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EU Pancreas: An Integrated European Platform for Pancreas Cancer Research – from Basic Science to Clinical and Public Health Interventions for a Rare Disease

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Key Words
COST Action BM1204 · Data integration · Early-stage researchers · Harmonization · Omics data · Pancreas cancer · Public health · Rare disease · Training and mobility

Abstract
Background: Large-scale international collaboration is essential to decipher relevant information in the context of omics-scale interrogations in cancer research. This is even more important for rare and fatal diseases like pancreas cancer (PC). ***Methods:*** The COST Action BM1204 is a unique platform to facilitate the collaboration of a broad range of European and international PC multidisciplinary research groups in order to: (1) integrate knowledge and experience in a multidisciplinary way 'from cell to society', (2) promote the application of uniform study tools and protocols, (3) foster their optimal use by early-stage researchers, (4) enhance the mobility and training of researchers, and (5) disseminate the results produced to the broader society. ***Results:*** This Action will develop novel interdisciplinary tools for collaborative research to improve our understanding of PC and its prevention, diagnosis and treatment. It also aims to answer questions related to the etiology, early detection, evidence-based and personalized treatment, and health management for PC. Furthermore, the Action will contribute to new insights into PC personalized medicine and beyond as well as to the understanding of complex and rare diseases taking PC

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as a best practice example. The Action aims at attracting young scholars across a range of disciplines in collaboration with more experienced researchers and enhancing active European participation in the international scenario of PC research. ***Conclusion:*** The ultimate aim is to foster PC research in Europe and to coordinate this effort with other international initiatives to reduce disease mortality.

Introduction

Pancreas cancer (PC) is a rare and fatal disease that poses formidable challenges to affected individuals and families, to researchers and to society. While PC as a concept involves several neoplasms, the most common morphology (90%) is ductal adenocarcinoma, which has a very poor prognosis [1]. The diagnosis of PC is not straightforward, and it is usually made very late in the disease process [2]. There is still a need for specific biomarkers for early-stage disease. Similarly, there are few markers that predict disease outcome. Surgery, the only effective therapy, is possible in less than 20% of the patients [3]. Most PC patients die within 6 months of diagnosis [4]. Furthermore, this dismal scenario makes PC an unattractive target for the pharmaceutical and biotech industries, making it an orphan disease.

The overall incidence of PC in Europe is 7.8 per 10^5 person-years [5]. Between 5 and 10% of the cases have a family history of PC [6–8], and 20% of this familial aggregation is associated with hereditary cancer syndromes caused by known genes [1]. The identification of individuals at risk remains a major research goal. The nongenetic factors (smoking, diabetes, higher body mass index) and most genetic factors linked to susceptibility to develop PC are relatively common in the general population and are associated with modest increased risks, therefore, being of limited use in identifying high-risk subjects for screening. Relatives of PC cases have a higher risk of the disease that increases with the number of affected family members [7, 9], suggesting that unaffected individuals with a family history of PC could benefit from screening. Eighty percent of familial cases have an unknown etiology (familial pancreas cancer), despite considerable efforts to identify novel high-penetrance genes [10]. Classical genetic studies (linkage analyses) have been quite unsuccessful in identifying mutations responsible for many of the familial pancreas cancer cases, most likely due to the small number of PC cases with available DNA for study and/or genetic heterogeneity across families. Additional research strategies are, therefore, required to unravel the genetic epidemiology of familial pancreas cancer. Whole-exome sequencing omics approaches have recently identified *PALB2* and *ATM* mutations in families with multiple cases of pancreas cancer [11, 12]. These discoveries may ultimately lead to the development of targeted therapies that are effective in a subset of patients.

The development of omics technologies at ever-reducing cost provides a new framework for the study of the genetic determinants of PC. The omics revolution and evolving approaches for data integration offer an enormous potential for basic research and its applications to healthcare. Capitalizing on this potential will require cutting-edge experience in technology and bioinformatics with close multidisciplinary collaboration between clinicians, epidemiologists, biologists, patient organizations and public health experts. Also required are novel and powerful computational methods to handle massive amounts of data. Furthermore, the low incidence and prevalence of PC, and the difficulties inherent in recruiting PC patients with appropriate biological material in a single study, render the establishment of large international consortia essential for the identification of new genes and other risk factors for PC.

