European Cooperation
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- COST -

Secretariat

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MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM1204: An integrated European platform for pancreas cancer research: from basic science to clinical and public health interventions for a rare disease

Delegations will find attached the Memorandum of Understanding for COST Action as approved by the COST Committee of Senior Officials (CSO) at its 185th meeting on 6 June 2012.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as
COST Action BM1204
AN INTEGRATED EUROPEAN PLATFORM FOR PANCREAS CANCER RESEARCH: FROM BASIC SCIENCE TO CLINICAL AND PUBLIC HEALTH INTERVENTIONS FOR A RARE DISEASE

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4154/11 "Rules and Procedures for Implementing COST Actions", or in any new document amending or replacing it, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to capitalise on emerging scientific and technological developments in the field of Pancreatic Ductal Adenocarcinoma (PDAC) to: (i) Identify new modifiable risk factors, and other environmental, genetic and epigenetic risk factors; (ii) Dissect the molecular complexity through *omics* technology and identify clinically relevant disease subphenotypes; (iii) Identify reliable predictive biomarkers of early-stage as well as novel molecular targets for tailored therapies; (v) Identify reliable genetic, epigenetic and tumour-related factors associated with the prognosis; and (vi) Assess the potential implementation of the findings into public health and clinical settings.

3. 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 56 million in 2012 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of Chapter V of the document referred to in Point 1 above.

A. ABSTRACT AND KEYWORDS

The application of the rapidly evolving *omics* technologies to cancer research is a reality and it has demonstrated that large-scale international collaboration is essential to decipher relevant information in the context of massive-scale interrogations. This is even more important for rare and dreadful diseases like pancreas cancer (PDAC). We propose the creation of a unique European platform to facilitate the collaboration of a broad range of European and international PDAC multidisciplinary research groups to integrate knowledge and experience in a multidisciplinary way "from cell to society"; promote the application of uniform study tools and protocols; foster their optimal use by Early-Stage Researchers; enhance the mobility and training of researchers; and permeate the society with the results originated by the Action. This Action will develop novel interdisciplinary tools that will improve our understanding of PDAC and its control by answering questions related to the aetiology, early detection and evidence-based and personalised treatment to enhance primary, secondary, and tertiary prevention, respectively, as well as on health management. The Action brings together a group of young scholars across a range of disciplines in collaboration with more experienced researchers and will allow Europe to actively participate in the international scenario of pancreas cancer research.

Keywords: pancreas cancer, rare disease, omics data integration, tool harmonization, Early-Stage Researcher training and mobility, public health and clinical interventions

B. BACKGROUND

B.1 General background

Pancreatic ductal adenocarcinoma (PDAC) poses important challenges to affected individuals/families, to society, and to researchers. PDAC is a rare and fatal disease. The diagnosis of PDAC is not straightforward, highly insufficient and there are no reliable biomarkers of disease. For most cases, diagnosis is made very late and it is equivalent to death within 6 months. Surgery, the only effective therapy, is possible in only 20% of patients and there are also few markers that predict disease outcome. Its incidence rate in Europe is 7.8 per 10^5 person-years; 10% of cases cluster in families, 20% of which are associated with hereditary cancer syndromes caused by known genes. The remaining familial cases have an unknown origin (familial pancreas cancer, FPC).

The identification of individuals at risk remains a major goal. The lifestyle factors associated with PDAC (smoking, diabetes, increased body mass index) and low penetrance genetic variants associated with sporadic PDAC are common in the population and confer a modest increased risk, being of limited use to identify high-risk subjects for screening. In FPC, relatives have an increased risk of PDAC, similar to that for familial breast or colorectal cancer and the risk increases with the number of affected family members. This suggests that healthy subjects with a family history of PDAC could benefit from screening (genetic and imaging). The genes responsible for FPC remain unidentified. This lack of knowledge is due to a small number of PDAC cases in these families and for study and to the considerable genetic heterogeneity among families. These difficulties make the classical genetic analysis (linkage analysis) unfeasible and raise the need of additional strategies. A whole-exome sequencing *omics* approach recently identified in *PALB2* and *ATM* mutations in affected families. This discovery has led to the use of a targeted therapy that might be successful in a subset of patients.

The development of *omics* technologies at reduced cost provides a new framework for the study of the genetic determinants of PDAC. The *omics* revolution has great potential for data integration and translation of basic research to applications in healthcare, requiring cutting-edge experience in technology and bioinformatics with close collaboration among clinicians, epidemiologists, biologists, patient organisations and public health experts in a multidisciplinary way. These applications require powerful novel computational methods to handle massive amounts of data as well as mathematical modelling.

