EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Brussels, 12 May 2023

COST 035/23

**DECISION**

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| Subject: | Memorandum of Understanding for the implementation of the COST Action “Precision medicine in biliary tract cancer” (Precision-BTC-Network) CA22125 |

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action Precision medicine in biliary tract cancer approved by the Committee of Senior Officials through written procedure on 12 May 2023.

**MEMORANDUM OF UNDERSTANDING**

For the implementation of a COST Action designated as

**COST Action CA22125**
**PRECISION MEDICINE IN BILIARY TRACT CANCER (Precision-BTC-Network)**

The COST Members through 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, 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 document amending or replacing them.

The main aim and objective of the Action is to coordinate a pan-European interdisciplinary effort to promote personalised approaches for patients with BTC, covering prevention, diagnosis, prognosis and therapy, by creating a life science ecosystem that supports interaction between basic scientists, clinicians, regulatory authorities, advocacy groups, SMEs and pharmaceutical industry partners. This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

## OVERVIEW

**Summary**
Biliary tract cancers (BTC) include a heterogeneous group of aggressive tumours with an increasing incidence in Europe. Limited knowledge of risk factors and the lack of biomarkers for diagnosis are responsible for frequent late detection. These tumours are characterised by high refractoriness to conventional chemotherapy, and an unmet need for development of novel therapeutic strategies. Targeted therapies have proven to be a good option for only subgroups of patients, but their access is unevenly distributed across Europe, requiring urgent implementation plans for patients' benefit.
**Precision-BTC-Network** aims to create a unique cooperative and interdisciplinary network of European multi-stakeholders, including basic researchers, clinical investigators, SMEs, European Commission and EU agencies, international scientific organizations, patient representatives, and industrial partners, to address the diversified, but interrelated challenges, in the implementation of precision medicine in the management of BTC.
The Action will be organized in four working groups involved in the development of a personalized management of patients with BTC: **Identification of epidemiological heterogeneity in Europe to apply precision prevention**, **Personalised early detection of BTC**, **Personalisation of treatment for patients with BTC**, **Patient-centric support management**, and two horizontal WGs will provide cross-sectional activities relevant to WG1-4 goals: **Artificial intelligence**, and **Drug development using preclinical models**.
The expected impact includes speeding up the development of diagnostic and prognostic biomarkers for BTC patients and bringing beneficial therapies and optimal management of these patients across Europe. In addition, the training of Young Researchers and Innovators in precision medicine in BTC will ensure further progress in the future.

| Areas of Expertise Relevant for the Action | Keywords |
|---|---|
| ● Clinical medicine: Oncology<br>● Basic medicine: Pharmacology, pharmacogenomics, drug discovery and design, drug therapy<br>● Clinical medicine: Databases, data mining, data curation, computational modelling<br>● Clinical medicine: Gastroenterology and hepatology | ● biliary cancer<br>● prevention<br>● early detection<br>● personalised treatment<br>● artificial intelligence |

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

Research Coordination
● Identification of epidemiological heterogeneity of BTC in Europe to apply precision prevention. Differences in risk factors, pathological and anatomical classification of each BTC subtype will be achieved, along with heterogeneity of incidence, and access to treatments and outcomes. This will permit implementation of a precision-medicine preventive strategy in at-risk populations.
● Development of a precision-approach for early diagnosis based on the identification of novel biomarkers in specific populations-at-risks, which will diversify the diagnostic pathway according to the risk factor-dependent biological and molecular mechanisms of development of the diseases.
● Optimization of personalised therapeutic therapies, which are currently reserved mainly to patients with iCCA harbouring specific targetable mutations. Exploration of other contributors in BTC development,

progression and drug resistance to expand the proportion of patients who can receive a personalized treatment. This will be coupled with identification of predictive biomarkers.
● Development of novel therapeutic strategies, based on a matched preclinical research programme that provides novel disease models, including vertebrate and invertebrate animal models, patients' derived models (cells, organoids, assembloids) and engineered devices for the recapitulation of the complex system of drug delivery within the morphological architecture of BTC.
● Development of innovative algorithms for the analysis of multi-omics data. Innovation will be delivered through the application of machine learning approaches and artificial intelligence for interpretation and exploration of multi-level "omics" data that can be integrated for a deeper knowledge of BTC biology and clinical behaviour and aid biomarker development.
● Use of artificial intelligence and deep learning for subgrouping patients based on their routinely obtained image data (pathological or radiological images) and association with prognosis and druggable targets.
● Delivery of a patient-centric supportive therapy. Identification of diversified patients' needs will be performed by promoting a more active engagement of patients, patients' representatives, nurses, and clinicians to develop consensus for medical staff and educational materials for patients, to reduce disparities in the delivery of best supportive care across Europe.
● Reduce disparities in BTC management in Europe, through programmes of educations of clinicians, patients, and lay public; dissemination activities in multiple languages to provide uniformed consensus for the research applications in the field of BTC. Particular attention will be focussed on the harmonisation of access to genomic profiling and precision-oncology.
● To ensure the dissemination and exploitation of all knowledge and results of the Action among all stakeholders through specific dissemination activities (dedicated website to be updated with relevant information), social media, presentation of results at meetings, creation of infographics and videos for the general public, and collaboration with industry.

Capacity Building
● To establish a collaborative environment for researchers in Europe and internationally stimulating the development of a joint research agenda, fostering the exchange of knowledge, expertise, research materials and data and encourages long-term collaborations, real-life data studies and prospective multicentre clinical trials.
● To support the creation of a new generation of experts in BTC management through the participation of YRIs in specific workshops, training schools, Short-Term Scientific Missions (STSMs), Virtual Mobility Grants and a mentorship programme. A young investigator (YI) group will help to maintain the Action's focus on YRIs.
● To work with patients and their representatives as important stakeholders in the Action to detect priority research questions in the field of BTC, identify gaps in clinical service relevant to BTC subjects and improve public education and awareness (European Commission and EU agencies).

# TECHNICAL ANNEX

## 1. S&T EXCELLENCE

### 1.1. SOUNDNESS OF THE CHALLENGE

#### 1.1.1. DESCRIPTION OF THE STATE OF THE ART

**Background and medical context.** Biliary tract cancer (BTC) refers to a **heterogeneous group of aggressive tumours** arising along the biliary tract, including cholangiocarcinoma (CCA), combined hepatocholangiocarcinoma (cHCC/CCA), gallbladder carcinoma (GBC) and ampullary cancer (AC) (1). The prognosis of patients with BTC is dismal, as the 5-year overall survival (OS) rate is less than 20%. This is due, at least in part, to the silent tumour growth, particularly in early disease stages, that commonly leads to **late diagnosis**. Therefore, only 20% of patients with BTC are candidates for surgery with curative intent. The relapse rate in patients undergoing surgery is >50%, so most patients will ultimately be treated with systemic therapy throughout their disease, and these tumours are characterised by being **highly refractory to conventional chemotherapy** based on gemcitabine plus cisplatin (2).