COST Action BM1204 is a European-funded initiative that proposes to unite all groups across Europe who are interested in PC research and provides an innovative and unique platform for collaborating and sharing information, ideas and experience. Here we describe the Action and the opportunities it provides for early-stage and established researchers to network and progress in their studies into this rare disease.

What Is COST?

COST is an intergovernmental framework for European Cooperation in Science and Technology (http://www.cost.eu). It builds capacity by connecting scientists throughout Europe and worldwide, prioritizing the provision of networking opportunities for ESR as well as the maximization of the impact of research on policy makers, regulatory bodies, national decision makers, and the private sector. It also increases the mobility of researchers across Europe and fosters the establishment of scientific excellence. Through its inclusiveness, COST supports the integration of research communities, leverages national research investments and addresses issues of global relevance. It contributes to reducing the fragmentation in European research investments and opening the European

Research Area to cooperation worldwide. In this way, it complements the activities of the EU Framework Programmes and contributes to the strengthening of Europe's research and innovation capacity.

COST funds activities in 9 key domains: (1) biomedicine and molecular biosciences (BMBS); (2) food and agriculture; (3) forests, their products and services; (4) materials, physics and nanosciences; (5) chemistry and molecular sciences and technologies; (6) earth system science and environmental management; (7) information and communication technologies; (8) transport and urban development; and (9) individuals, societies, cultures and health. It also encourages trans-domain proposals. The BMBS domain covers all areas of medicine as practiced in Europe as well as basic, preclinical and clinical medical research developed to materialize the 'bench to bedside' concept (http://www.cost.eu/domains_actions/bmbs). BM1204 is one of 35 Actions currently funded within BMBS.

What Is COST Action BM1204?

COST Action BM1204 is a 4-year funded initiative with 20 participating countries that began December 14, 2012 (http://www.cost.eu/domains_actions/bmbs/Actions/BM1204?). Participating countries are listed at: http://www.cost.eu/domains_actions/bmbs/Actions/BM1204?parties. The overall objective of the Action is to create a platform of collaborative research that aims to capitalize on emerging scientific and technological developments to: (i) identify new modifiable risk factors and other environmental, genetic and epigenetic risk factors for PC and pave the road for the development of risk prediction algorithms; (ii) dissect the molecular complexity of PC and identify clinically relevant disease subphenotypes by the application of omics technologies; (iii) identify reliable biomarkers of early-stage PC; (iv) identify reliable predictive biomarkers in PC as well as novel molecular targets for tailored therapies; (v) identify reliable genetic, epigenetic and tumor-related factors associated with the prognosis for PC 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.

The specific objectives of the Action are to:

- construct a strong network of European centers to develop unified biobanks that store individual epidemiological and clinical information and, therefore, represent fundamental resources for future PC research in Europe;
- evaluate the applicability of selected omics technologies to identify chemical, epigenetic, genetic, and molecular markers relevant to PC prevention and treatment to be utilized in the public health and clinical settings;
- 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 is likely to facilitate the discovery of novel biomarkers and therapeutic targets;
- unite and train early-stage researchers from different disciplinary backgrounds across Europe; 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 PC research needs and impacts.

The scientific focus of the Action is organized around the following key areas:

(1) 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, and toenails). This task tackles 2 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 suboptimal control selection).

(2) Establishment of a framework for building and assessing risk-prediction models for PC. 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. PC is a complex disease and interactions are likely to exist between risk factors (in time and space dynamic); risk prediction models need to account for this complexity and dynamics.

(3) 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 des-

moplastic reaction. It also tackles major difficulties that current researchers encounter in evaluating and reproducing 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 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 PC.