The low incidence and prevalence of PDAC and the difficulties inherent in recruiting pancreas cancer cases with appropriate biological material in a single study render the establishment of large international consortia essential to lead to the identification of new genes and other risk factors for PDAC, both sporadic and familial. Furthermore, studying PDAC can serve as a raw model for rare diseases in general, contributing to the International Rare Disease Research Consortium (IRDiRC) goals. This is of high importance not only for clinical practice, but also for public health, since almost all common complex diseases are in the end a sum of rare subtypes.

The Action proposes to unite all groups across Europe who are interested in PDAC research and provide an innovative and unique platform for collaborating and sharing information, ideas and experience. Several large PDAC studies are underway in the United States and some have formed consortia; a major limitation of these is that the collaborations were established after the studies were initiated and the individual study designs, protocols and data collected are heterogeneous. This pan-European network will initiate and support integrated, interdisciplinary collaborative projects that address the many missing pieces in the PDAC puzzle, thereby enabling research under a common conceptual and methodological framework.

The Action will develop a novel and timely research platform in PDAC integrating several domains – biological, clinical, public health, regulatory and commercial. It will seek to understand what causes PDAC, what biological processes are involved, how this cancer can be prevented, how it can be detected earlier using reliable biomarkers, how it can best be treated, how we can identify who will benefit from targeted treatment, and how to translate these findings effectively and efficiently in a timely manner into the healthcare system for the benefit of PDAC patients. Therefore, this COST Action aims to consolidate and extend scientific research on PDAC over recent years, develop methodological tools to integrate emerging *omics* data and apply the findings to clinical practice and Public Health in a transnational and interdisciplinary collaborative effort by using the highly innovative Learning-Adapting-Leveling (LAL) model. This COST Action will build on existing collaboration among participants and will be of high European added value by: (i) integrating and translating emerging evidence-based information specifically adapted to the European situation; (ii) supporting an interdisciplinary approach through the incorporation of bioscientists to the network; (iii) offering Early-Stage Researchers a better opportunity to develop academic networks with more established researchers.

B.2 Current state of knowledge

The Action will bring together theoretical and methodological approaches and tools used within various disciplines to study PDAC. Such an undertaking is ambitious since the various lines of enquiry have their own historical trajectories. Nevertheless, the Action, aims to bring these trajectories together to examine them as a whole within a broader geographical context that extends across and beyond Europe.

Presently, there are few studies of this type in Europe, with the exception of the recently initiated collaborative PanGen-EU Study that is currently running in 30 centres from seven European countries and that has already included 1600 cases and 800 controls. This study was built upon the collaborations established within the Framework Programme 6 Study MOLDIAG-PACA. While it primarily fits a case-control design, the case series is converted into a cohort that is followed-up to allow clinical studies to be carried out. Centrally trained study coordinators recruit subjects, collect epidemiological data and biological samples that are stored in a purpose-built centralised database. The biomarker determinations and the coordination of data storage and analysis, and the study in general, will take advantage of the recommendations formulated by this Action. All researchers and groups participating in the PanGen-EU Study will be involved in this Action. Furthermore, a current Framework Programme 7 (FP7) study (EPC-TM-Net) is providing important results on the role of the microenvironment in pancreas carcinogenesis.

While these projects are of great value in identifying key factors involved in the development and progression of PDAC, they do not explore the potential of *omics* data integration in dissecting the biological complexity of PDAC nor of the identification, validation, replication, and applicability of biomarkers to clinic practice and Public Health interventions. Furthermore, the major health policy and societal hurdles about this life-threatening rare disease are not addressed by the previously funded FP projects. The Action will explore these challenges as they arise in different settings in the healthcare system on a pan-European level.

B.3 Reasons for the Action

The Action will enable us to make a leap forward in our understanding of pancreas cancer. The use of emerging high-throughput techniques and analytical methods on a scale not seen to date will be ground-breaking and generate novel findings that will impact on research worldwide.

The reasons for the Actions are indicated below.

Immediate Scientific/Technological benefits

*T*he establishment of appropriate standards and quality controls in all aspects of research, from clinical specimen collection to *omics* analysis and data processing will greatly increase the effectiveness and comparability of different studies and individual research centres. Optimized protocols for sample storage, processing, and data integration will be disseminated to the broader scientific community. The establishment of a cooperative research network will increase the knowledge on PDAC.

Future scientific/technological benefits.

The foundations for future biomarker validation and translational studies will be set up, elucidating the specific statistical, clinical and methodological tools required, and establishing unified clinical biobanks. The basis for the establishment of resources and infrastructures dedicated to pancreas research in Europe will be set up. This is urgently needed to enhance the visibility and excellence of European research in this field. The integration of new *omics* approaches will provide insights in this cancer, which will subsequently lead to the development of innovative therapeutic approaches and targets. Enhancement of the activities of the private sector will be achieved through the dissemination of the optimized standardized protocols and guidelines and the application of the highly innovative LAL model.The fostering of collaborations achieved during the Action will give rise to competitive proposals for research funding.