Although BTC is still considered a rare cancer, **its incidence is alarmingly increasing worldwide** (3), becoming a significant health, social and economic problem, particularly among males, except for GBC, which is the only type more frequent in women (4).

Rare cancers, like BTC, do not receive enough attention and allocation of resources to help identify risk factors, biomarkers for diagnosis and prognosis assessment, and new treatment modalities that permit a personalised management of these patients, although this has been changing in the past few years. Adding to the problem, the incidence rates of BTC are increasing and the age of incidence in at-risk populations is falling, although data are only available from some European countries (5-8). Trends are similar to those in the US (9), where overall the numbers have been described as almost equalling those of hepatocellular carcinoma (HCC), which is the most frequent liver cancer.

It is accepted that chronic inflammation of the hepatobiliary tract is a hallmark of oncogenesis in BTC, regardless of anatomical location, and multiple risk factors have been identified (age, gallstones, cirrhosis, Lynch syndrome, fatty liver, diabetes, alcohol, chronic infections, drugs, inflammatory bowel disease, or germ line mutations, among others). Some risk factors are shared by several tumour types, while others are more specific to one specific tumour type (10), and some are associated with a high risk of BTC development, while others only slightly increase the risk of BTC, but are highly prevalent. Cirrhosis and biliary tract stone disease are risk factors of CCA and GBC, respectively, and a particular case is patients with primary sclerosing cholangitis (PSC), as this rare disease is usually diagnosed in subjects aged 30-40 years and the risk of developing CCA is high at a young age (11). Regarding AC, knowledge of risk factors and tumour development is scarce. Overall, in a significant percentage of patients, no underlying cause is identified at the time of diagnosis, so work remains to be done **to develop cost-effective and realistic surveillance programmes for early detection** of these tumours in high-risk groups (12-14), as well as for **their prevention**.

Technological advances in molecular characterisation and the approval of several targeted therapies are changing the therapeutic landscape for advanced BTC. Precision medicine has become a central element of treatment, as up to 40% of BTC harbour a potentially targetable molecular abnormality, although the molecular characteristics are very different for each type of BTC and comprehensive data for GBC and AC are still missing (15, 16). Progress still needs to be made in ensuring that all patients have access to molecular testing to identify those who are candidates for targeted therapies. For the majority of patients, no druggable alterations are identified, leading to an unmet clinical need to identify markers to improve outcomes with available therapies and to develop more effective biomarker-driven treatment strategies.

The **Network** of Precision Medicine in biliary Tract Cancer (**Precision-BTC-Network**) will make a difference by focusing on improving the overall clinical outcome of this disease and, as the data presented above show, it is clear that this challenge can only be met by applying a **precision medicine approach that personalises early detection, prevention and treatment**. Early detection of BTC is

key for improving patients' outcomes, as survival has been shown to be higher in patients diagnosed at stages I/II (17-19). Important efforts have been made to identify non-invasive biomarkers, in some cases using omics technologies (proteomics, transcriptomics, metabolomics, metagenomics), for screening and early detection, as well as to predict prognosis of BTC patients (20-21); several biomarker panels have been proposed to differentiate tumours that may share anatomical location, which is key for each patient to receive the most appropriate treatment; however, prospective studies in large cohorts of patients from different countries are needed to establish the validity of biomarker panels. The use of personalised treatment strategies has confirmed their validity in a subgroup of patients with BTC, however, it is key that new therapeutic strategies are developed for all patients with BTC based on the study of biomarkers that go beyond the mutational landscape. Omics techniques have also proved to be useful to elucidate biological processes, and to discover new drug targets. The analysis of high-throughput omics datasets is computationally demanding, and the interpretation of results is even more complex, requiring expertise in multiple disciplines. Successfully integrating the different approaches that will lead to measurable advances in prevention, early detection, and personalised treatment of BTC requires a multidisciplinary strategy that includes artificial intelligence to integrate a large amount of clinicopathological, genetic, serological, histological, and radiological data (22). These resources can only be developed at the crucial scale and capacity in the framework of a collaboration between institutions and, **at present, there is no network of cooperating multidisciplinary centres comprising these types of tumours**.

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

Beyond an anatomopathological classification, BTC displays several molecular and biological features that increase heterogeneity. An "all-comers" approach that disregards this level of inter-patient heterogeneity is destined to fail in the translation of basic research to clinical applicability. Recent advancements (i.e. targeted therapies with FGFR2 inhibitors and IDH inhibitors) have highlighted how a deep understanding of the biological and molecular bases of BTC can favourably impact patients' lives. However, to date a limited number of recurrent and actionable molecular alterations have been identified, while there remains a critical need to understand the mechanisms that contribute to BTC formation and development, and influence drug response. Understanding epigenetic mechanisms, dysregulated gene networks, deranged immune responses, the effect of underlying liver diseases, primary and acquired resistance and the interplay between different cell types within the microenvironment driving the complexity of BTC will enable a precision-medicine approach to both prevent tumour development and increase the therapeutic index for patients with BTC.
**BTCs are too often diagnosed at a late stage** due to the lack of appropriate biomarkers that can assist in guiding surveillance and early diagnosis in at-risk populations (i.e. PSC, cirrhosis, biliary tract stone disease), where **personalised prevention strategies** can be applied. If the identification of novel targets and development of linked therapeutics remains the major unmet need in patients with BTC, a more **personalised delivery of existing therapies** is also necessary, along with a **more uniform access to treatment across Europe**.

**The aim of Precision-BTC-Network is to coordinate a pan-European interdisciplinary effort to promote personalised approaches for patients with BTC**, covering prevention, diagnosis, prognosis and therapy, based on integration of retrospective and prospective pan-European studies, by creating a life science ecosystem that supports interaction between basic scientists, clinicians, regulatory authorities, and advocacy groups, as well as small and medium-sized enterprises (SMEs) and pharmaceutical industry partners. This will provide the critical mass of expertise, connections, and integration to address the innovation needed for the implementation of personalised management in BTC. Through the strategic establishment of research collaborations, conferences, meetings, workshops, training schools, scientific exchanges, mentoring programmes and educational events, we will establish the infrastructures for the expansion of preventive and therapeutic opportunities for BTC patients in Europe and beyond.
This Action is aligned with the European Commission report of the Mission Board for Cancer "Conquering Cancer: Mission Possible" (Recommendation 3: Support the development and implementation of effective cancer prevention strategies and policies within Member States and the EU; Recommendation 4: Optimise existing screening programmes and develop novel approaches for screening and early detection; Recommendation 5: Advance and implement personalised medicine approaches for all cancer patients in Europe; Recommendation 6: Develop an EU-wide research programme on early diagnostic and minimally invasive treatment technologies).
The timeliness of this Action originates from: i) the need to establish a multidisciplinary community focused on BTC as a priority area of attention, ii) epidemiological data suggesting a progressive increase in BTC incidence across Europe, iii) the decreasing age of onset in at-risk-populations, where