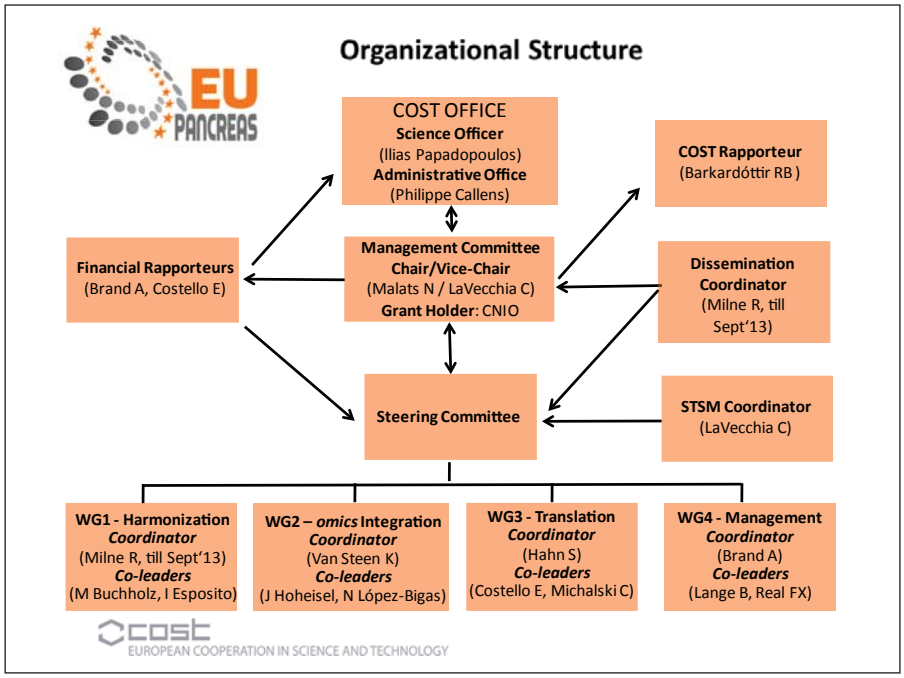
(4) Translation of findings into clinical practice: This axis includes the identification and prioritization of the main PC management areas that would benefit from further research on PC markers. The critical examination of the 'novelty' of biomarkers for (early) diagnosis, prognosis and prediction of treatment response is essential in order to prioritize them for validation and replication in independent studies and populations. 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.

(5) Therapeutic approaches towards individualized 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.

(6) Development of European PC-best practice guidelines for translating genome-based information into evidence-based health interventions by using the LAL model [13]. 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 public health assessment tools including health needs assessment, health technology assessment and health impact assessment. The current shift towards a systemic understanding of disease etiology ('systems thinking') and personalized medicine is a major challenge. PC can serve as a model for rare diseases as well as for information and communication technologies-driven personalized medicine. Systems biomedicine triggered by omics technologies will become the leading healthcare paradigm in the following decades for predictive, personalized, pre-emptive, and participatory medicine [14]. It will help to reshape current research, policy-making and healthcare practices ('from cell to society') [15]. 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 2 European flagship projects: Public Health Genomics European Network (PHGEN, http://www.phgen.eu) and IT Future of Medicine (ITFoM, http://www.itfom.eu). Furthermore, the collaboration with European Networks of Rare Diseases (EPIRARE, http://www.epirare.eu 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).

The Action is funded by the EU COST Office to carry out specific activities. These include networking, planning and scientific meetings, workshops, training schools, short-term scientific missions (STSMs), and the dissemination of information. Further details are proved below. The grant is held and managed by the Spanish National Cancer Research Centre (CNIO, www.cnio.es).

The scientific structure of the Action is organized around 4 working groups (WGs) that carry out the following tasks: WG1: harmonization of research tools, WG2: integration of omics data, WG3: translational research, and WG4: PC patient management. Each WG has an assigned coordinator and leadership team. In addition, an STSM Coordinator and Dissemination Coordinator have been assigned to reinforce the training and dissemination objectives. The work of the Action is overseen by a Management Committee (MC, http://www.cost.eu/domains_actions/bmbs/Actions/BM1204?management), comprising up to 2 representatives from each participating country. It is led by the Action Chair with support



Color version available online

Fig. 1. EU Pancreas (COST Action 1204).

provided by the Vice Chair, a Scientific Officer and an Administrative Officer from the COST Office, and an Action Rapporteur. All key decisions are made by the MC. More direct oversight of the working group activities in the context of the overall objectives of the Action is maintained through a Steering Committee composed of the Action Chair and Vice Chair, each working group coordinator and the STSM and Dissemination Coordinators (fig. 1). An Action website is currently being created at http://www.eupancreas.com.

