the analysis of data of clinically annotated specimens from previously conducted/ongoing trials in cholangiocarcinoma patients with adequate follow up.
- To create multiple registries of data related to crucial, inter-related, and multidisciplinary aspects of the cholangiocarcinomas, pre-neoplastic conditions, and diseases at risk, like, clinical-epidemiological data registry, histo-morphological data registry, radiological features, molecular profiles, and biomarker signatures.

#### Capacity Building

- To create a mutual strategy to optimize the training capacities related to cholangiocarcinoma currently available at different cross-border stakeholders via Short-Term Scientific Missions.
- To improve institutional capacities of participating centres by providing support to reach a minimum set of standards that ensure high-quality research activities through Short-Term Scientific Missions.
- To establish effective channels of communication between preclinical researchers, clinicians, small/medium enterprises, industry representatives and regulatory bodies through annual cholangiocarcinoma conferences and joint meetings with regulatory authorities.
- To facilitate exchange of professional expertise and research material or data between experienced researchers and Early Career Investigators through workshops and training schools.
- To provide mentorship to Early Career Investigators with the adequate education and prepare them to be actively involved in future cross-border multicentre studies.
- To engage in patient and public enrolment, involving cholangiocarcinoma patients as a specific target group in prioritising research questions in CCA field, identifying gaps in clinical service relevant to CCA subjects and improving public awareness (European Commission and EU Agencies).
- Contribute to the development of the mission, vision and aspirations for a global alliance against cholangiocarcinoma.

# 1. S&T EXCELLENCE

## 1.1. CHALLENGE

### 1.1.1. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Cholangiocarcinoma (CCA) includes a heterogeneous group of cancers affecting the biliary tree, whose etiopathogenesis remains largely unknown (1, 2). CCA is considered one of the deadliest cancers (1-6) and its **incidence** is increasing constantly and dramatically in Europe (1, 2). Accordingly, the **mortality** from CCA is increasing worldwide in the last decades (3-6). On the contrary, the mortality rate of the majority of cancers decreased in the same period (5). Notably, CCA is the **most frequent cause of cancer metastases of unknown origin** (7), suggesting underestimation of incidence and mortality rates for CCA. Although CCA subtypes share common features, there are important inter- and intra-tumour variability affecting the pathogenesis and outcome (1). **CCA heterogeneity** has limited the discovery of biomarkers and novel therapeutic options, hampering the development of tools for early diagnosis and effective treatment. CCA is commonly asymptomatic at early stages, being often **diagnosed in advanced stages**, when the disease is found disseminated (1, 2). This limits the effectiveness of the current therapeutic strategies, which are preferably based on surgical resection, because owing to high CCA chemoresistance, antitumour drugs have none or only mild effects (1, 2). As a result, CCA prognosis is dismal, with a 5-year survival rate of <20% (1, 2). **Differences in survival exist among European countries**. In general, relative survival is lower in Eastern Europe than in Central and Southern Europe (6). In sum, CCA is a rising clinical and social problem in Europe, constituting a major challenge for researchers, clinicians, national health systems and society. Still, **coordinated multidisciplinary pan-European studies are lacking**. As such, the **EURO-CHOLANGIO-NET** (European Cholangiocarcinoma Network) aims to set up a pan-European-wide interdisciplinary co-operative network of stakeholders, including scientists, clinicians, regulatory authorities, small and medium enterprises (SMEs) and industry partners, to address the CCA problem. Through the creation of shared data registries inherent main relevant basic or clinical-epidemiologic aspects, conference calls, meetings, workshops, clinical ground rounds, scientific exchanges as well as training schools, **this Action will coordinate efforts aiming at advancing the understanding of CCA to translate basic research and preclinical findings into clinical practice**. For this purpose, this Action will be organized in 7 Working Groups (WGs) dealing with interrelated aspects of CCA. WGs will work as coordinated networks of stakeholders and will employ resources and tools to construct efficient connections, exchanges and promote capacity-building objectives (i.e. data registries, young researchers mobility, meetings, seminars, consensus guidelines and more). Coordinated activities will be key to carry out research actions, guidelines elaboration, and translational activities related to personalized medicine, clinical trials and more. The Action will generate educative and informative initiatives and facilitate networking activities with business partners and European research infrastructures. The Action will also provide scientists with a unified and dedicated website with online tools to facilitate interaction and exchange of information among participants and stakeholders, including patients.

### 1.1.2. RELEVANCE AND TIMELINESS

The epidemiological trend of CCA shows a constant and dramatic increase in incidence and mortality worldwide (1-8), clearly depicting CCA relevance among others types of cancer. The incidence of CCA in European countries ranges from 1 to more than 4 cases/100,000 (1). However, the difficulties with classification coding for CCA, and with the varied terminology that is used, determine an underestimation of CCA burden. In a recent report, the four ICD-10 (International Classification of

Diseases) subcodes were considered (8). This report showed that in England alone (not the whole of the UK), in 2013, 1,965 new CCAs were diagnosed with an incidence rate of 3.65 per 100,000 individuals, while, 2,161 deaths and a mortality rate of 4.01 per 100,000 individuals were registered. The number of deaths and the year mortality rate per 100,000 individuals for the CCA in the period from 2010 to 2013 in England tragically surpassed the ones for the hepatocellular carcinoma (HCC), with 7,743 vs 6,899 deaths, respectively (8). Indeed, mortality for primary liver cancer has become more uniform across Europe over recent years, with an evident decline of HCC mortality, but, in contrast, CCA mortality has substantially increased in most of Europe (3). Liver cancer mortality rates are expected to rise by 58% in the UK between 2014 and 2035, i.e., to 16 deaths per 100,000 people by 2035 (4). Considering epidemiology trend in primary liver cancer, half of deaths for primary liver cancer will be due to intrahepatic CCA (3, 4). Furthermore, when the mortality rates for all malignancies are considered, the untargeted problem of CCA emerged clearly. Indeed, while 19 malignancies (comprising breast, lung, colon, etc.) showed a reduction of the mortality rate from 1990 to 2009 (US data), the mortality rate for malignancies of liver and bile ducts increase of more than 40% and 60% in female and male, respectively (5). **Timeliness:** The timeliness of this Action also originates from the early and fragmented knowledge concerning CCA heterogeneity, particularly at epigenetic and molecular levels, from the growing demand for translational science, and on the rising potential of novel laboratory or clinical-applicable technologies. The timing of the Action intersects with great advances of the molecular characterization of CCA and therefore with the possibility of personalized therapy. Promising candidates for targeted personalized therapy have very recently emerged, including potential driver *FGFR* gene fusions and somatic mutations in *IDH 1/2*, *PRKACA* or *PRKACB* gene fusions, and *ELF3* mutations (9). A precision genomic medicine approach is dependent on an enhanced understanding of driver mutations in each subtype and stratification of patients according to their genetic drivers (9). **This will only be made possible by means of networking.**

## 1.2. OBJECTIVES

### 1.2.1. RESEARCH COORDINATION OBJECTIVES

**A global objective of the EURO-CHOLANGIO-NET** is to create a unique co-operative, interdisciplinary European network encompassing clinical investigators (hepatologists, oncologists, surgeons, radiologists, pathologists, geneticists, immunologists, epidemiologists), basic scientists (molecular biologists, pharmacologists, biochemists, chemists, bioinformatics), European RTD Organizations, SMEs, European Commission and EU Agencies, and International Organizations, in order to face the multilevel heterogeneity of CCA by addressing specific but interrelated challenges in different research fields. The aim of this Action cannot be accomplished at an individual country level, especially when considering a type of cancer with the complexity and heterogeneity of CCA. The interdisciplinarity of the challenge and magnitude level of expected outcomes require an intensive and large collaboration at the pan-European level to exploit complementarities.