personalised prevention medicine should be applied and the rising demand for cost-effective processes and tools to schedule screening, iv) the growing number of promising biomarkers identified in retrospective studies, which need to be validated in prospective ones before they can be used in the clinic, v) availability of molecular characterisation of BTC tumours and the discovery of novel actionable targets, which argues for individualized treatment options and increasing opportunity of clinical trials for patients with BTC in various therapeutic lines, vi) the recent immunotherapy data highlighting that patient selection is necessary for a successful approach, vii) the increasing knowledge of the heterogeneity of tumour microenvironment, which leads to diversified therapeutic opportunities and development of novel immunotherapeutic options, viii) the rising application of artificial intelligence to cancer prevention, diagnosis and therapy, which needs to be implemented in BTC, and ix) the growing interest in BTC by young investigators, who need specialised education and training.
Taken together, these data support the need for a global effort towards the implementation of a personalised approach to BTC management, which leverages on the initial success of personalised oncology strategies that have demonstrated how a targeted approach is essential to boost success. However, it is mandatory that this strategic line is applied beyond the mutation:drug binomial, as mounting preclinical and clinical data support the contributing role of risk factors, microenvironment, epigenetic changes and metabolic/immunological rewiring in the development and progression of BTC. In addition, it is imperative that a patient-oriented and personalised approach beyond therapeutic development is applied in early diagnosis, prevention, and patient care.
**This will only be possible through networking,** where multidisciplinary stakeholders come together not only to define opportunities, but also to **implement plans for the delivery of personalised medicine in BTC across Europe,** including Inclusiveness Target Countries (ITCs), but also Near Neighbour Countries (NNCs), and International Partner Countries.

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

### 1.2.1. APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE OF THE ART

BTC includes a diverse group of tumours originating throughout the biliary tract, with multilevel heterogeneity in the clinical presentation, biological behaviour, genomic features, drug response and symptoms. Its management remains unharmonized across Europe due to differences in risk factors, diagnostic approaches, therapeutic accessibility, education, and socio-economic factors.
To date, advances in BTC research and management have been driven by the work of many individual groups without overall coordination, replicating efforts in small independent cohorts. This complicates the translation of basic research advances into practice-changing clinical applications, the chance to obtain large sources of research funding and spin-off of innovation. Moreover, the visibility achieved in international societies is fragmented.

From the recent BTC research activities and successes we have learned that:
- BTC is a rare disease with heterogeneity among patients that requires multi-institutional **joint efforts** for the translation of basic discoveries into clinical applications [i.e. only multicentre clinical trials have reached a statistically powered platform to inform clinical practice (ABC trials, ClarIDHy, FIGHT202)].
- Investigation of therapeutic strategies based on analogies with other tumour types have failed to prove a benefit in BTC patients [i.e. exploration of activity of drugs on the basis of their activity in other tumour types without a deep understanding of the biology (Amebica trial; Keynote-028)].
- Impact on patients' lives has emerged from a **paired effort between basic science and clinical research** with clinical experimentation based on solid preclinical evidence [i.e. approval of novel therapeutic strategies based on a deep understanding of the molecular features of intrahepatic CCA (e.g. FGFR2 inhibitors after the discovery of FGFR2 fusion-driven CCA].
- **Increased awareness of BTC and support from patients' representatives** has enabled a domino effect on policy makers [e.g. change in CCA subtypes coding with ICD-11 (intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA)].

However, significant challenges remain, representing the limitations for a widespread social and medical impact on BTC:
- **Early diagnosis remains an unmet need** due to the lack of a personalised plan that, based on the integration of multiple data, provides tools for prospective validation in subjects at risk of BTC (e.g. PSC, hepatolithiasis, liver cirrhosis, etc.).
- **Surveillance and preventive strategies continue to be elusive** due to the lack of clinical/biological characterisation of BTC patient subgroups that would allow implementation of precision programmes.
- **Underrepresentation of certain European patient populations** in registries and clinical trial cohorts (i.e. Eastern European patients).

- **Therapeutic advances are limited to a small subgroup of patients** due to a lack of knowledge of the driving forces of development and progression in most of BTC cases, with several biological and molecular areas (beyond genetics) left unexplored.
- The predominance of effective therapeutic strategies in BTC are based on “all-comers” approaches (i.e. chemotherapy, immunotherapy), which **reduces the therapeutic index of these treatments**.
- **Heterogeneity in the implementation of advances** in BTC management is observed across Europe, with substantial delays in ITCs.

To address these challenges and meet these demands quickly and effectively the Precision-BTC-Network Action relies on four major drivers: i) **international multidisciplinary collaboration**, ii) **innovative scientific impulse**, iii) **continuous training, with special attention to next generation of investigators, including from ITCs** and iv) **social education and awareness**.

Progress beyond the state-of-the-art will be achieved by:
- Breaking down the boundaries between medical disciplines by fostering communication between stakeholders, coordinating a harmonious plan with a multi-directional exchange of information, where clinical research takes advantage of preclinical findings (translation) and basic research is informed by results and patients' needs (reverse translation/orientation).
- Facilitating communication and knowledge sharing between academia and industrial partners to define criteria for the translation of academic discoveries into market products.
- Delivering innovation by combining multidisciplinary efforts among medical and biological researchers, clinicians, engineers, patient representatives, biotechnologists, biomedical informaticians, chemists, and epidemiologists.
- Joining forces to achieve representation of ethnicities across Europe in large BTC cohorts to enable statistical confidence for the generation of practice-changing data.
- Harmonising BTC management in Europe (patient and clinician educational plans, identification of disparities in screening/surveillance programmes, access to treatment and availability of molecular profiling to overcome service heterogeneity).

### 1.2.2. OBJECTIVES

#### *1.2.2.1. Research Coordination Objectives*

The global objective of Precision-BTC-Network is to create a unique cooperative and interdisciplinary network of European multi-stakeholders, including basic researchers, clinical investigators, SMEs, European Commission and EU agencies, international scientific organizations, patient representatives, and industrial partners, to address the diversified, but interrelated challenges, in the implementation of precision medicine in the management of BTC.
Specific Research Coordination Objectives of the Precision-BTC-Network Action are:
**Identification of epidemiological heterogeneity of BTC in Europe to apply precision prevention**. Differences in risk factors, pathological and anatomical classification of each BTC subtype will be achieved, along with heterogeneity of incidence, and access to treatments and outcomes. This will permit implementation of a precision-medicine preventive strategy in at-risk populations.
**Development of a precision-approach for early diagnosis** based on the identification of novel biomarkers in specific populations-at-risks, which will diversify the diagnostic pathway according to the risk factor-dependent biological and molecular mechanisms of development of the diseases.
**Optimization of personalised therapeutic therapies**, which are currently reserved mainly to patients with iCCA harbouring specific targetable mutations. Exploration of other contributors in BTC development, progression and drug resistance to expand the proportion of patients who can receive a personalized treatment. This will be coupled with identification of predictive biomarkers.
**Development of novel therapeutic strategies**, based on a matched preclinical research programme that provides novel disease models, including vertebrate and invertebrate animal models, patients’ derived models (cells, organoids, assembloids) and engineered devices for the recapitulation of the complex system of drug delivery within the morphological architecture of BTC.
**Development of innovative algorithms for the analysis of multi-omics data**. Innovation will be delivered through the application of machine learning approaches and artificial intelligence for interpretation and exploration of multi-level “omics” data that can be integrated for a deeper knowledge of BTC biology and clinical behaviour and aid biomarker development.