Working Groups

The work plan involves a feedback process in which the WGs individually address problems and bring them back to the plenum of groups. These WGs are strongly linked to each other. Each of them has distinct tasks which define the main type of expertise required: epidemiologists, pathologists, 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, health technology assessment agencies, industry, SMEs, patient organizations, and Public Health and rare disease experts in WG4. It should be emphasized, however, that completion of the tasks of each group can only be achieved by continuous information exchange between them.

WG1: Research Tool Harmonization

This group aims to address and reach a consensus on the following issues: (i) definition of PC 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) contrasting this terminology across research groups and countries, and across settings and contexts. This comparison will identify commonalities and differences and explore key variables that cut across different cases; (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 centers to follow uniform protocols for the sample collection and databasing; and (v) establishment of criteria to assess the quality of existing body fluid and tissue banks for PC research to enhance the distribution of biological material from patients with PC within Europe.

WG2: Integration of Omics Data

WG2 considers 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 is used as a model, and its potential extension to other omics data is 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, and the incorporation of domain knowledge into the knowledge discovery process using innovative statistical and bioinformatics approaches.

WG3: Translational Research

This WG addresses the following questions and tasks: (i) identification of the most challenging and urgent clinical research questions (early diagnosis vs. prognosis vs. drug efficacy, etc.); (ii) assessment of candidate markers for PC and the definition of the special research needs in each case; (iii) review of current biomarker research in PC (white paper) and assessment of the state of current biomarker research (discovery phase vs. 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: PC Patient Management

This group approaches the following challenges: (i) identification of European centers focused on individualized medicine approaches for PC treatment, (ii) training workshops on personalized and targeted therapy strategies for young physicians and basic scientists, (iii) establishing the framework for the development of evidence-based PC-best practice guidelines and its translation into the healthcare systems in Europe by involving all relevant stakeholders and by using the previously mentioned LAL model, and (iv) orchestrate the Action activities with European networks of rare diseases by adopting their standards in impacting society.

Activities Funded by the Action

The Action planned activities funded by COST, as outlined in its Vademecum (http://cost-winemo.org/docs/COST_Vademecum_Grant_System.pdf) are:

Meetings

These meetings including MC, Steering Committee and working group meetings are held in a COST country participating in the Action. A good balance from the various countries participating in the Action is ensured by the MC. Experts and keynote speakers from nonparticipating countries are also invited.

STSMs

These missions contribute to the scientific objectives of the Action. These exchange visits are designed to strengthen existing networks by allowing scientists (and particularly young researchers) from Action-participating countries to go to an institution in another COST country to foster collaboration, learn a new technique or apply instruments and/or methods that are not available in their own institution.

Training Schools

The schools aim to widen the knowledge of the Action activities, providing intensive training on an emerging subject, and/or familiarizing participants with equipment or know-how in an institution from a participating country.

Dissemination

White papers and books, brochures, flyers, CD-ROMs, and DVDs resulting from the action are planned. In addition, for Action BM1204, dissemination methods will be 'tuned' to the specific target audiences through the action website, policy briefs, press releases, panels at international conferences, scientific publications, and stakeholder meetings. In this regard, the Action co-sponsors key-speakers for the Pancreatic Cancer Forum to be held at the Spanish National Cancer Research Centre, Madrid, Spain, on November 29–30, 2013. The European Pancreatic Club (EPC) executive committee has also been approached and some activities in the 2014 Meeting in Southampton, UK, will be co-organized with the Action.