#### **Specific research challenges of the EURO-CHOLANGIO-NET:**

- **Basic Science:** Characterization and improvement of cellular and animal models of CCA through analysis of histomorphology, pathological background, immunology, transcriptome, proteome, metabolome; development of translational research platforms, such as tissue collection, and genetic and epigenetic characterization of patient-derived CCA xenografts (PDXs). CCA PDXs will be used to screen for candidate pathways and/or therapeutics and to identify determinants of heterogeneity in patient response to therapy. Three-dimensional cultures (or “organoids”) obtained from CCA patients are amenable to the detection of genetic and/or epigenetic changes associated with cancer malignancy and drug sensitivity and may thus lead the way for targeted approaches.
- **Development of a common, updated characterization and classification of CCAs:** The Action will collect scattered information from relevant stakeholders and work towards a global definition of CCAs based on the cells of origin, pathological background of each histological subtype of CCA, relevant signaling pathways and potential druggable molecular targets. Information will also include characterization of the etiopathogenetic determinants involved in CCA subtypes.
- **Molecular profiling:** Use of innovative, high-throughput technologies designed to facilitate the comprehensive “omic” assessment of genomes, transcriptomes, proteomes and metabolomes of patients affected by CCA and promotion of initiatives and actions to gain insights into the transcriptome/proteome/metabolome and molecular profiling of the distinct histological and clinical subtypes of CCA, through mass screening of human tumours.
- **Epidemiology and clinical characterization:** To investigate the progression of the disease over the lifespan of individuals with CCA for improving healthcare; to update the classification of CCA subtypes and provide novel insights about genetics (GWAS studies), epigenetics, pathogenesis, signaling

pathways, and test new emerging therapies in future clinical trials; to validate and implement CCA associated biomarkers as molecular predictors of therapeutic response, treatment resistance and disease outcome; to design and conduct phase I and/or phase II clinical studies aiming at the validation and implementation of precision biomarkers.

- Early diagnosis biomarkers: To gain insights into the determination of new sensitive and specific non-invasive biomarkers for the early diagnosis of each CCA subtype, as well as to predict prognosis and treatment response, including approaches based on liquid biopsies to enable non-invasive assessment of tumour heterogeneity and monitor tumour dynamics.
- Development of novel therapeutic targets/tools: To develop or define novel drugs and strategies to be investigated at the preclinical and clinical levels in the search of potential therapeutic tools that could result from data derived from the other activities of the network and/or the pharmaceutical industry, and to conduct updated experimental models, such as PDXs, translational studies based on the analysis of data and/or of clinically annotated specimens from previously conducted/ongoing trials with adequate follow up.

### 1.2.2. CAPACITY-BUILDING OBJECTIVES

The EURO-CHOLANGIO-NET will bring together outstanding, yet currently fragmented, groups from European countries. Capacity building efforts will focus on improving the research agenda to carry out high quality studies. Alongside, the Action will also aim to support the exchange of knowledge and expertise through cross-border interdisciplinary research, training and teaching. Special emphasis will be given to support research studies undertaken by Early Career Investigators (ECIs). ECIs will also be provided with an intensive framework of cooperation, through focused workshops, Short-Term Scientific Missions (STSMs) and training schools, aiming to develop a group of ECIs with interest and skills in CCA. Accordingly, the specific capacity-building objectives include:

#### **Training:**

- To create a mutual strategy to optimize the training capacities related to CCA currently available at different cross-border stakeholders via STSMs.
- To improve institutional capacities of participating centres by providing support to reach a minimum set of standards that ensure high-quality research activities through STSMs.
- To establish effective channels of communication between preclinical researchers, clinicians, SMEs, industry representatives and regulatory bodies through annual CCA conferences and joint meetings with regulatory authorities.
- To facilitate exchange of professional expertise and research material or data between experienced researchers and ECIs through workshops and training schools.

#### **Mentoring:**

- To provide mentorship to ECIs with the adequate CCA education and prepare them to be actively involved in future cross-border multicentre studies.

#### **Patient and public involvement:**

- To engage in patient and public enrolment, involving CCA patients as a specific target group in prioritising research questions in CCA field, identifying gaps in clinical service relevant to CCA subjects and improving public awareness (European Commission and EU Agencies).
- Contribute to the development of the mission, vision and aspirations for a global alliance against CCA.

## 1.3. PROGRESS BEYOND THE STATE-OF-THE-ART AND INNOVATION POTENTIAL

### 1.3.1. DESCRIPTION OF THE STATE-OF-THE-ART

The state-of-the-art in both basic and clinical CCA research, and even management, has been driven by the efforts of many unassociated research groups which are usually beset with inadequate funding, scarce visibility in scientific societies, and a lack of coordination between basic research and clinical scientists. On the contrary, it is generally accepted that a personalized CCA diagnostic work-up and therapeutic approach must be managed by dedicated centres with multidisciplinary expertise (1, 2). CCA can be surgically curable if diagnosed at early stages and, therefore, efforts must be made to identify populations at risk for strict follow-up and early diagnosis (1, 2). Although most CCAs are diagnosed de novo without apparent background liver disease, there are well-established risk factors that clearly indicate that CCA emerges in the context of bile duct inflammation (1). Molecular, biochemical or biological tumour markers or radiological tools finely evidencing bile duct inflammation and/or activation of reactive cholangiocytes and peribiliary glands could be useful for CCA diagnosis

and may represent valuable innovative biomarkers for large-scale screening campaigns dedicated to identifying subjects at risk.