**Use of artificial intelligence and deep learning for subgrouping patients** based on their routinely obtained image data (pathological or radiological images) and association with prognosis and druggable targets.
**Delivery of a patient-centric supportive therapy.** Identification of diversified patients' needs will be performed by promoting a more active engagement of patients, patients' representatives, nurses, and clinicians to develop consensus for medical staff and educational materials for patients, to reduce disparities in the delivery of best supportive care across Europe.
**Reduce disparities in BTC management in Europe**, through programmes of educations of clinicians, patients, and lay public; dissemination activities in multiple languages to provide uniformed consensus for the research applications in the field of BTC. Particular attention will be focussed on the harmonisation of access to genomic profiling and precision-oncology.
**To ensure the dissemination and exploitation of all knowledge** and results of the Action among all stakeholders through specific dissemination activities (dedicated website to be updated with relevant information), social media, presentation of results at meetings, creation of infographics and videos for the general public, and collaboration with industry.

#### *1.2.2.2. Capacity-building Objectives*

The main capacity-building goal of this Action is to develop the critical mass of researchers working on the topic by leveraging and embedding scientific excellence across the European BTC community and by steering the future research agenda for the implementation of a precision medicine programme in BTC across Europe.
The specific capacity-building objectives of the Precision-BTC-Network Action include:
**To establish a collaborative environment** for researchers in Europe and internationally stimulating the development of a joint research agenda, fostering the exchange of knowledge, expertise, research materials and data and encourages long-term collaborations, real-life data studies and prospective multicentre clinical trials.
**To support the creation of a new generation of experts in BTC management** through the participation of YRIs in specific workshops, training schools, Short-Term Scientific Missions (STSMs), Virtual Mobility Grants and a mentorship programme. A young investigator (YI) group will help to maintain the Action's focus on YRIs.
**To work with patients** and their representatives as important stakeholders in the Action to detect priority research questions in the field of BTC, identify gaps in clinical service relevant to BTC subjects **and improve public education and awareness** (European Commission and EU agencies).

# 2. NETWORKING EXCELLENCE

## 2.1. ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

### 2.1.1. ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

There is no other EU or international project aiming to improve the personalized management of patients with all types of BTC. The Precision-BTC-Network Action will address existing challenges with the expansion of a database of clinical data, which already includes around 2000 patients with BTC from hospitals of several European countries, with data from more patients collected in small hospital registries across Europe. The aim is to build one large European clinical registry containing information of patients with CCA, GBC and AC from numerous centres in European countries, which will serve as a basis for expanding the information available, enabling the collection of a greater amount of data in associated registries, including clinical follow-up data, histomorphology images, radiological images, and molecular profiling data. The exploitation of data with artificial intelligence will permit to advance in precision prevention, diagnosis, treatment, and the development of future clinical trials.
Some related initiatives are underway in the US, South America, and Asia to establish clinical and risk factor data registries, and this pan-European Action plans to synergise with these networks to generate international collaborative studies and to support global dissemination and promotion of the results.
For the first time, this Action will increase the communication between clinicians, basic researchers, and drug developers to define vulnerabilities in BTC that can be exploited for the development of diagnostic tools and novel personalised therapeutic strategies. Although in all types of BTC there is an urgent need to advance knowledge of the tumours, prevention, diagnosis, personalised treatment and specific care, information in AC or cHCC-CCA is even more scarce, and the broad collaboration will allow progress in all to be made more effectively. At present, no COST Actions involving research on personalised management of patients with BTC have been funded.

The Action will be in contact with EU and international agencies working on related issues in other cancers [International Agency for Research on Cancer (IARC), European Organisation for Research and Treatment of Cancer (EORTC), the European Clinical Research Infrastructure Network (ECRIN) and the Organisation European Cancer Institute (OECI)] to exchange information and best practices and be updated on new developments that could be of special interest for patients with BTC.
In addition, this Action will provide the basis for the generation of collaborative proposals for upcoming funding opportunities. This may include both European and international efforts.

## 2.2. ADDED VALUE OF NETWORKING IN IMPACT

### 2.2.1. SECURING THE CRITICAL MASS, EXPERTISE AND GEOGRAPHICAL BALANCE WITHIN THE COST MEMBERS AND BEYOND

The Precision-BTC-Network Action will initially be supported by a large number of experienced researchers from different fields, YRIs, diagnostic and pharmaceutical companies, SMEs and other stakeholders interested in addressing the challenges and objectives described above, but initial members of the Action will actively work to involve more participants from other countries with a wide geographic distribution, especially from ITCs, support their integration, increase the critical mass and make the results more impactful. Collaborations with international partners are also in place and all necessary actions will be taken to increase the internalisation of the Action.
Scientific committees of the most relevant European scientific societies, such as the European Society for Medical Oncology (ESMO), the International Liver Cancer (ILCA), the European Association for the Study of the Liver (EASL) and the United European Gastroenterology (UEG), International Hepato-Pancreato-Biliary Association (IHPBA), as patient' associations will be represented in the Working Groups (WGs) and will contribute to the dissemination of the activities and results of the Action to key stakeholders, which will facilitate the recruitment of new participants.
It is worth noting that this Action will ensure an appropriate gender balance and involvement of minorities in all its activities. Actions will be taken for the promotion of equal gender opportunities, with attention to engage gender balanced YRIs, but also maintain gender representation in leadership and decision-making bodies (at least 40% of the minority gender in the Management Committee (MC) and WG leadership team). Gender, YRIs and minority balance will also be considered during organizations of all the activities (i.e. conferences, meetings, workshops, etc.).
Engagement of YRIs will be actively sought, as discussed throughout the document.

### 2.2.2. INVOLVEMENT OF STAKEHOLDERS

The Precision-BTC-Network plans to involve all European stakeholders (Figure 1) under the umbrella of excellence, inclusion, and equity. The most active members will be encouraged to take leadership positions in the WGs.

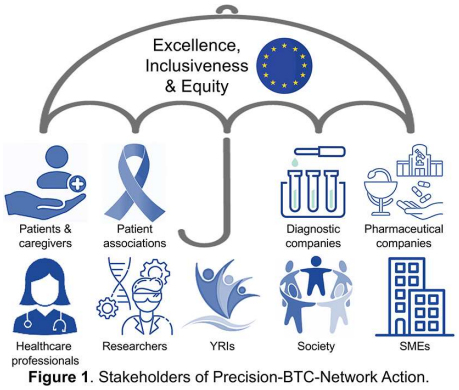


**Figure 1**. Stakeholders of Precision-BTC-Network Action.

**Healthcare professionals and Researchers**. Clinical investigators, nurses, and basic and translational researchers from different specialities in hospitals, research institutes, and universities will be approached to have multidisciplinary teams that permit the development of all the activities proposed in each WG.