Future societal/economic benefits

The foundations for the translation of individualized *omics* data into the clinical arena will be established with clear societal and economic benefits: diagnostic, predictive and prognostic markers for PDAC may replace current invasive and costly approaches. Young researchers will be trained on the use of state-of-the-art technologies applied to PDAC which are widely used in the private sector (biotech companies, pharmaceutical and medical industry). Through the dissemination activities of *EUPlat4PanCRes*, public awareness on the potential of novel markers and findings in disease prevention, diagnosis and prognosis will increase.

B.4 Complementarity with other research programmes

To our knowledge, no other COST Actions of this type exists. COST funding for this proposal would complement existing funding to carry out and share cutting-edge research. The on-going nature of the PanGen-EU study ensures the feasibility of this project. The complementary European FP research projects referred to in section B.2 are focused on more specific research questions related to PDAC. In addition, the involvement of the Public Health Genomics European Network (PHGEN) will guarantee the timely and effective translation of the findings into the European health care systems. One partner of this COST Action, the IPHG has developed a LAL model to facilitate the evaluation of new technologies within healthcare systems though the involvement of all relevant stakeholders (e.g. industry, policy makers, patients, clinicians, third-party payers). This will provide a great opportunity to work towards translating emerging evidence and knowledge related to PDAC into healthcare systems. EPIRARE will link the Action with the other European networks focusing on rare diseases while collaboration will be established with international initiatives on the same topic such as the International Pancreas Cancer Consortium (PanC4). It is a long-term goal of the Action to form the basis of one or more Framework Programme applications in the future.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The main objective of the Action is to capitalise on emerging scientific and technological developments to: (i) Identify new modifiable risk factors, and other environmental, genetic and epigenetic risk factors for PDAC and pave the road for the development of risk prediction algorithms; (ii) Dissect the molecular complexity of PDAC through *omics* technology and identify clinically relevant disease subphenotypes; (iii) Identify reliable biomarkers of early-stage PDAC; (iv) Identify reliable predictive biomarkers in PDAC as well as novel molecular targets for tailored therapies; (v) Identify reliable genetic, epigenetic and tumour-related factors associated with the prognosis for PDAC patients; and (vi) Assess the potential of the findings to be translated into public health and clinical settings, emphasizing their impact in high-risk groups.

These issues require urgent attention in order to reduce the burden of this deadly disease. Through this integrative strategy, the Action will strengthen Europe's capacity to and manage, and even exploit, the intended and unintended impacts of these processes.

C.2 Objectives

The objectives of this Action are:

- Capacity building in order to build a strong network of European Centres to develop unified biobanks that store individual epidemiological and clinical information and therefore represent fundamental resources for future PDAC research in Europe;
- Evaluate the applicability of selected *omics* technologies to identify chemical, epigenetic, genetic, and molecular markers to be utilized in the public health and clinical setting. This will be achieved by disseminating the expertise within the respective centres and designing appropriate feasibility and reproducibility studies;
- Optimize methodologies (epidemiological, statistical, *omics*-technology, and bioinformatic) to integrate and interpret data. This is a very important and innovative research area since appropriate data integration greatly facilitates the discovery of novel biomarkers and therapeutic targets;
- Unite and train young researchers from different disciplinary backgrounds in distinct European countries. While they are a main target of the Action, experienced and established researchers will also be drawn upon to deepen and broaden the expertise of the network;
- Disseminate the information gathered to the scientific community and increase public awareness about PDAC research needs and impacts. In quantitative terms, it is expected that at least 30% of the working papers will be co-authored across countries, while each year, 12 STSM are envisaged to take place across the network. At the Action's workshops, young researchers should constitute 60% or more of participants. The Action will organise specific sessions relating to the 6 axes described below (section D) relating to changing the scenario of PDAC research, the translational potential of the results, and their future impact on society.

C.3 How networking within the Action will yield the objectives?

The objectives of *EUPlat4PanCRes* will be achieved by bringing together scientists working on relevant fields in a manner that will allow fruitful interactions, the dissemination of expertise and the fostering of collaborations. Specifically, this Action will:

- Extend the network across Europe and internationally;
- Create a web-based directory of international groups involved in PDAC research and open access to core standardized documents;
- Organise a series of virtual and face-to-face meetings for Early-Stage Researchers and experienced researches across Europe;
- Organise biannual short-term international stays for Early-Stage Researchers;
- Disseminate the results to key agencies within Europe and the European Commission through workshops involving public, scientific and regulatory stakeholders. To this end, special efforts will be made to employ infrastructure developed in European Framework Programs (e.g. available e-learning platforms such as the European Multimedia Bioinformatics Educational Resource-EMBER).