### 1.3.2. PROGRESS BEYOND THE STATE-OF-THE-ART

The creation and implementation of functional networks among the participants of the Action will undoubtedly enhance translational research outputs; EURO-CHOLANGIO-NET, an innovative pan-European networking effort, will allow to conduct projects fostering innovative approaches for early diagnosis, screening and prevention of CCA, but also the use of multimodal treatments involving conventional and targeted approaches, drugs successfully used in other neoplasms that may find application in CCA, orphan drugs and, most interestingly, novel drugs that may be applied to CCA, making them appealing and economically sustainable therapies. Through trans-European networking, EURO-CHOLANGIO-NET will move forward beyond the state-of-art by:

- 1) Harmonizing and merging pre-existing institutional data registries to overcome the limitation in the number of cases which have precluded the obtaining of a critical mass of CCA cases necessary to unveil epidemiology features in stratified population of patients and risk factor impact or establish clinical-pathology and molecular correlations. Widespread geographic coverage will take into account the differences in incidence, risk factors and mortality among European countries and will permit a subanalysis of specific CCA phenotypes to detect differences among diverse populations.
- 2) Designing and developing novel translational research studies exploiting/combining resources from previously scattered clinical registries, bio-banks and epidemiology-type resources. By doing so, translational research on the aetiology, pathogenesis and prognosis of poorly characterized CCA will be linked to an integrated use and facilitated access to biospecimens from patients stored in different biorepositories.
- 3) Developing and exploiting CCA translational research platforms (e.g., PDX models/organoids/tissue collections) for multiple studies, especially drug discovery.
- 4) Implementing precision biomarkers for better characterization and stratification of CCA patients. With this Action, it will be possible to analyse a larger cohort of samples, using innovative, high-throughput “omic” technologies to identify novel non-invasive biomarkers and therapeutic targets for CCA.
- 5) Stakeholders will actively participate in the harmonized and complementary endeavours addressing the pitfalls of CCA studies and identify opportunities to progress beyond conventional methods and strategies. This COST Action will consist in a network structure to synthesize upon existing evidences in the field, but also to facilitate collection of important and pan-European additional information concerning research tools and clinical management of CCA patients.

### 1.3.3. INNOVATION IN TACKLING THE CHALLENGE

There have been small registries collecting CCA cases both retrospectively and prospectively in Europe and United States (US) at institutional level, and one US patient registry belonging to an American charity. However, they remain disconnected with no adequate networking strategies as well as lacking multidisciplinary involvement. Moreover, lack of case-control groups has limited the validation and exploitation of potential non-invasive biomarkers and new therapeutic tools for CCA. The EURO-CHOLANGIO-NET will pursue an innovative approach in tackling CCA by creating a platform involving multidisciplinary stakeholders systematically focused on areas of CCA where consensus and harmonisation are essential to make substantial progress. Further, the large database and gathered knowledge provided by the Action will allow:

- Developing a strategy for identifying cases retrospectively and prospectively and in-depth phenotyping to allow comprehensive analysis of factors linked to CCA. This approach has a potential to improve CCA detection, diagnosis and prevention.
- Defining translational use of pre-clinical in vitro and experimental animal systems.
- Identifying strategies for early diagnosis, accurate prognosis and prediction of treatment response.
- Developing novel therapeutic tools to improve prognosis.
- Developing an improved biological-based CCA classification.
- Developing refined markers for characterization and staging.
- Creation of faster, optimized workflow protocols for CCA translational research.
- Creation of a platform for a more direct research/clinic interaction with CCA patients.
- Facilitate the engagement with patient associations and society.

## 1.4. ADDED VALUE OF NETWORKING

### 1.4.1. IN RELATION TO THE CHALLENGE

CCA is a poorly characterized, complex and heterogeneous type of cancer whose research requires groups from individual countries to establish a mutual network to share experiences, cases, data, research questions and solutions in order to achieve a significant progress. The EURO-CHOLANGIO-NET will create a critical mass of researchers, larger cohorts, datasets and biorepositories, and consensus to bring both depth and breadth to the research that is needed. The fact of involving multidisciplinary teams is essential to identify critical gaps in research and prioritisation of questions for future research programmes. Basic scientists and clinicians will work with regulators and industries to identify mutual needs and synchronise their efforts to overcome the current lack of concordance between experimental models and clinical CCA. Transfer of skills through workshops will expand the pool of next generation of researchers in CCA and start-up companies. The network will promote the expansion of CCA educational and research activities and its wide dissemination across Europe. The network of leading experts will have the credibility to promote the adoption of scientific evidence-based achievements by regulatory authorities and influence policy changes. Moreover, this Action will put effort on the inclusion of institutions from Inclusiveness Target Countries.

### 1.4.2. IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

There are national CCA patient charities which are eager and ready to sustain any efforts of scientists and physicians in creating an internationally coordinated action plan. At the moment only a small patient registry exists in the US. The Action plans to be more than a patient registry, and rather address the CCA challenge through innovative networking strategies. The Action intends to work closely with the only CCA charity in Europe, and with a US CCA patient registry belonging to a charity based in US. The lack of such a coordinated pan-European action plan at this moment precludes significant scientific, technologic and clinical advances in diagnosis and therapy of CCAs, and additional funding resources dedicated to tackle this disease. EURO-CHOLANGIO-NET is an original unique European network. An initiative with a more limited focus aimed at establishing a registry of clinical and risk factor data, is ongoing in US. The EURO-CHOLANGIO-NET will interact with this US network to generate collaborative studies. This COST Action will also create the bases for the generation of proposals suitable for upcoming funding opportunities. This Action is aligned with the EU strategies on Research and Innovation and Public Health in the framework of Horizon 2020 and 2030.

## 2. IMPACT

### 2.1. EXPECTED IMPACT

#### 2.1.1. SHORT-TERM AND LONG-TERM SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS

This COST Action will set up the first multinational and multidisciplinary collaborative network focused on discovery and translational research in CCA; furthermore, the critical mass that the Action will gather is expected to have a transformative long-term impact on the field. A systemic dissection of the CCA multilevel heterogeneity will open a new horizon in the research of this cancer. Part of the EURO-CHOLANGIO-NET will be based on the unique opportunity of studying a large number of cases from different hospitals and countries, and on the expected results in terms of innovative diagnostic and therapeutic approaches.

**Scientific Impact: Short-term:** Through its collaborative network, the Action will reduce redundancy, promote efficient use of resources and increase the overall productivity of European research groups. ECIs, basic scientists and clinicians will benefit from training schools and professional workshops paving the way for a durable scientific impact. Consensus in case definitions, phenotyping, study endpoints among research groups will be part of research outputs. **Long-Term:** The collaborative research network will provide a platform to develop and evaluate accurate (sensitive and specific) novel non-invasive markers for CCA early diagnosis and to predict prognosis and treatment response, as well as novel strategies to treat CCA. Interaction between industry, academia, scientists, clinicians and EU Commission and EU Agencies will stimulate the shift of CCA healthcare strategies from a reactive to preventive practice. The network will be able of developing research proposals suitable for Horizon 2020 or similar ambitious programmes.

**Technological Impact: Short term:** The Action will harmonise the protocol for the collection of well-characterized, homogenous cases of CCA and matched controls with linked biological samples; these will constitute the ideal resources for conducting studies using system biology approaches for biomarker discovery. **Long term:** Development of innovative in vitro/in silico models which incorporate the concepts of genetic factors influencing CCA development. Setting up programmes to discover novel accurate non-invasive biomarkers of CCA. Development and validation of the efficacy of new therapeutics.