**Patients, Caregivers and Patient organizations** will be invited to actively participate in the activities of the WGs, will be informed of advances in the field of BTC, and will be the recipients of important deliverables to help them better understand their disease and different aspects of its personalized management. Participation of Action members in congresses organised by patient associations will be encouraged and patient representatives will be invited to Action meetings to learn first-hand about their needs.
A major effort will be made to raise awareness of the disease in **Society**, especially among groups at risk of developing BTC, and to promote appropriate follow-up for early detection. The Action also rely on the support of Members of the European Parliament (MEPs) Against Cancer and several European national cancer associations for the dissemination of relevant information to society.
**YRIs** (PhD students, postdocs, and medical residents) will be encouraged to join the network and participate in workshops, meetings, training schools, STSMs, and the career and scientific mentorship programme. A YRI will be assigned as a supporting co-leader in each WG, allowing him/her to be trained in these leadership tasks. They will be encouraged to participate by presenting results at the annual meetings.

**Biotech and Pharmaceutical companies and SMEs** will be approached to participate in the network, and attend meetings organised by the Action and during the life of the project the Action will seek to foster collaborations and further engagement to accelerate the development of new diagnostic techniques and treatments, as well as expand the number of these stakeholders.
**Scientific societies** will be involved in the network, as renowned members of the largest European scientific organizations will be approached to participate in different WGs and to endorse activities that may be of interest to their members, such as the mentorship lectures. Regulatory bodies, policy makers, Think Tanks and professional associations will facilitate the effective implementation of social actions.

# 3. IMPACT

## 3.1. IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAK-THROUGHS

### 3.1.1. SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

Precision-BTC-Network will build an inclusive, interdisciplinary network to advance research in, and the delivery of, a personalised management of BTC. The critical mass that the Action will gather is expected to have a long-term transformative impact on the field, with an impact that will extend beyond the borders of Europe and infiltrate the worldwide BTC community. A deep understanding of the heterogeneity of BTC, coupled with a comprehensive and personalised programme of biomarker and therapeutic development, will optimise the management of patients with BTC and open new horizons in this field. ***Patients with BTC*** will be the ultimate beneficiaries of this Action, as they will receive education and personalised care and, in the long term, will benefit from the new diagnostic and therapeutic algorithms. ***For the researchers and clinicians*** involved in the network, the Action will present an opportunity to expand their professional networks and establish new collaborations. ***For YRIs***, the Action will provide a training programme that will focus not only on BTC-specific medical and research knowledge but will involve nurturing leadership skills and career development to achieve a sustainable impact on the continuation of the Action's activities beyond its timeframe. ***Industrial/biotech partners*** will have the opportunity to leverage preclinical discoveries and inform their pipelines for a more focussed and synergistic development plan. The concerted research activities enabled by this Action will increase knowledge on BTC and the development of novel therapeutic strategies that will enable ***policy makers*** to take evidence-based decisions.

Scientific impact:
**Short term**: Through its collaborative network, the Action will reduce redundancy, generate consensus/guidelines, promote efficient use of resources, and increase the overall productivity of European research groups. YRIs, researchers and clinicians will benefit from training schools, professional workshops, and mentoring programmes as well as from a knowledge-sharing plan that will break the fence of specific disciplines. Interactions between industrial and academic partners will have a bi-directional impact to optimise resources and promote a synergic therapeutic development plan. **Long term**: Precision-BTC-Network will provide a platform for the development of precision approaches in prevention, diagnosis, and treatment with discovery of ad-hoc prevention strategies, early diagnostic biomarkers, predictive biomarkers of response to therapies and the development of novel personalised therapeutic approached based on a solid scientific knowledge. The network will also be able to maximise the resources and implement coordinated research plans that will attract further fundings (i.e. applications to Horizon Europe or similar ambitious programmes).

Technological impact:
**Short term**: The Action will harmonise protocols for collection of clinically annotated BTC biospecimens and integrated clinical, radiological, and histological details which will constitute a coordinated European platform for methodologically sound biomarker development in a rare and heterogeneous disease. New algorithms will be developed for the application of artificial intelligence to integrate multi-omics data (e.g. for improving personalized diagnosis, selecting best treatments, predicting treatment responses, and beyond), which will have an impact on the research community beyond BTC. Novel technological tools (patients-derived models and bioengineered devices) will be developed for understanding the heterogeneity and complexity of BTC. **Long Term**: Development of innovative *in vivo/ex vivo* BTC models with specific genomic/genetic backgrounds, immune response deregulation, microenvironment contributors. Development of novel biomarkers to address potential aetiology-related diagnosis, therapeutic interventions, and palliative care; novel strategies for personalised medicine based on patient stratification and novel therapeutic compounds.

Socio-economic impact:
**Short term**: Precision-BTC-Network will raise public awareness about BTC, familiarise the lay public with symptoms and warning signals, increase awareness in GP practices for a quicker and more effective recognition of the disease. Educational material for patients with BTC will be developed covering treatment opportunities and access to molecular testing and personalised medicine throughout Europe. **Long Term**: The activities of this Action will have an impact on two main pillars: i) prevention and early detection, which will reduce the burden and healthcare costs, ii) more efficacious therapeutic strategies (including novel drug developments in collaboration with chemists), which will have an impact on the healthcare system by reducing the costs of hospitalisations related to preventable side effects from treatments and those related to disease progression from ineffective therapies. In addition, the impact of more efficacious drugs will have an impact on life expectancy and quality of life, with downstream effects on workforce and economic market.

## 3.2. MEASURES TO MAXIMISE IMPACT

### 3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

**Knowledge creation**. The Network will represent a diverse group within the field of BTC including epidemiologists, gastroenterologists, oncologists, surgeons, nurses, basic researchers, translational researchers, pharmaco-economists, computer scientists, bioengineers, patient representatives and communication technology experts. Exchange of information and communication across them will ensure a critical mass of knowledge and troubleshooting for the implementation of a development plan that is based on critical thinking and multidisciplinary input, with the patients' needs at the centre. YRIs will receive training and knowledge and will also be involved in establishing long-lasting contacts for future collaborations by participating in meetings, workshops, training schools and STSMs. This network will have access to outstanding research facilities and diverse patient groups and has extensive experience in leading research projects and clinical studies. Precision-BTC-Network will promote collaboration with industrial partners (pharmaceutical and biotechnology companies) to improve the commercial application and exploitation of the technological advances.

**Transfer of knowledge**. The Action will embrace stakeholders such as European patient associations and scientific/clinical societies at national and European level. Altogether, Precision-BTC-Network will ensure the development of the critical mass of researchers and stakeholders with experts from various domains to guarantee the transfer of knowledge and the achievements of its objectives. In addition, exchange of knowledge will be achieved through i) regular virtual WGs meetings (six-monthly) where novel collaborative proposals will be presented to involve members across the network and progress updates will be shared, ii) formal in-person occasions for interactions (i.e. annual meetings) and progress updates, iii) STSMs that will not only boost YRI training but also promote collaborative projects among international groups, iv) paired activities with international clinical and research societies for the study of cancer and of the liver, to expand the impact beyond network members and increase the Action visibility, v) meetings with pharmaceutical/biotechnologies companies to define minimum sets of criteria for moving preclinical discoveries along the early/late development phase, vi) discussions with policy makers providing them with updated guidance position statements generated by the Action.
The Action will also aim to support the exchange of knowledge and expertise through cross-border interdisciplinary research, training, and teaching.