C.4 Potential impact of the Action

The Action will have an impact at the:

- Scientific level by capacity-building, making available standardized protocols, optimizes data integration guidelines including diagnostic, predictive and prognostic markers. Databases generated through this effort will be reference points for researchers and clinicians and will form the basis for the development of personalized medicine approaches.

- Technological level, the basis for core resources building for PDAC research in Europe will be established, including European wide clinical reference centres, facilities for biological specimen processing, and centres for *omics* determination, and bioinformatics analysis. Therefore, extensive interactions with the private sector will be set-up for the exploitation of the findings by using the LAL model as a bridging pipeline from basic sciences (TT) to implementation in the health care system.
- Clinical level, the Action will initiate the discovery and validation of novel therapeutic targets and diagnostic and prognostic biomarkers/biomarker profiles. Clinical research will cover evidence-based therapy towards individualized treatment. The Action will also establish the framework for translation of research into clinical practice and for guidelines for patient management.
- Public Health level, the Action will benefit different European countries and the European Commission agencies associated with translational tasks including foresight, ethical and economic aspects, public engagement and health literacy.
- Society**,** *EUPlat4PanCRes* will contribute to control PDAC and to decrease the disease burden of PDAC. High-risk family members may especially benefit from these. Young researchers will increase their competitiveness in seeking employment in the medical and public health field as well as pharmaceutical industries. Furthermore, the Action will increase awareness on an understudied dreadful disease.
- European level, *EUPlat4PanCRes* can be seen as a raw model for all rare diseases in Europe and beyond, since it will accelerate and increase the likelihood of successful market introduction of PDAC specific health innovations. While challenging existing European frameworks for assessing effectiveness of these healthcare interventions, it will provide solutions meeting the Europe 2020 goals of growth, innovation and social inclusion, as well as contributing to the Innovation Union and Horizon 2020 goals. Thus, *EUPlat4PanCRes* is of high European added value, since the project results are expected to: (i) Strengthening European economy through support for a challenged area of European innovation; (ii) Providing competitive advantage for European industry and research; (iii) Improving health for Europeans and globally, with consequent positive effects on health systems; (iv) Sustaining EU credibility with regard to commitments made across a range of European policies, including those on health, economic growth, social inclusion and development, (v) Promoting European goals and values in health.

C.5 Target groups/end users

In light of the above-mentioned benefits of this Action, the likely end-users of *EUPlat4PanCRes* include:

- Basic scientists working in the PDAC field from different disciplines;
- Physicians and nurses involved in the management of patients with PDAC and in the biological sample collection for research purposes;
- The private sector which, in collaboration with basic scientists, will be involved in the development and commercialization of the novel diagnostic, predictive and prognostic tests;
- Patients with PDAC and their families;
- Policy makers and regulators;
- Students at the universities participating in, and affiliated members of, the network. In addition, the Action will disseminate its results to the citizen-based organisations with a substantive interest in the impact of the new biosciences.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The scientific innovation of this Action lies in its comprehensive approach, using multiple high-throughput state-of-the-art *omics* technologies and the integration of the data generated using cutting-edge analytical methods. This approach will allow to fully exploring their potential to understand the mechanisms involved in the development and progression of PDAC. The scientific focus of *EUPlat4PanCRes* is organized around the following:

- Harmonization of research tools - establishment of standardized operating procedures for databasing of epidemiological, clinical, follow-up and *omics* data and for acquiring, processing and storing biological samples (blood, saliva, urine, tissue, toenails). This task tackles two of the main problems of current pancreas research: the difficulties in obtaining fresh tumoral tissue from patients and the lack of comparability of individual research studies due to differential use or misuse of clinical terminology, different biological specimen processing and storage procedures, and inappropriate study design (including insufficient statistical power and sub-optimal control selection);
- Establishment of the framework for building and assessing risk prediction models for PDAC. The aim of this axis is to provide the scientific community, Public Health experts and policy makers with the conceptual basis of such models according to published evidence. PDAC is a complex disease and interactions are likely to exist between risk factors; risk prediction models need to account for this complexity;
- Definition of quality controls and optimized protocols for the various *omics* methodologies in use for germline and tumoral DNA, RNA, as well as protein research. This task involves the consideration of new, innovative approaches. Pancreatic tissue poses a challenge due to the high levels of proteases and the associated desmoplastic reaction. It also tackles major difficulties that current researchers encounter in evaluating and reproducing the results from individual *omics* laboratories. These difficulties partially stem from the lack of appropriate quality controls and lack of knowledge of the technical characteristics (accuracy, resolution, reproducibility, linearity etc.) of each *omics* technology. Another contributing factor is the presence of a plethora of technical protocols for sample preparation and bioinformatic algorithms to deal with the raw data generated. While the use of different protocols and algorithms is a reality, the optimization of a single protocol or algorithm for each specific type of experiment and adherence to common protocols across different laboratories are essential to any collaborative work. The establishment of guidelines to be homogeneously applied across the participating teams will increase the efficacy of the interpretation of results. The vast amount of data acquired by the contemporary *omics* methods require databases and mining tools that will allow comparisons of different samples, generation of reference profiles as well as both statistical and graphical information about the samples under examination. Furthermore, the integration of *omics* data within and between studies is a must to tackle the complexity of PDAC;