**Socioeconomic impact: Short term:** The EURO-CHOLANGIO-NET will raise public awareness about CCA given the extensive list of risk factors potentially linked to CCA and the considerable threat CCA poses on the public health. **Long term:** The knowledge of risk factors (genetic, epigenetic, environmental, life style) may improve the early detection of CCA and improve prevention. This, together with the development of new accurate non-invasive biomarkers and effective therapeutics, will reduce burden and healthcare costs. This Action will provide the clinical and scientific bases for the adoption by European Commission of appropriate policies to increase the public assurance of safety.

## 2.2. MEASURES TO MAXIMISE IMPACT

### 2.2.1. PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

The Action aims to involve all relevant stakeholders. The outcomes are expected to affect a spectrum of disciplines. Accordingly, the Action will ensure that the outcomes are disseminated to all relevant stakeholders. The main stakeholders include: (1) patient advocacy groups; (2) clinicians; (3) scientific researchers; (4) SMEs and pharmaceutical industry; (5) European Commission and EU Agencies, and (6) International Organization. Stakeholders will meet at both focused and general Action events as specified under the management structure. As part of this, meetings with European and National regulatory agencies and policy makers will be held, providing them with updated guidance position statements generated by EURO-CHOLANGIO-NET. The Action will be announced at targeted conferences and workshops in Europe, partnering with the European scientific society for the study of the liver and patient associations to reach the maximum number of stakeholders and ensure networking. A website will be set up describing the COST Action and its objectives, where current and prospective stakeholders can contact the Management Committee (MC). The Action will also encourage researchers from other international and national networks to integrate their efforts within this cross-disciplinary platform by inviting them to the planned Conferences/Workshops and other relevant activities. It will also work with national and international scientific societies to integrate CCA sessions into their regular conferences with contribution from EURO-CHOLANGIO-NET stakeholders. The involvement of patients and the general public will be assured by contacting specialized patient organizations and public health associations, which have already anticipated their endorsement.

### 2.2.2. DISSEMINATION AND/OR EXPLOITATION PLAN

**To whom:** The dissemination plan will target the multidisciplinary participants of the Action, academic and research communities, clinicians and healthcare professionals, patients and public health organizations, general public, pharmaceutical and biotechnology companies in addition to national and European regulatory bodies and policy makers.

**How the Action will do the dissemination:** The Action will invest in diverse dissemination methods in order to adequately reach the aforementioned target audiences. The dissemination tools for each group of activities will be chosen from the ones listed below: Action Logo; Action Website; Web Action Presentation; Workshops, Training Schools, Conferences and other Publications; Presentation Material for Meetings, Conferences and Exhibitions; Promotional Brochures; Action Fact Sheets; Promotional Posters; Information for Industry professionals; Information for Students; Network of Experts (Mailing List & Workshops).

#### DISSEMINATION PLAN

**Website:** This will ensure clear presentation of the aims and objectives of the Action as well as announcements of recent achievements and upcoming events. The website will also detail the source and nature of all Action funding and will feature an electronic discussion forum to encourage interaction and foster collaborative dialogue. A link to the EURO-CHOLANGIO-NET web site will be added in the web site of all participating institutions, charities and foundations.

**Design and development of a CCA mobile App:** Developing an application for Android and iOS operating systems will facilitate communicating findings to the public, interacting with stakeholders in addition to announcing future events organized by the Action.

**Social media:** Different social networking platforms such as Facebook, LinkedIn and Twitter will be used to encourage communication with healthcare professionals, researchers and the public.

**Newsletters, Linking & e-mailing:** Using appropriate languages, announcements for public and professionals, and calling for support of relevant national stakeholders will be issued by the partners.

**European SMEs:** Results and deliverables will be shared with SMEs operating in biomedical, technology and economic sectors to support pre-clinical development and clinical applications.

**Journal Publications:** Research findings will be made available to the scientific community through publications in peer-reviewed scientific journals with highlighted acknowledgement of the COST Action. Reviews on newly identified, still inappropriately addressed key CCA issues will also be published.

**Conferences:** Results of the Action will be disseminated at international conferences/workshops.

**Media campaigns:** National and/or international press agencies will be called upon, as appropriate, throughout the lifespan of the Action. Informative presentations to patients and the general public will be organized as “info day”.

**European Commission and EU Agencies:** Results and achievements will be regularly communicated to these Institutions to enhance CCA awareness and improve management in Europe.

#### EXPLOITATION PLAN

The Action will generate innovative opportunities in the industry-driven field of biomarkers and new therapeutic tools. There will be important potential for knowledge transfer to set the stage for a novel generation of start-up companies in the field. From the perspective of pharmaceutical industry, areas that will likely be able to capitalize are: (1) **Expertise and knowledge:** The access to a multidisciplinary expert network will help optimize efficiency and ensure completeness in drug development; (2) **Technology:** It will facilitate the access to advanced tools supporting mechanistic understanding and improving diagnosis, and monitoring of CCA via academic sites of excellence as well as SMEs; (3) **Education:** This Action will represent a professional mainstay in educating other clinical investigators of different specialities on detecting, assessing and monitoring patients with CCA; (4) **Data:** The network will constitute the foundation for sharing and pooling data necessary to encounter potential CCA signals during clinical development programmes; (5) **Alignment:** This network will serve as an exciting opportunity to come up with a balanced, global perspective on CCA best practices; (6) **Intellectual Property and Patenting:** Participants of this Network will sign an agreement form for the management of Intellectual Property. A centralized plan to file patent applications will be prepared and managed by a Business Management Team. Exploitation also includes joint grant applications for Horizon 2020 or similar funding programmes, stemming directly from the Research Coordination and Capacity Building outcomes.

## 2.3. POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

### 2.3.1. POTENTIAL FOR SCIENTIFIC, TECHNOLOGICAL AND/OR SOCIOECONOMIC INNOVATION BREAKTHROUGHS

As the EURO-CHOLANGIO-NET COST Action will enable the formation of a structured European Reference Network on CCA, its potential for innovation lies in its comprehensive approach, providing a framework for accessing large and well-characterized European cohort of CCA cases from different European countries. This will guarantee the implementation of future, robust interdisciplinary, multicentre clinical, observational and interventional studies. A very relevant feature of EURO-CHOLANGIO-NET in terms of **scientific breakthrough** potential is the development of translational bidirectional inter-connections among the basic science researchers and the clinical and technological experts dedicated to the diagnosis and cure of CCA. The registries and WGs will create new and significant data that will enable studies on many different aspects of the disease for years to come. Reciprocal interconnections among the WGs through multidisciplinary translational initiatives will give rise to a high potential for significant and revolutionary **scientific breakthroughs**, such as: 1) consistent nomenclature and clinical classification; 2) correct epidemiologic profile and risk factor stratification; 3) macroscopic and microscopic subclassifications correlated with specific biological properties and therapeutic response; 4) accurate non-invasive biomarkers for differentiating CCA subtypes and/or for early diagnosis and prognosis and response to novel therapies; 5) new radiologic tools for early diagnosis; 6) personalized medicine for CCA patients; 7) clinical trials; 8) innovative therapeutic targets and multidisciplinary therapeutic approaches. Expected **technological breakthroughs** will include: 1) development and exploitation of translational research platforms (e.g., CCA PDX models/organoids/tissue collections) to study antitumour drug efficacy; 2) Design and conduct of translational research studies exploiting/combining resources from the clinical registry, containing also epidemiology-type resource and bio-repositories; 3) implementation of novel biomarkers for better stratification of the clinical cohorts of CCA. The potential **socioeconomic breakthroughs** constitute an important motivation for implementing the Action. Owing to the challenges related to investigation and