**Career development**. The Action will strengthen partnerships between members from different fields of expertise and at different stages of their careers. Special emphasis will be given to support the career of young members by engaging in research studies undertaken by YRIs. They will also be provided with an intensive framework of cooperation, through focused workshops, STSMs, Virtual Mobility Grants and training schools, aiming to develop a group of YRIs with interest and skills in BTC. An active engagement of YRIs will be sought and promoted through assignment of key roles in WGs (i.e. each WG will be co-led by a senior and a YI). A mentor-mentee programme will be established where YRIs will have the possibility to be provided with guidance and support by international professionals. An advisory young investigator committee will be implemented to provide and maintain the Action's focus on YRIs and will participate to the leadership management to make sure that the involvement of YRIs is steered according to their needs.

### 3.2.2. PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

**Dissemination target audience**: The dissemination plan will target the multi-disciplinary members of the Precision-BTC-Network, academic and research communities, healthcare professionals, clinicians from different domains, patients, patient representatives, and patient advocates, the general public, public health organizations, pharmaceutical and biotechnological companies, and European regulatory agencies.

**Dissemination plan**: Precision-BTC-Network will invest in diversified technologies for the dissemination plans, including Action Website, Action Logo, Action Web presentation, conferences, workshops and training schools, publications, proceedings from meetings, promotional brochures, Action fact sheets, promotional posters, and network of experts mailing lists.
Website: A website will be created to clearly present the aims and objectives of the Action to the public. It will also provide an opportunity to announce achievements and progress, as well as to promote upcoming events. It will also detail the source and nature of the Action funding and will foster collaborative dialogue through an electronic discussion forum.
Social media: Precision-BTC-Network will activate a profile on different social media platforms (e.g. Twitter, Facebook, LinkedIn) that will be used to promote the visibility of the Action and interactive connection with the world within and outside the network. It will also be used to promote events and disseminate progress achieved through the collaborative nature of the Action.
Newsletter, linking and e-mailing: Action participants will use newsletters to update on progress and ongoing activities, to promote inclusiveness and to facilitate the continued adherence of interested stakeholders.
Scientific publications: Publications in peer-reviewed journals will be used to disseminate scientific advances. Acknowledgement of the COST Action will be ensured, and COST funds will be allocated to promote open access to increase dissemination of the results.
Conferences: Presentation at national and international congresses will be pursued and funds will be allocated to promote the participation of YRIs in conferences to present their data.
Media campaigns: National and/or international press agencies will be contacted, as appropriate, to increase dissemination of the Precision-BTC-Network messages and progress. Infographics and videos will be created to facilitate the communication of complex data.
European Commissions and EU agencies: achievements and results will be regularly communicated to these institutions to increase BTC awareness and improve the management of BTC patients in Europe.

**Exploitation plan**: Precision-BTC-Network aims at raising new opportunities in the field of biomarkers and therapeutic tools through the generation of new start-ups, academic spin-offs, and interaction with industry. The areas of collaboration with industry that will have the greatest potential for capitalisation will be:
i) *Expertise and Knowledge transfer*: Access to a diversified pool of experts in BTC will optimise the academically- and industry-led drug development pathway; ii) *Technology:* access to innovative tools will lead to better diagnosis and treatment of patients with BTC; iii) *Data*: the network will provide the foundation for sharing and pooling data during clinical development programmes; iv) *Alignment*, as Precision-BTC-Network is intended to serve as an opportunity to deliver a balanced global and unbiased perspective on BTC best practice; v) *Funding securing*: joint grant applications will be pursued using the results stemming from coordinated research; vi) *Intellectual property and patenting*: Expert advice on intellectual property protection, data protection and ownership, ethical protocols, collaboration agreements, patients information sheets and approvals will be available within the network. Indirectly, the Action will also contribute to advances that may lead to exploitable results in specific research projects funded through additional sources. In this case, protection of intellectual property for a given project will be in accordance with the policy and guidelines of each member institution and funding society. Non-disclosure agreements will be used on case-sensitive materials and confidentiality will be maintained during meetings. All stakeholders will adhere to the Responsible Research and Innovation principles.
Precision-BTC-Network will also exploit the insights gained from discussion, knowledge exchange and new collaborative work between the members to steer research projects, implement practice change studies, and educate other clinical investigators and researchers on the application of precision medicine in BTC.

# 4. IMPLEMENTATION

## 4.1. COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

### 4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

The Action proposes 6 WGs. Four of them will be involved in the development of a personalized management of patients with BTC, prevention, early diagnosis, treatment, and support, while two horizontal WGs will provide cross-sectional activities that are relevant to the goals of WG1 to WG4. Precision-BTC-Network Action will build on a multi-directional collaboration across all WGs which will be facilitated through periodical (six-monthly) individual WG meetings and annual general meetings for the planning of inter-groups initiatives.

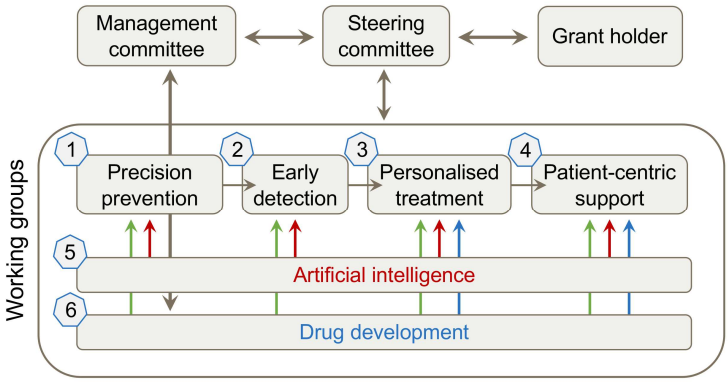



**Figure 2**. Working Groups Precision-BTC-network Action

In addition, members of the Action will be encouraged to participate in more than one WG to boost inter-group activities. New collaborations outside the Action will be explored, if deemed necessary.

**WG1. Identification of epidemiological heterogeneity in Europe to apply precision prevention**

The aim of this WG is to identify the epidemiological heterogeneity and natural course of BTC in Europe to define a strategy of precision prevention based on the prevalence of risks factors, molecular traits, and genomic features.