- Translation of findings into clinical practice. This axis includes the critical examination of the "novelty" of biomarkers for pancreas cancer management. Registering all candidate biomarkers for (early) diagnosis, prognosis, and prediction of treatment response is essential in order to prioritize them for validation and replication in independent studies and populations. Such a Registry of Markers for PDAC needs to record measures of the quality of evidence for each biomarker, including study design, sample size, technology, statistical tests, independent replication, etc. Having this information available at the European level will place the clinical routine in a real setting while envisioning a positive scenario for the patients suffering of this cancer and their families;
- Development of therapeutic approaches towards individualised treatment - The new approaches to clinical trial design including personalized therapies require collaboration of multiple institutions and scientists of different disciplines in order to harmonize strategies, combine results, integrate knowledge and facilitate progress. Several groups involved in this Action plan use molecular-guided therapies. The coordination of their work should contribute to accelerate discovery, validation, and implantation of novel therapies in the clinical setting;
- Development of European PDAC-best practice guidelines for translating genome-based knowledge into evidence-based health interventions by using the LASL model. A large gap exists between *omics* research and its translation not only into clinical and technological applications, but also into the healthcare system, this being the task of public health, requiring new models combining Technology Transfer and Health Technology Assessment. The current shift towards a systemic understanding of disease aetiology (“systems thinking”) and personalised medicine is a major challenge. PDAC can serve as a model for rare diseases as well as for ICT-driven personalised medicine. Systems biomedicine triggered by *omics* technologies will become the leading healthcare paradigm in the following decades for predictive, personalised, pre-emptive and participatory medicine. It will help to reshape current research, policy-making and healthcare practices (“from cell to society”). Since this new paradigm is largely incompatible with current practice of the various stakeholders, there is a pressing need to actively involve these stakeholders from the beginning in the Action. This task will be carried out in close collaboration with the two European flagship projects PHGEN (Public Health Genomics European Network) and ITFoM (IT Future of Medicine).

Furthermore, the collaboration with European Networks of Rare Diseases (EPIRARE, and EUROPLAN) represents a synergistic platform on which to apply the Action results through both dissemination (i.e. brochures, website links, joint activities) and training activities (courses, summer schools).

EUPlat4PanCRes will achieve its objectives by bringing together scientists with an in-depth knowledge on the various aforementioned aspects of PDAC, *omics* technology, and integrative statistics and bioinformatics analysis. The Action is characterized by a very strong multidisciplinary character. The "know-how" and the necessary infrastructure, including a wide range of state-of-the-art of *omics* technologies, are available through the participating investigators. Training and mobilization of early-stage investigators and dissemination of the expertise and individual results and input from various partners will be coordinated and carried out through scientific meetings and STSM with a clear focus on the objectives outlined above.

D.2 Scientific work plan methods and means

In order to reach optimal efficiency in achieving the objectives the following Working Groups (WG) are foreseen:

- WG1 – Harmonization of research tools;
- WG2 – Integration of *omics* data;
- WG3 – Translational research;
- WG4 – PDAC patient management;

The workplan involves a feedback process in which the WGs individually address problems and bring them back to the plenum of groups. These WGs will be strongly linked to each other. Each of them has distinct tasks which define the main type of expertise required:

- Epidemiologists, clinical researchers, and basic scientists in WG1;
- Basic scientists, bioinformatics, and statisticians in WG2;

- Clinical researchers, basic scientists, statisticians, and epidemiologists in WG3
- Clinical researchers, clinical epidemiologists, policy makers, HTA agencies, industry, SMEs, patient organisations, Public Health and rare disease experts in WP4.