treatment of CCA, the critical mass generated by this Action will be required to achieve scientific and clinical advances along with the awareness across Europe of this poorly understood and deadly cancer. Breadth and strength of the network expertise will contribute to substantial influence on professional societies and policy makers. The Action will also provide a concrete procedure to align current clinical practice guidelines governing the management of CCA with the state-of-the-art evidence in cost-effective treatment adherence interventions. Although the experience of the internationally distinguished research groups involved in the Action will minimize the risks of failure in the scientific objectives and, at the same time, excellent experimental facilities and theoretical resources are available at the participating institutions, risk factors directly related to the research concepts and results will be continuously monitored at regular meetings, frequent e-sessions and discussions dedicated to specific problems. **Barriers/obstacles:** Regulatory rules concerning the use of clinical data and samples will be an obstacle that will be overcome by the stipulation of material transfer agreements, approvals of local institutional ethics committees, and by obtaining informed consent from patients. The Legislation and Ethics WG will coordinate and assist as necessary in the drawing up of material transfer agreements to create bio-banks. Generation and administration of the registry database as well as control of the CCA patient data from every centre will be managed by the Representative of the WG at each institution. One of the WGs will be in charge of facilitating the combination of the data, transfer of samples between countries, data storage, legal issues regarding samples and data sharing. The network will adhere to national ethics and/or internal review board decisions as well as the EU ethics and data protection law. Should discrepancies among researchers and the WG Leaders appear, these will be discussed to make changes or additions to the list of definitions and/or variables for a better understanding. Problems due to input bias and data validation will be prevented by accepting only high degree of similarity (>90%) between locally collected data and those of the coordinator study. When this threshold is not reached, additional training will be given to enhance data consistency and reproducibility. The Action will generate explicit definitions for each variable to ensure internal validity and uniform data acquisition. Patient data will be anonymous and each patient in the registry will receive an individual code based on the acronym of the city and number of the patient. A patient identification record will be kept at each specific centre. Quantitative or qualitative statistical tests will be implemented for the baseline data depending on the study variables. Patient's informed consent will be modified to meet the needs of local Ethical Committee.

## 3. IMPLEMENTATION

### 3.1. DESCRIPTION OF THE WORK PLAN

**General view:** The EURO-CHOLANGIO-NET Action has been conceived as a multidisciplinary integrated and coordinated network consisting of complementary WGs. To accomplish the specific objectives, 7 WGs will be formed. Close cooperation and exchange of knowledge between WGs will be essential. Of primary importance will be the role of WGs in creating complementary data registries dedicated to the collection of observational, experimental, retrospective, and prospective data related to the specific challenges and aims of each WG, and in collecting, organizing and analysing samples from patients or pre-clinical experimental studies. Notably, several unconnected clinical-epidemiological data registries already exist at institutional level in several European Countries accounting already for 1000-1500 CCA cases in total. From the merging of those pre-existing registries and by recruiting new cases during the first 24 months of this Action it can be predicted to have a critical mass of ~2000 cases, which will allow to start on time all activities planned in this Action. Moreover, biobanks of biological samples will be readily available and will be harmonized to start a myriad of correlation studies. Notably, samples for histomorphological analysis have already been collected in a highly experienced centre to obtain preliminary data to set-up the proposed histology data registry. The network creation will increase enormously the possibility to create a true centralized European histomorphological data registry. Finally, the Action will devote an important effort to develop and standardize pre-clinical models of CCA because, although several ones already exist, there is a lack of homogenous analysis and evaluation of the correlation with features of human CCA. An additional, important effort of all WGs will be directed towards shared understanding between academia, pharmaceutical industry and regulatory agencies.

**Timing organization:** During the first 24 months of the Action, patients will be recruited and data will be collected. Each WG will work separately to analyse specific samples and data. According to the implementation plan the collection will be done locally or in a centralized institution. Outputs and deliverables will be included in a dedicated data registry. During the second half of the Action timespan, data contained in each registry will be inter-correlated. Patients will be recruited from European CCA referral centres participating in the EURO-CHOLANGIO-NET Action. To be included in the data registry,

patients must have been diagnosed with any subtype of CCA (intrahepatic/iCCA, perihilar/pCCA or distal/dCCA), and radiological imaging and/or histological analysis must have been done (inclusion criteria). No patient with an uncertain or unclear diagnosis will be included (exclusion criteria). Data will be collected retrospectively starting from 2010 and prospectively. Ethical approval will be obtained in every participant institution. For the data management of the Clinical-Epidemiology registry the Action will use the online REDCap™ (Research Electronic Data Capture) platform (<http://project-redcap.org/>) to create the registry database, which will be coordinated by the representative of the Clinical-Epidemiology WG at each institution. Registries created by the other WGs will be handled electronically by the web platform according to the specifics of the data to be included and the expertise of the representative. Each researcher will receive training and each centre will be responsible for their cohort of CCA patients. The MC will manage the collaboration between WGs as well as external communication activities, the dissemination plan, and the exploitation of EURO-CHOLANGIO-NET results. The Action will also set up dedicated and specific data registry web system platforms in collaboration with each WG representative. Creation and administration of the databases as well as control of CCA patient data from any given centre will be managed by the representative of the specific WG at each institution. To avoid the recurrent problem of the lack of testing/implementing histomorphology and molecular classifications in the clinic, a dedicated WG has been further developed mainly including the representative/Leaders of all the other WGs with the main task to set guidelines for implementation/suggestions/investigate the possibility for “next step”.

**Gender issue:** The whole network agrees on the relevance of the gender balance for the best functioning and success of the EURO-CHOLANGIO-NET. Accordingly, woman researchers and principal investigators will be in leading positions in most WGs and in general within this Action.