**Tasks & Activities**

- Creation of a digital interconnected platform for multiple data sharing.
- Delineating differences in the risk factors for each type of BTC.
- Exploring regional differences in incidence, mortality, and access to molecular classification/treatments across European countries.
- Establishing correct and consistent practice regarding the diagnosis, classification, and coding of BTC based on the new International Classification of Diseases 11th Revision (ICD-11 and ICD-O5).
- Exploring histo-morphology and molecular traits of populations at risk to personalize the definition of risk of cancer development.
- Exploring the genomic features of PSC-, cirrhosis- and biliary tract stone disease-associated BTC to identify a personalised tumour risk and management.
- Exploring preventive measures in at-risk populations (e.g., aspirin, statins, metformin).
- Identify age of onset of mutational profile from start of inflammatory stimulus for the development of a personalised prevention strategy.

**WG2. Personalised early detection of BTC**

The aim of this WG is to identify risk-factor specific minimally invasive biomarkers that can help in the personalised early detection of BTC in at-risk groups of patients (PSC, liver cirrhosis, biliary tract stone disease). The Action will have a unique platform for key prospective studies in populations at risk. Samples from patients with BTC from biobanks (tumour tissue, serum/plasma, bile, urine, stools) will be used to perform analyses of different types of biomarkers (proteins, metabolites, ctDNA, RNAs, microbiome), including the use of “omics” technologies, in large number of samples.

**Tasks & Activities**

- Development of guidelines on Standard Operating Procedures (SOPs) and Data Quality Management (DQM) to allow integrative data analysis.
- To create a catalogue of sample availability in biobanks and radiological registries of each type of BTC.
- Selection of candidate tissue-based, biofluid-based, imaging-based, or a combination thereof biomarkers for different types of BTC.
- Explore the ability of selected panels of biomarkers to diagnose BTC in cohorts of individuals at risk of developing BTC.
- Correlation of biomarkers with histological subtypes, genomic profile, epigenetic profile, imaging features (radiomics) and/or underlying diseases.

**WG3. Personalisation of treatment for patients with BTC**

The **aim** of this WG is to optimize therapeutic strategies of patients with BTC by expanding the opportunities for a precision-oncology approach, through the application of biomarker-driven strategies, development of novel approaches targeting the microenvironment and implementation of patient-centric individualization of drug choice.

**Tasks & Activities**

- To develop tissue and non-invasive biomarkers for predicting efficacy of immunotherapy.
- To define novel strategies of immunotherapy personalised towards the immune phenotype of BTC subsets.
- To identify the population of responders to platinum and Poly (ADP-ribose) polymerase (PARP) inhibitor therapies.
- To identify mechanisms of primary and secondary resistance and to develop combinatorial targeted therapies to overcome resistance.
- To define and personalise therapeutic opportunities for rare subsets of BTC, such as adenosquamous biliary cancers, intraductal papillary neoplasia of bile ducts and combined HCC/CCA.
- To promote clinical trial designs that include prospective testing of biomarkers for validation.
- To personalise peri-operative strategies in the management of BTC based on clinical and biological biomarkers.
- To facilitate the implementation of patient-derived organoid-based individualization of BTC treatment in clinical trials.

**WG4. Patient-centric support management**

The **aim** of this WG is to provide personalised coaching for the improvement of health-related quality of life (QoL) of patients with BTC. We will implement patients' centric palliative care interventions and develop BTC-dedicated educational material that contributes to their psychological well-being and enables them to make decisions as part of the multidisciplinary team that is built around the patient.

**Tasks & Activities**

- To conduct surveys of patients, caregivers, clinicians, and nurses to identify patients' specific needs. Participants in the surveys will be recruited at Action events with participation of all the stakeholders.
- To create educational material to cover the needs of patients with BTC; nutritional support, exercise, and management of symptoms and complications (sarcopenia, cachexia, etc).
- To reduce disparities in palliative therapy by providing access in different languages to educational material (information sheets, infographics, videos).
- To facilitate the access to support groups, in collaboration with patient associations and advanced practice nurses.

**WG5. Artificial intelligence**

The **aim** of this WG is to support WG1-4 to utilize the vast amount of data collected to assist in addressing personalized diagnosis, prognosis, and treatment of BTC patients.

**Tasks & Activities**

- Explore the potential of artificial intelligence to predict prognosis and molecular features from haematoxylin-eosin histology and other common stains in BTC.
- To determine the usefulness of radiomics as biomarkers for diagnosis and prognosis.
- To find correlation between histological biomarkers, clinical features, imaging features, patient's outcome, and prognosis.
- To develop algorithms to predict prognosis or the response to treatments in patients with BTC.

**WG6. Drug development using preclinical models**

The **aim** of this group is boosting a preclinical platform of personalised drug discovery by integrating the design and development of novel compounds with the testing of these compounds in appropriate models that take into consideration BTC heterogeneity and complexity.

**Tasks & Activities**

- To widen the horizon of personalised oncology by developing novel effective molecules towards specific subsets of BTC, matched to genomic, epigenetic, proteomic, metabolomic, and metagenomic features of the tumour.
- To individualise drug repurposing in preclinical patient-derived avatar models harbouring patients' specific co-occurring genomic alterations.
- To generate vectorised compounds that facilitate drug accumulation in biliary tract cells to increase the benefit/toxicity ratio of targeted drugs.
- To develop microenvironment-targeting compounds towards BTC tumours rich in stromal activation.

- To develop clinically relevant animal BTC models to support target discovery and target engagement in personalised medicine.
- To develop microfluidic devices to mimic human perfusion and drug delivery *in vivo* for drug discovery projects.

### 4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

| WG | Year | Deliverables |
|---|---|---|
| WG1 | Y1 | ✓ Establishing a pan-European registry for patients with all subtypes of BTC |
| | Y2-4 | ✓ Publications derived from data analyses from the pan-European registry database of BTC |
| | Y4 | ✓ Surveillance guidelines in patients at risk of developing BTC |
| WG2 | Y1 | ✓ Guidelines on SOPs and DQM for collection and storage of BTC biological sample |
| | Y2-4 | ✓ Scientific publications on the diagnostic performance of different types of biomarkers in BTC |
| | Y4 | ✓ Scientific publication on the association of based-image biomarkers and histomorphology in biliary cancers |
| | Y4 | ✓ Publication of a Consensus on MRI in BTC |
| WG3 | Y1 | ✓ Systematic review on the gaps of delivering precision oncology in biliary cancers |
| | Y2 | ✓ Publication of a retrospective analysis of the clinical outcome of biliary cancers, including GBC and AC |
| | Y3-4 | ✓ Publication of the optimization of biomarker development for patient stratification and development of novel strategies for personalised treatment in BTC |
| WG4 | Y1-2 | ✓ Publication derived from surveys to stakeholders about specific needs in personalized management of patients with BTC |
| | Y1,3 | ✓ Patient education sheets and videos in different languages with useful information for patients/caregivers (disease, treatments and their potential adverse events, etc) |
| | Y4 | ✓ Publication of oncology nursing care in BTC patients |
| WG5 | Y1-2 | ✓ Review on challenges of artificial intelligence to assess the reliability of models, provide clinical products and in holistic data integration |
| | Y3-4 | ✓ Scientific publication on the association of artificial intelligence based-image biomarkers, histomorphology and genomic data in BTC |
| WG6 | Y1 | ✓ Review on challenges for the development of novel therapeutic strategies in BTC |
| | Y2-4 | ✓ Scientific publication on preclinical models developed for the application of drug discovery and drug validation and developing novel compounds to be taken into clinical experimentation |
| | Y3 | ✓ Proceedings from an academia-pharma interaction |
| All WGs | Y1-4 | ✓ Material and reports of training schools and bi-annual meeting |
| | Y2-4 | ✓ Publication of results of mentoring program and recordings of mentorship lectures available online |