It should be emphasized however, that completion of the tasks of each group can only be achieved through continuous information exchange between the groups. The specific objectives and workplan for each of the WGs are:

- WG1 – Research tool harmonisation will address and reach a consensus on the following issues: (i) Definition of PDAC and establishment of widely accepted pertinent terminology (pathological staging system, pathological subtypes, definition of preneoplastic lesions, genetic profiling, definition of high risk patients etc.); sporadic, hereditary and familial pancreas cancer will be considered; (ii) These data will be contrasted and compared across all groups and countries, and across settings and contexts. This comparison will identify commonalities and differences and explore key variables that cut across different cases. These variables will be built into the tools established; (iii) Development of protocols for patient enrolment as well as for monitoring; (iv) Standardization of biological sample collection, processing and storage protocols as well as of epidemiological and clinical questionnaires. This also includes an assessment of the ability of participating centres to follow uniform protocols for sample collection and databasing; and (v) Establishment of criteria to assess the quality of existing body fluid and tissue banks for pancreas cancer research to enhance the distribution of biological material from patients with PDAC within Europe.
- WG2 – Integration of omics data will consider the following aspects: (i) Optimization and standardization of methods for the omics analysis of pancreas tumoral and normal tissue samples; (ii) Establishment of standardized approaches for *omics* data deposit. To this end, the Web-Based Platform for Mining Pancreatic Expression Datasets will be used as a model and its potential extension to other *omics* data will be assessed; and (iii) Identifying and documenting the available algorithms for *omics* data integration. Issues to be considered include: the data high dimensionality - small sample size problem, the inherently noisy nature of the data, the stability and reproducibility of the models, the incorporation of domain knowledge into the knowledge discovery process using innovative statistical and bioinformatics approaches.

- WG3 – Translational research will address the following questions and tasks: (i) Identification of the most challenging and urgent clinical research questions (early diagnosis versus prognosis versus drug efficacy etc.); (ii) Design a registry of candidate markers for pancreas cancer and definition of the special research needs in each case; (iii) Review of current biomarker research in PDAC (white paper) and assessment of the state of current biomarker research (discovery phase, versus phases of confirmation or validation of already discovered biomarkers); (iv) Definition of optimal controls for each disease subtype so as to increase the reliability of current and future biomarker discovery, confirmation or validation studies; and (v) Definition of sample size standards for biomarker discovery, confirmation and validation studies. This is an area of special interest since inappropriate use or even complete statistical negligence has resulted in the publication of several insignificant or even misleading results in the past.
- WG4 – PDAC patient management will approach the following challenges: (i) Identification of European centres focused on individualised medicine approaches for pancreatic cancer treatment; (ii) Training workshops on personalised and targeted therapy strategies for young physicians and basic scientists. (iii) Establishing the framework for the development of evidence-based PDAC-best practice guidelines (HTA) and its translation into the healthcare systems in Europe by involving all relevant stakeholders (HIA); and (iv) Orchestrate the Action activities with European networks of rare diseases by adopting their standards in impacting society.

The objectives of the Action will be reached through network workshops and activities. Apart from the interdisciplinary Working Group meetings, the Action will arrange targeted expert meetings with scientists, health managers, and stakeholders, focussed on the different axes, to ensure on-going engagement with their concerns. Apart from online meetings, the Management Committee will meet twice per year to develop integrative papers and reports, prepared for different audiences. Relevant lecturers and guests will be invited to these meetings, the aim being to bring in knowledge and thus strategically strengthen the competence of the Action.

E. ORGANISATION

E.1 Coordination and organisation

The Action will make efforts to continuously increase knowledge and communicate research results.

Dissemination methods will be 'tuned' to the specific target audiences through:

- An Action website built and dedicated for communication and promotion of information on on-going research and other activities. This task will be assigned to a partner (web-site coordinator). The website will have a password-protected intranet for exchange of information and unpublished data between partners and an open section accessible to the general public. The website will also contain information on the *EUPlat4PanCRes* activities (meetings, workshops, etc.), proceedings of meetings, links to publications of participants, links to related institutions and organisations, job announcements as well as material and presentations from the didactic activities;
- Policy briefs to disseminate the Action's activities and results beyond the targeted community (public media, policy-makers, and other stakeholders, target groups such as those with familial and hereditary PDAC);
- Press releases**,** in connection to events, and local advertisements when useful;
- A brochure describing the Action objectives and planned activities to be distributed to scientists, industry representatives, policy and society;
- Panels in international conferences. At a later stage, the findings generated will be disseminated to the scientific community through:
- Scientific publications in specialized and peer-reviewed journals. To increase the visibility of the Action, the proceedings of WG-meetings will be published as special issues in international

- Stakeholder Meetings will be organised to promote the timely translation of the results of the Action into policies on national, European and international level. The Action will be actively involved in policy forums such as European Health Forum Gastein (EHFG). The Action's results will be communicated to the next generation of PDAC scientists, especially those from developing regions through Short-Term Scientific Missions, to foster exchange of ideas and technology transfer. *EUPlat4PanCRes* members will disseminate their results in Teaching Activities (lectures, seminars, and summer schools) at their home universities and institutes.