### 3.1.1. DESCRIPTION OF WORKING GROUPS

#### WG1. PRECLINICAL

WG1 aims at reviewing the current knowledge and expertise on preclinical models and technologies that assess experimental systems of CCAs. This WG will systematically address issues regarding the histomorphology, pathological background, cells of origin, transcriptome, proteome, and molecular profiling of the distinct models of CCA with respect to human subtype counterparts. All scientists developing models of CCA, particularly animal models, primary human cultures, organoids and related PDXs will contribute to WG1 by sharing data using dedicated customized sheet forms created in an ad hoc joint workshop during year 1. This WG is essential to support translational research in CCA and will collaborate closely with the remaining WGs.	
<b>Tasks &amp; Activities</b>	
<ul style="list-style-type: none"> <li>• To review available experimental models of CCA and their usefulness for preclinical studies.</li> <li>• To conduct workshops on experimental models of CCA, including organoids, either from resected tumours tissue, from resected lymph node or from bile.</li> <li>• To generate a data registry based on standardized sheet forms.</li> <li>• To deliver STSMs to ECIs with a focus on <i>in vitro</i> and <i>in vivo</i> models.</li> <li>• To identify targets for therapies that will be available for further tests in preclinical experiments.</li> <li>• To translate the scientific evidences into regulatory language, practices and recommendations.</li> </ul>	
<b>Year</b>	<b>Key milestones and deliverables</b>
1	Conference proceedings of the kick-off meeting of experts to update the state of the art and define the <i>in vitro</i> and <i>in vivo</i> experimental models of cholangiocarcinomas to be included in the experimental model registry.
1	Report of the workshop for data sheet forms creation describing each model to be included in the registry and for definition of standard operating procedures (SOPs) for the collection and storage of biological samples related to experimental cholangiocarcinoma.
1	Publication of a systematic review to update the list of current and potential <i>in vitro</i> and <i>in vivo</i> models.
1-4	Conference proceedings of the training school to focus on <i>in vitro</i> and <i>in vivo</i> models of cholangiocarcinomas dissected through a multidisciplinary and translational approach.
2	Conference proceedings of workshop of Working Group 1 and Working Group 2 and Working Group 3 to update the state of the art of correlations studies of pre-clinical experimental

	models of cholangiocarcinomas with the human diseases, and to set up the scheme to correlate data included in the registries.
3	Original article establishing criteria for identifying the correct preclinical models of each subtype of cholangiocarcinomas.
3	European guidelines on the use of preclinical models of cholangiocarcinomas in drug experimentation.
3	A consensus paper on the evidences and the role of experimental <i>in vitro</i> and <i>in vivo</i> models of cholangiocarcinomas in the personalized medicine.

## WG2. IN-DEPTH HISTOMORPHOLOGICAL PHENOTYPING

<p>This WG will deal with the histological characterization of CCA in relationship with the pathological background, involvement of cancer stem cells, relevant signalling pathways and potential therapy targets. Histological samples (average 300) will be collected in a single highly experienced centre. These will be digitalized and analysed by other expert participants among network centres. Data obtained will be correlated to clinical, molecular and radiologic features provided by other WGs. This WG will interact with the rest of the network to promote multidisciplinary translational actions.</p>	
<b>Tasks &amp; Activities</b>	
<ul style="list-style-type: none"> <li>• To collect samples and data to set up the digitalised European registry. To review current knowledge on CCA histology and clinical-pathology; To harmonize nomenclature, clinical measurements, definitions, classification and outcomes.</li> <li>• To conduct workshops to discuss and validate data and outputs.</li> <li>• To share collected data with other WGs, through the registry.</li> <li>• To organize STSMs for ECIs with a focus of histomorphology.</li> </ul>	
<b>Year</b>	<b>Key milestones and deliverables</b>
1 & 2	A digitalised European histological cholangiocarcinoma registry.
1	Publication on the definition of histomorphological features and criteria for diagnosis and classification of cholangiocarcinoma subtypes.
3	Scientific publications on definition of the pathological background in which each specific cholangiocarcinoma subtype emerge and characterization of the cells of origin.
3	Monothematic conference proceedings on histomorphology diagnosis and classification of cholangiocarcinomas involving European Scientific Societies and World Health Assembly Members to sensitize the Institutions concerning the problems related to the classification and codification of cholangiocarcinomas in International Classification of Diseases (ICD) and ICD-Oncology (ICD-O).
4	An international consensus document for a practical guideline on histological diagnosis and classification of cholangiocarcinomas.

## WG3. MOLECULAR PROFILING

<p>The main effort of this WG will be aimed at creating a data registry. The first 24 months will be dedicated to recruiting samples (average 300) and collecting data. The recruitment of samples and clinical information will be similar to WG2. Samples will be collected and analysis will be performed pertaining genomic and epigenomic alterations within the tumour and surrounding tissue in a single highly experienced centre. During the second half of the Action, these data will be correlated to the clinical, histomorphology, and radiologic features provided by the respective WGs.</p>	
<b>Tasks &amp; Activities</b>	
<ul style="list-style-type: none"> <li>• To define the transcriptome, proteome and metabolome of each CCA subtype.</li> <li>• To define molecular profiling of each CCA subtype.</li> </ul>	

- Because there are no genome wide association studies (GWAS) for CCA, an important task will be to carry out a GWAS in genomic DNA (gDNA) from >2000 CCA patients.

Year	Key milestones and deliverables
3	Scientific publications on Genome Wide Association Study (GWAS) from 2000 patients with cholangiocarcinoma,
2-4	Scientific publications on transcriptome (mRNA and non-coding RNAs), proteomics, and molecular profiling (single-nucleotide variants, FGFR2 fusions, copy number alteration, DNA methylation profiling) of different clinical, etiological and histomorphological cholangiocarcinoma subtypes.

#### WG4. EPIDEMIOLOGY, CLINICAL CHARACTERIZATION AND TRIALS

The aim of WG4 will be the creation of a data registry using the online REDCap™ (Research Electronic Data Capture) platform (<http://project-redcap.org/>). From this registry, new and key data will be derived that can be used to generate specific guidelines for patients and physicians for the standard care of CCA. Considering the lack of consistency and heterogeneity among CCA studies, it is imperative to set standards for clinical trials design and establish precise endpoints to assess the efficacy of novel interventions or for exploring novel biomarkers in CCA.

##### Tasks & Activities

The primary goal of the clinical-epidemiology data registry will be to establish a follow-up of the natural history of CCA in European countries:

- To determine the current management of patients and outcomes.
- To broaden the current CCA classification by introducing information about morphological, immunohistochemical, genetic and molecular parameters.
- To elucidate the role of environmental factors in the development and progression of CCA.
- To compare the effectiveness of different therapies (e.g., standardised surgical approaches).
- To select patients for clinical trials. To explore the access to clinical trial for patients, the patients' outcomes and treatment strategies and consistency across countries.
- To propose guidelines on CCA management.
- To attract support for planning, setting-up and coordinating observational and interventional multicentre clinical trials in CCA.

Year	Key milestones and deliverables
1	Standard Operative Procedures (SOPs) for the collection and storage of all biological samples (liver biopsy, serum, plasma, DNA, urine and stool) related to cholangiocarcinomas.
1	Submission of abstracts to International Congresses on liver diseases and cancer with the data analysis from the European Cholangiocarcinoma Registry.
2	Monothematic conference proceedings on cholangiocarcinoma jointly with European Professional Societies addressing standard of care practice of management of cholangiocarcinoma patients.
2-4	Consensus documents on the diagnosis, classification, assessment and treatment of cholangiocarcinomas in addition to standardization of nomenclature to harmonize the criteria used for cholangiocarcinoma diagnosis and classification in clinical practice across Europe.
2-4	Publications of the data and correlation studies derived from the European Cholangiocarcinoma Registry Database.