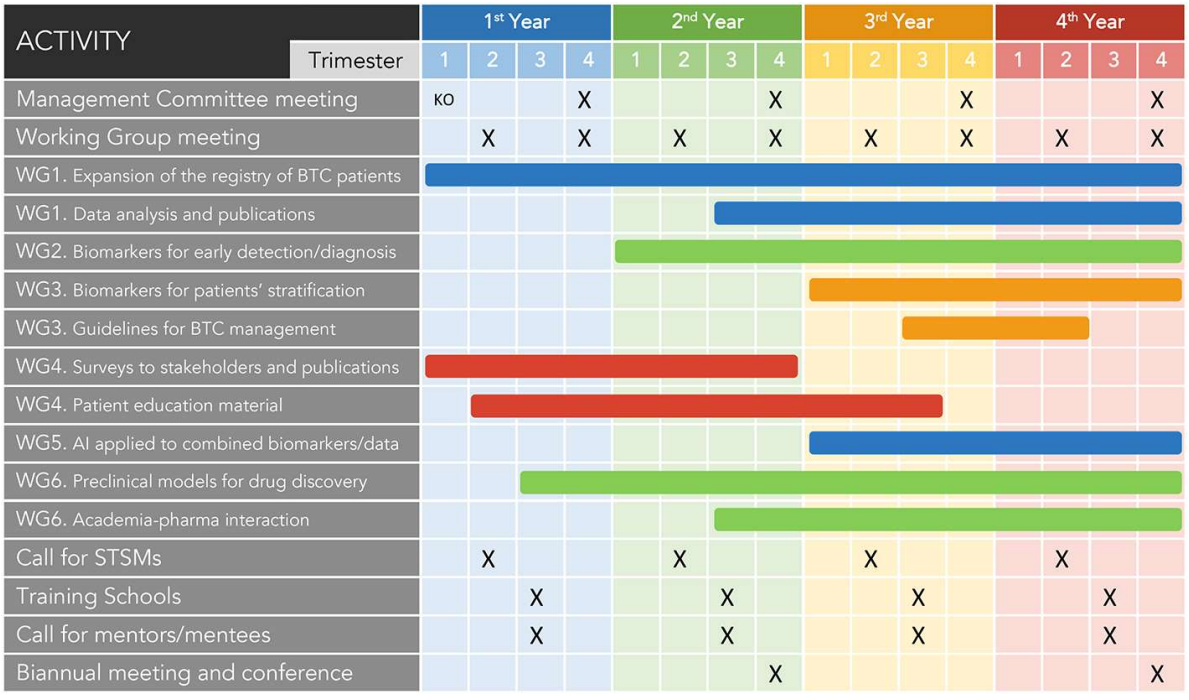
### 4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

The risks are considered small because some collaborations between clinicians, basic researchers, academia, and patient associations are already established, although it will be necessary to expand the network to include additional stakeholders that facilitate the output and promote collaboration with Pharma to accelerate translation from discovery to clinic. Specific contingency plans for potential risks are presented below:

| Risks | Contingency plans |
|---|---|
| Reduced number of members in specific areas/WGs | WG Leaders will contact researchers with key expertise, and visibility will be given to the network to attract all those who may be interested in participating, especially ensuring that gender, geographic coverage, YRIs and ITCs objectives are achieved |

| | |
|---|---|
| Poor stakeholder involvement | WG Leaders will be selected among the most active members of the network and a junior group will be created to favour their participation and the mentoring of future leaders |
| Complexity of executing projects with many participants | Participants will be organized into smaller groups dedicated to specific projects to make the overall network more manageable, but the activities will be disseminated so that those who are interested will be able to participate |
| Difficulty to achieve the objectives on time | The MC will maintain a continuous dialogue with WG leaders and will monitor work progress and the completion of tasks and milestones, distributing workloads if necessary |
| Difficulty to achieve some objectives that require funding | Participants will have funding available that will allow analyses on selected patient samples and it is planned to continue to call for national and European projects to expand the analyses. In addition, contacts have been made with companies interested in funding part of the transcriptome/RNA sequencing, and whole-exome sequencing analyses |
| Lack of cooperation between academia and companies | Different activities, such as conferences, workshops, meetings and STSMs will be organized to facilitate networking and reduce the problem |
| WG Leaders cannot complete their mandate | We will nominate WG co-Leaders "elect" (senior and junior) who will work with the Leaders and will replace them in case they have other obligations during the duration of the project |

### 4.1.4. GANTT DIAGRAM




AI, artificial intelligence; KO, Kick-off meeting.

## REFERENCES


1. Valle JW, et al. Ann Oncol. 2016;27(suppl 5):v28-v37.
2. Mayr C, et al. Expert Opin Investig Drugs. 2022;31(2):221-233.
3. Banales JM, et al. Nat Rev Gastroenterol Hepatol. 2020;17(9):557-588.
4. Jackson SS, et al. Hepatology. 2022;75(2):309-321.
5. Barner-Rasmussen N, et al. United European Gastroenterol J. 2021;9(10):1128-1135.
6. Vithayathil M, Khan SA. J Hepatol. 2022;S0168-8278(22)02988-9.
7. Dušek L, et al. Cas Lek Cesk. 2019 Spring;158(2):52-56.
8. de Jong EJM, et al. Eur J Surg Oncol. 2021;47(7):1742-1749.
9. Javle M, et al. Oncologist. 2022;oyac150.
10. Lamarca A, et al. ESMO Open. 2022;7(1):100378.
11. Karlsen TH, et al. J Hepatol. 2017;67(6):1298-1323.
12. Bailey A, Shah SA. Hepatobiliary. 2019;120(5):847-850.
13. Muñoz-Martínez S et al. Hepatoma Res. 2022;8:30.
14. Zaccari P, et al. United European Gastroenterol J. (in press)
15. Marin JJG, et al. Br J Cancer. 2020;123(7):1047-1059.
16. Scott AJ, et al. J Clin Oncol. 2022:JCO2102576.
17. Izquierdo-Sanchez L, et al. J Hepatol. 2022;76(5):1109-1121.
18. Zhu J, et al. Am Surg. 2022:31348221074238.
19. Hwang JS, et al. J Gastroenterol Hepatol. 2021;36(8):2315-2323.
20. Tominaga H, et al. Cancers (Basel). 2021;13(16):4220.
21. Mocan LP, et al. World J Gastroenterol. 2022;28(15):1508-1525.
22. Haghbin H, Aziz M. World J Clin Oncol. 2022;13(2):125-134.