How to Participate in the Action

Investigators interested in joining the action should first check whether they are from a COST country, collaborating state, near neighbor country, or international partner coun-

try (http://www.cost.eu/about_cost/cost_countries). If eligible, they should then check whether or not their country has joined the Action (http://www.cost.eu/domains_actions/bmbs/Actions/BM1204?parties) and contact the relevant country or Action representatives. Detailed information on how to join this Action is provided on the COST website (http://www.cost.eu/participate/join_action).

Conclusions and Outlook

The COST Action BM1204 is a unique platform to facilitate networking with a broad range of European and international PC multidisciplinary research groups to integrate knowledge and experience in a multidisciplinary way. By funding meetings, STSM and training schools, it intends to attract young scholars across a range of disciplines to collaborate with more experienced researchers. The ultimate aim is to foster PC research in Europe and to coordinate this effort with other international initiatives and consortia, such as ICGC, Panc4 and TCGA, to reduce disease mortality.

Furthermore, the Action will contribute to new insights into PC personalized medicine and beyond as well as to the understanding of complex and rare diseases, taking PC as a best practice example. Thus, this Action has the potential to prepare for the various future organizational changes in healthcare systems in Europe and beyond. The real paradigm shift depends on the willingness to restructure the current policies and to support knowledge transfer from basic sciences to maximize the benefits to PC clinical practice and public health. So far, all stakeholders, including policy makers and the private sector, are struggling to translate the emerging knowledge into healthcare systems. Public Health Genomics is the area ensuring that scientific advances in genomics triggered by innovative technologies are effectively and responsibly, and in a timely manner, translated into health policies and practice for the benefit of population health. The Action adapts the 'from cell to society' pipeline in the PC scenario.

These new insights are being obtained from genomics, proteomics, transcriptomics, metabolomics, epigenomics, microbiomics, and other 'omics' technologies. As these data are integrated by the use of information and communication technologies, we will come close to achieving an understanding of the PC systems biology and systems biomedicine that also incorporates environmental contributions, such as lifestyle, toxic agents, social and economic factors as well as health systems determinants. In this way, we can begin to envisage new approaches to the promotion and management of high-risk PC population across the entire life course and to consider a future involving truly personalized healthcare, in which technological advances are placed at the service of population health.

However, the evidence we now require to demonstrate the benefit of new technologies may need to follow a new paradigm. What is needed is an assessment of individual benefits rather than overall effects in large populations or even subpopulations of patients. Thus, public health assessment and evaluation tools included in the innovative LAL model, which is also applied in this COST Action, will address concepts such as 'personal utility' rather than clinical utility. Also, these developments and the involvement of patients have brought forward the concept of P4 (predictive, preventive, personalized, and participatory) medicine, which is no longer a vision, but a mission. In this EU Pancreas COST Action, we go beyond the P4 medicine in demonstrating that (1) common complex diseases can be considered in terms of a constellation of 'rare' diseases, each of which reflects a complex biological system, (2) we are moving away from a traditional classification of disease and towards groups of shared pathology that can be described as 'diseasomes' or disease nodes, (3) we are moving away from a focus on risk factors within biostatistical models of populations and towards an emphasis of individual pathways or networks, and (4) we emphasize personal rather than clinical utility.

Until now, we still see just incremental progress and changes leading to personalized (stratified) medicine and precision medicine. However, combined genomic and phenotypic analysis has become possible thanks to the increasing role of information and communication technologies in healthcare, driven by improved technological options and the interoperability of various technologies. The complexity of the task when applied to diagnosis and therapy demands algorithms and mathematical models to reduce uncertainties. As a result, efforts are now being made to generate computational models of individual persons ('virtual patients'). Such models are applied in this COST Action as well. They can be used to follow individuals throughout their lifetime and enable health professionals to virtually simulate and optimize treatments. Traditional medical decision-making may turn into in silico decision-making. In this way, it becomes possible to improve the safety, quality, effectiveness, and efficiency of healthcare services. This is expected to significantly improve the treatment of patients with PC, which is a rare and fatal disease that poses substantial challenges to affected individuals and families.