#### WG5. EARLY DIAGNOSTIC BIOMARKERS

The main objective of this WG will be to establish radiologic/histomorphological correlations in the first phase and radiologic and genomic correlations (radiogenomic) in the second phase. Digital files of patient imaging examinations performed routinely and not for the purposes of this Action will be

collected on a secured web platform in an anonymous manner by participants from each clinical centre (imaging biobank). This registry will be composed of data provided by the participants concerning general and clinical information and specific analytical data derived by imaging examinations. Paired biologic samples from a growing number (>300) of CCA patients from several European countries are routinely collected. Biobanks will be ready available to test diagnostic biomarkers on tissue and biologic samples (cells, liver biopsy, serum, plasma, saliva, urine and stool).

#### Tasks & Activities

- To carry out the analysis of CCA imaging data and correlations with data from the histomorphology, genomic and clinical-epidemiology registries.
- To establish the best imaging modality to detect early changes in the wall of the bile ducts.
- To explore new imaging biomarkers (i.e., texture analysis; diffusion-weighted imaging; perfusion analysis) to differentiate patients with benign structures *versus* patients with CCA.
- To correlate imaging biomarkers with histological subtypes, genomic profile (radiogenomic analysis) or clinical presentation (e.g. CCA on primary sclerosing cholangitis *versus* CCA on cirrhosis/fibrosis).
- To determine new early biochemical tumour markers for screening, diagnosis and CCA prognosis.

Year	Key milestones and deliverables
2	Publication of a standardized protocol for magnetic resonance imaging (MRI) diagnostic in cholangiocarcinoma patients to allow future prospective studies.
2	Publication of a systematic review on non-invasive biomarkers used for diagnostic, prognostic or for therapeutic follow-up purposes in cholangiocarcinoma.
2-4	Reports of workshops of Working Group 2, Working Group 3 and Working Group 5 to define the state of the art of correlations studies of radiological tools and biomarkers in homogeneous clinical, etiological and histomorphological cholangiocarcinoma subtypes, and to set up the scheme to correlate data included in the registries.
3-4	Original articles describing the correlations of the histomorphology or homogeneous molecularly featured subtypes of cholangiocarcinoma with Magnetic Resonance Imaging features,
4	Scientific publications on the diagnostic performance of radiological tools or biomarkers in homogeneous clinical, etiological and histomorphological cholangiocarcinoma subtypes.

#### WG6. DEVELOPMENT OF NOVEL THERAPEUTIC TARGETS AND TOOLS

The aim of this WG will be to develop or define novel drugs and strategies to be investigated at the preclinical and clinical levels in the search of potential therapeutic targets and tools that could result from data derived from the other WGs and/or the pharmaceutical industry, and to conduct translational studies based on the analysis of data and/or of clinically annotated specimens from previously conducted/ongoing trials with adequate follow up.

#### Tasks & Activities

- To identify molecular targets for the development of novel therapeutic approaches.
- To define the genetic signature of chemoresistance in CCA.
- To incorporate well-defined experimental models of CCA to the evaluation of novel therapies.
- To harmonize the use of novel biomarkers of CCA with the screening of antitumour drugs and therapeutic strategies.
- To carry out pilot pre-clinical studies using already available and novel drugs and therapeutic strategies.

Year	Key milestones and deliverables
1 & 2	A systematic review and technical publications on validation of tools for individualized prediction of the lack of response of cholangiocarcinoma patients to specific chemotherapy.
2	Conference proceedings of the workshop on interdisciplinary projects for the development of drug chemotherapy and gene therapy in chemosensitization in cholangiocarcinoma field.

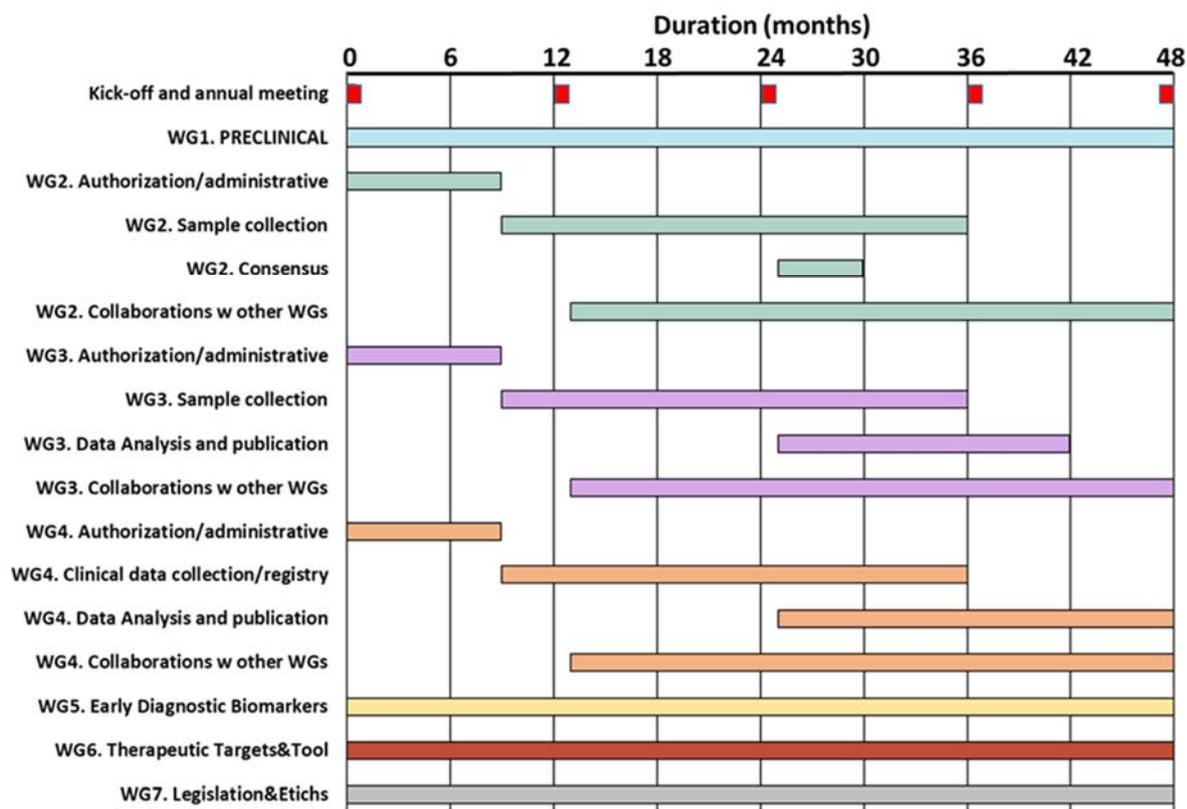
3	Original article describing the molecularly bases of mechanisms of chemoresistance to available drugs for the treatment of cholangiocarcinoma.
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### WG7. LEGISLATION AND ETHICS