MC/WG meetings will take place twice a year and will encourage participation of all members. To increase the visibility of *EUPlat4PanCRes*, they will be organized as satellites to major scientific conferences. The inclusion of international experts in the MG/WG meetings will guarantee that state-of-the-art of *omics* technologies as well as innovative, integrative analytical methods are mastered by Early-Stage Researchers, who will as a result be at the cutting-edge of their respective fields. This will be done with senior experienced researchers, with a focus on building bridges between established and novel methods and technologies, and integrating knowledge from diverse fields. Thus, the Action will ensure that the vast experience all groups and countries bring to the network is shared in a multidisciplinary way and passed on to early-stage researchers, who will be encouraged to rotate the MC/WG meetings to potentiate their training on research management and to take the lead on individual projects.

E.2 Working Groups

Each Working Group (WG) will be comprised of experts and Early-Stage Researchers from different disciplines. WG and meetings will be inclusive and will foster active participation. The integration between WG will be facilitated by cross-cutting themes (i.e. globalisation and innovation). This will encourage integration across the WGs and will ensure clear expectations on network members from the start. Participation in the modelling, policy and dissemination plan will ensure collaboration beyond individual WG responsibilities.

The WG will act as think-tanks and will provide input for workshops and publications. All scientists participating in the Action will be invited to join one or more WG. The WG coordinators will be appointed by the MC during the kick-off meeting. The main responsibilities of the WG-coordinators include: (i) Ensure frequent interaction with the other MG members and the members of the other WG; (ii) Coordinate the activities within each WG so as to meet the objectives of the Action; (iii) Actively participate in the organization of scientific activities of the WG; and (iv) Report on the progress of the WG to the Action Chair and the MC.

E.3 Liaison and interaction with other research programmes

Most participants are already successfully collaborating. Additional groups from across Europe have been incorporated. Liaison with other programmes/organisations will include: (i) Interaction with other European programmes such as PHGEN and EPIRARE. This will guarantee a timely and effective translation of the findings into the health care systems; (ii) Improving contact with other researchers (Pancreatic Cancer Case-Control Consortium, EPC, and National Pancreatic Research Groups). These workshops will be open to all participants; (iii) Promoting training and interdisciplinary harmonization, collaborating with European Organizations and Professional Societies; (iv) Approaching pharmaceutical and biotechnological companies to delineate programmes of common interest; (v) Recruit potential additional members of the Action.

E.4 Gender balance and involvement of early-stage researchers

This Action will respect an appropriate gender and will foster the involvement Early-Stage Researchers (ESRs) to broadly spread the spirit and activities of the Action. It is worth emphasizing that ESRs and women have already played a major role in the conception and delineation of the objectives of *EUPlat4PanCRes*. It is therefore expected that Early-Stage Researchers and women scientists will also play leading roles in the management of the Action.

F. TIMETABLE

The duration for *EUPlat4PanCRes* is 4 years. The Kick-off meeting will mark the start-point of the Action.

ACTIVITY	YEAR 1	YEAR 2	YEAR 3	YEAR 4
Coordination	X X X X	X X X X	X X X X	X X X X
Kick-off meeting	X			
Website generation & update	X X X X	X X X X	X X X X	X X X X
Annual Reports	X	X	X	X
MC meetings	X X	X	X	X
SC meetings	X X X X	X X X X	X X X X	X X X X
WGs meetings	X	X	X	X
Workshops/summer schools		X X	X X	X X
Short-Term Scientific Missions	X X	X X X X	X X X X	X X
Final conference				X

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: BE, CZ, DE, EL, ES, FR, IE, IT, NL, PL, RS, SE, SI, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 56 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

The target audience of the *EUPlat4PanCRes* Action consists of epidemiologists, geneticists, cellular and molecular biologists, oncologists, gastroenterologists, general surgeons, pathologists, bioethicists, patient organisations, experts in rare diseases and public health, and policy-makers working on PDAC research in both academic- research institutions and industrial settings as well as working in governmental European bodies. Both senior and Early-Stage Researchers will be approached in different steps of the Action. Participation in the Action will be open and flexible regardless of the availability of independent funding and the extent of participation in individual projects.