Appendix

COST Action BM1204 (EU Pancreas) Members

Management Committee Members: Núria Malats (SP, chair), Carlo LaVecchia (IT, vice-chair), Kristel Van Steen (BE), Drazenka Macic and Timur Ceric (BH), Juan Iovanna (FR), Stephan Hahn and Jorg Kleeff (GE), Maria Gazouli and Christos Dervenis (GR), Peter Hegyi and Ralph Ruhl (HU), Amir Shafat and Linda Sharp (IE), Anwar Rayan (IL), Adriano deCarli and Giampolo Tortora (IT), Audrius Sileikis and Giedrius Barauskas (LT), Angela Brand (NL), Sonja Eriksson Steigen and Tone Ikdahl (NO), Ewa Malecka-Panas (PL), Filipe Santos Silva (PT), Traian Sorin Barbu and Irinel Popescu (RO), Maria Durisova and Magdalena Majekova (SK), Vita Dolzan (SL), Roger Milne (SP, until Sept. 2013), Lutfi Genc and Hatice Yildirim (TK), Eithne Costello and Tajana Crnogorac-Jurcevic (UK). *Steering Committee Members*: Angela Brand, Stephan Hahn, Carlo LaVecchia, Núria Malats, Roger Milne (until Sept. 2013), Kristel Van Steen. *Dissemination Coordinator*: Roger Milne (until Sept. 2013). *Short Term Scientific Mission Coordinator*: Carlo LaVecchia. *Financial Rapporteurs*: Angela Brand and Eithne Costello. *WG1 – Harmonization of research tools – leadership team*: Roger Milne (coordinator, until Sept. 2013), Malte Bulchholz (co-leader), Irene Esposito (co-leader), Carlo la Vecchia, Bill Greenhalf, Vita Dolzan, Linda Sharp, Fiona Campbell, Gunter Kloeppel, Bas Bueno de Mesquita. *WG2 – Integration of omics data – leadership team*: Kristel Van Steen (coordinator), Jorg Hoheisel (co-leader), Núria López-Bigas (co-leader), Alvis Brazma, Raph Herwig, Eric Van Cutsum, Darlene Goldstein, Ewan Birney, Anwar Rayan, Claudio Bassi, Andrew Biankin, Aldo Scarpa. *WG3 – Translational research – leadership team*: Stephan Hahn (coordinator), Eithne Costello (co-leader), Christoph Michalski (co-leader), Juan Iovanna, Marlène Dufresne, Claude Chelala, Hermant Kocher, Ewout Steyerberg, Daniela Cecconi, Matthias Löhr. *WG4 – PC patient management – leadership team*: Angela Brand (coordinator), Bodo Lange (co-leader, Francisco X. Real (co-leader), Inaki Gutierrez-Ibarluzea, Roza Adany, Denis Horgan, Domenica Taruscio, Bonnie Wolff-Boehnisch, Hans-Peter Dauben, Traian Sorin Barbu. *COST Action Rapporteur*: Rósa Björk Barbardorttir. *COST Scientific Officer*: Ilias Papadopoulos. *COST Administrative Officer*: Philippe Callens. *Other Action Members*: Ivana Holcatova, Hermann Brenner, Daniele Campa, Federico Canzian, Cosmeri Rizzato, Jutta Lüttges, Thomas Gress, Detlef Bartch, Tonia Vlahou, Cristina Fillat, Mònica Bayés, Ivo Gut, Marta Gut, Magda Gasull, Víctor Barberá, Miquel Porta, Xavier Molero, Eric Duell, Eduardo González-Couto, Alfredo Carrato, Carmen Guillén, Paola Martinelli, Manuel Hidalgo, Christopher Heeschen, Alfonso Valencia, Ma Luz Calle, Roderic Guigó, Ghislaine Scelo, Paolo Boffetta, Patrick Maisonneuve, Cristina Bosetti, Domenica Taruscio, Ersilia Lucenteforte, Suzanne Jeurnink, Franzel Van Duijnhoven, Witold Zatonski, Ljiljana Petronijevic, Caroline Verbeke, John Neoptolemos.

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