This WG will govern and assist in the drawing up of Material Transfer Agreements (MTAs) to create sample biobank established in the objectives of other WGs. This WG will also manage and coordinate the approvals of local institutional ethics committees, and the obtaining of informed consent from patients for the use of data and samples.	
<b>Tasks &amp; Activities</b>	
<ul style="list-style-type: none"> <li>• To organize and coordinate MTAs and transfer of samples among countries.</li> <li>• To supervise data storage and data sharing and administration of the registry databases.</li> <li>• To deal with legal and ethical issues.</li> </ul>	
<b>Year</b>	<b>Key milestones and deliverables</b>
1	Technical publication of a Quality Plan and Good Practice Policies that apply to all COST participants of EURO-CHOLANGIO-NET.
1	Approvals of local institutional ethics committees related to creation of databases of multidisciplinary aspects concerning cholangiocarcinoma.
2	Report on the management of the informed consent from patients for the use of data and samples.

White Books & roadmaps will be released at the end of this Action by the MC which will coordinate contributes from all WGs: “The White Book of EURO-CHOLANGIO-NET story” and “Beyond EURO-CHOLANGIO-NET White Book”.

#### 3.1.2. GANTT DIAGRAM



### 3.1.3. PERT CHART (OPTIONAL)

### 3.1.4. RISK AND CONTINGENCY PLANS

**Risk of insufficient quality:** The Action will have measures to ensure an internal peer-review process, either through institutional processes or as a part of the COST Action, prior to wider sharing of scientific outputs. In addition, all key documents will undergo external peer-review process.

**Risk of Action costs going over the estimated budget:** Although the MC will try to prevent this circumstance, in case of cost overruns, the network will not request additional funding although it may ask for permission to adjust some activities.

**Risk of insufficient extent of dissemination:** To prevent this risk, the Action will use a wide variety of communication channels.

**Risk of insufficient collaboration:** The CG will review, on a regular basis, the contributions of each collaborator to ensure equivalent and efficient contribution of all participants.

**Risk of failure to attract ECIs:** To prevent this risk, a call for participation in Training Schools and professional workshops will take place 3 months before the planned date of the activity.

**Risk of unsatisfactory training schools and workshops:** While the MC will benefit from the vast experience of collaborators to ensure the delivery of high-quality training schools and professional workshops, ECIs will be asked for their feedback concerning the quality and the benefit achieved by these activities. The MC will identify the relevant recommendations to be adopted in future activities.

**Risk of failure to attend meetings:** The failure of any collaborator or WGs representatives to physically attend meetings will be compensated by setting teleconferences and webinars.

**Risk of personal conflicts:** Conflicts within the Action will be resolved through direct negotiations, or if this is not successful, parties in conflict will have access to a Conflict-Resolution Board, composed by three members of the Management Committee, which shall be empowered to rule on all aspects of the Action activities with the exception of extreme cases involving ownership and use of intellectual property rights and legal or financial liabilities.

## 3.2. MANAGEMENT STRUCTURES AND PROCEDURES

Management Committee (MC) members will be nominated by the COST National Coordinator in each of the COST countries. The MC will be responsible for activities of WGs. At its first meeting, the Action Chair, Vice-Chair, WGs Leaders, Task Coordinators (ECIs Coordinator, Gender-Balance Coordinator, Website Coordinator, the Training Schools/STSMs Coordinator), the Business Management Team and the Conflict-Resolution Board will be elected. The MC will nominate a Core Group (CG) consisting of the Chair, Vice-Chair, the WG Leaders and Coordinators. The CG will verify and approve all operational and day to day decisions mandated by the MC, synchronize scientific and STSMs activities, and help the Chair in the efficient running of the Action. They will establish frequent communication through E-mailing and teleconferences. The MC will be assisted by the Advisory Board. This will be appointed in Year 1, and will be in charge of advising on dissemination and society-related issues, and ethical/regulatory issues, upon request of the MC. Several participants and members of the advisory boards have been involved and had experience in similar projects, comprised COST Action coordination. All WGs will have a Leader and a Vice-Leader who will report on the progress of the WG in relation to the deliverables achieved and its dissemination, propose modifications and innovations. MC will be responsible of definition and management of Action Strategy, including planning of activities and dissemination strategy, decision on whether to approve the participation of additional COST Countries and institutions in Non-COST Countries, and to perform reporting duties. The Action will pay particular attention to ensure enough representation of ECIs and gender balance on all Committees/WGs as well as promoting their participation as speakers and chairs in Workshops and Conferences sessions. The annual report from each WG will include a section detailing the participation of ECIs and gender balance in its activities. ECIs will be actively involved in the Action through the organization of STSMs and Training Schools. STSMs will be encouraged to extensively exchange scientific data and technical knowledge and skills within the network. With the cooperation of the ECIs Coordinator, Cross-disciplinary Training Schools will be organized. The Website Coordinator will be responsible for maintaining the website and solve all technical contingencies.

## 3.3. NETWORK AS A WHOLE

EURO-CHOLANGIO-NET is a coordinated pan-European network that could be imagined as the home of the European CCA research, which will virtually employ the European leading research groups in

different specific fields of research/interest interconnected through WGs by a iterative process involving people, data registry, information and bio-banking, thanks to tools and resources provided by the Action.

## References

1. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. Bridgewater J, et al. *J Hepatol*. 2014;60:1268-89.
2. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. Khan SA, et al. *Gut*. 2012 Dec;61(12):1657-69.
3. A comparison of trends in mortality from primary liver cancer and intrahepatic cholangiocarcinoma in Europe. Bertuccio P, et al. *Ann Oncol*. 2013 Jun;24(6):1667-74.
4. Cancer incidence and mortality projections in the UK until 2035. Smittenaar CR, et al. *Br J Cancer*. 2016 Oct 25;115(9):1147-1155.
5. Advances in targeted therapies for hepatocellular carcinoma in the genomic era. Llovet JM, et al. *Nat Rev Clin Oncol*. 2015 Jul;12(7):408-24.
6. Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer and pancreatic cancer in Europe 1999-2007: Results of EUROCORE-5. Lepage C, et al.; EUROCORE-5 Working Group. *Eur J Cancer*. 2015 Oct;51(15):2169-2178.
7. Cancer of unknown primary site. Varadhachary GR, Raber MN. *N Engl J Med*. 2014;21;371:757-65.
8. Rare and less common cancers: Incidence and Mortality in England, 2010-2013. A Report from Public Health England, National Cancer Registration and Analysis Service. [http://www.ncin.org.uk/publications/rare\\_and\\_less\\_common\\_cancers](http://www.ncin.org.uk/publications/rare_and_less_common_cancers)
9. Emerging molecular therapeutic targets for cholangiocarcinoma. Rizvi S, Gores GJ. *J Hepatol*. 2017 Sep;67(3):632-644.