In the first step, the key audience will be scientists, bioethicists and public health scientists who will be informed about the activities and results of this Action and invited to actively contribute to it by joining the Action. At a later step, the target participants will become more heterogeneous, including scientists, and clinicians dealing with daily lives of patients on a practical level; European, national/regional policy-makers; private charities or funding organizations; stakeholders from industry focusing on the development of novel diagnostic kits; patients/family groups and the "lay public", who need to know about the disease and their impact on patients and families as well as on the advances in its research. Moreover, the Action will also approach other European research groups participating in projects with complementary interests to *EUPlat4PanCRes* (described in B4), as well as European and International societies, organizations and networks such as: European Pancreatic Club, United European Gastroenterology Federation, Medical Research Council, American Pancreatic Association, International Association of Pancreatology, Pancreatic Cancer Case-Control Consortium, European Platform for Rare Disease Registries, Public Health Genomics European Network, European Public Health Association, IT Future of Medicine, etc. Furthermore, representatives from the European Commission such as DG SANCO and EC-JRC Institute for Health and Consumer Protection will be involved to streamline the development of the PDAC best practices and guidelines.

H.2 What?

EUPlat-PanCRes will communicate research results and continually increase knowledge about on-going research. In order to achieve this, the Action will make use of the insights that will come out of the Action. As it aims to counteract unregulated uncertainty by way of highlighting processes and consequences, it is of great importance that the research is outreaching. The Action will prepare its findings in an accessible language and form. Several dissemination methods will be applied. They will be tuned and targeted to the specific audiences that the action seeks to address. The target population will be approached through:

- An Action-specific website will be built and dedicated to communication and promotion of information on on-going research, seminars, publications and other activities. The MC will assign this task to a partner (web-site coordinator). Part of the website will be accessible to the general public, whereas a section will be password-protected for the exchange of specific information and unpublished data between partners. The website will also contain information on the *EUPlat-PanCRes* activities (meetings, workshops, etc.), proceedings of meetings, links to publications of participants, links to related institutions and organisations, job announcements as well as material and presentations from the didactic activities;
- Policy briefs to disseminate the Action's activities and results beyond the targeted community, to reach the public media and policy-makers as well as other stakeholders and concerned target groups such as those with familial and hereditary PDAC;
- Press releases will be made in connection to events as well as advertisements in the local media whenever useful;
- A brochure will be generated at the beginning of Action describing its objectives and planned activities. This will be distributed to scientists, representatives from the industry, policy and society in major international conferences and meetings;
- Panels in international conferences presenting the actions conducted by the Action. At a later stage, the findings generated by the Action will be disseminated to the scientific community through;

- Scientific publications in specialized and peer-reviewed journals either in the form of original, review, or technical articles**.** To increase the visibility of the Action, the proceedings of WG-meetings and final conference will be published as special issues in international high impact journals such as Pancreatology or Public Health Genomics;
- To promote the timely translation of the PDAC results of the Action into policies on national, European and international level Stakeholder Meetings will be organized and *EUPlat4PanCRes* will be actively involved in policy forums such as European Health Forum Gastein (EHFG).

Moreover, the Action's results will also be communicated to the next generation of PDAC scientists, especially originating from developing regions through Short-Term Scientific Missions**,** to foster exchange of ideas and technology transfer. In addition, members of *EUPlat4PanCRes* will be encouraged to disseminate the results in their Teaching Activities (lectures, seminars, and summer schools**)** at their home universities and institutes.

MC/WG meetings are planned to take place on a regular basis, ideally every six months, in various geographic regions, in order to encourage participation of all interested members. To increase the visibility of *EUPlat4PanCRes*, they will be preferably organized as satellites to major scientific conferences in the field, such as those mentioned above. The inclusion of international experts in the MG/WG meetings will guarantee that state-of-the-art and other high-throughput technologies as well as innovative, integrative analytical methods are mastered by Early-Stage Researchers, who will as a result be at the cutting-edge of their respective fields. This will be done in partnership with senior experienced researchers, with a focus on building bridges between established and novel methods and technologies, and integrating knowledge from diverse fields. By organising the abovementioned activities, the Action will ensure that the vast experience the multitude of participating groups and countries bring to the network is shared in a multidisciplinary way and passed on to early-stage researchers, who will be encouraged to rotate the MC/WG meetings to potentate their training on research management and to take the lead on individual projects.

H.3 How?

The *EUPlat4PanCRes* Action will disseminate as widely as possibly its activities and findings, capitalising on existing mediums of exchange. The MC will be responsible for implementing all of the above activities. The representative members of each country will be responsible for disseminating the activities of the Action to research groups within their countries, industrial partners, medical societies and representatives of the society. Each MC member is therefore, expected to generate, regularly update and circulate to other MC members a list of target groups with contact information. For regional meetings and other activities, the MC will delegate responsibilities to WG-coordinators and members of the WGs depending on their specialty. In addition, the MC will be responsible for providing all necessary information regarding the above-mentioned activities and their outcome as well as revise the dissemination plan according to the Domain Committee recommendations.