European Cooperation in the field of Scientific and Technical Research - COST -

Brussels, 21 November 2012

BM1206

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM1206: Cooperation Studies on Inherited Susceptibility to Colorectal Cancer

Delegations will find attached the Memorandum of Understanding for COST Action as approved by the COST Committee of Senior Officials (CSO) at its 186th meeting on 20 - 21 November 2012.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as

COST Action BM1206
COOPERATION STUDIES ON INHERITED SUSCEPTIBILITY TO COLORECTAL CANCER

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 comprehensively understand the impact of inherited susceptibility in CRC for profiling individual disease risk and performing early screening and treatment monitoring. By doing so, new molecular biomarkers will be implemented and validated for personalized CRC medicine.

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 40 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

Colorectal cancer (CRC) is one of the most frequent neoplasms worldwide and an important cause of morbidity in the developed world. It is necessary to identify individuals with a medium-high CRC risk in order to develop adequate preventive measures. The identification of inherited genetic factors involved in CRC susceptibility can help to profile individual disease risk and may enable early screening and treatment monitoring. Participants interested in networking in this Action include 19 research groups actively working on CRC genetics with high success and with access to more 50,000 CRC cases and 50,000 controls through cohorts in 11 countries. This Action will permit to articulate the cooperation between these research groups in Europe in order to comprehensively understand the impact of inherited susceptibility to CRC and to describe the genetic landscape of this disease, providing a highly innovative and unconditional tool for personalized CRC medicine with a future application in early screening and treatment monitoring for this disease.

A.2 Keywords: Colorectal cancer, genetic susceptibility, risk profiling, treatment monitoring, genotype-phenotype correlation

B. BACKGROUND

B.1 General background

Colorectal cancer (CRC) is one of the most frequent neoplasms and an important cause of mortality in the developed world. For 2015, 473,258 new cases are predicted and 233,901 will die from this disease in Europe. Therefore, it is necessary to identify individuals with medium-high CRC risk in order to develop adequate preventive measures. As other complex diseases, CRC is caused by both genetic and environmental factors. Although environmental causes such as smoking and diet are undoubtedly risk factors for CRC, twin studies have shown that 35% of the variation in CRC susceptibility involves inherited genetic differences. The identification of genetic factors underlying CRC susceptibility can help to profile individual disease risk and be useful for early screening and treatment monitoring. Specifically, the clinical surveillance of at-risk individuals may allow early detection of the disease and possibly ad hoc therapies translating into decreasing morbidity and mortality expectations. Then, the research topic of this Action will be the identification of inherited genetic factors involved in CRC susceptibility.

This Action will permit to comprehensively understand the impact of inherited susceptibility to CRC and to describe the genetic landscape of this disease. Participants encompass 19 groups actively working on CRC genetics that are already part of a consortium with access to more than 50,000 CRC cases and 50,000 controls. These groups have collectively been highly successful, with already available funding to achieve this Action's research objectives, and publication of the main articles of genetic susceptibility to CRC in the past 6 years. COST is an intergovernmental framework for European Cooperation in Science and Technology that allows the coordination of nationally-funded research on a European level. COST contributes reducing the fragmentation in European research investments and opening the European Research Area to cooperation worldwide. Therefore, COST funding will be the best mechanism for supporting this Action, enabling to continue and build on that international lead, as well as to be able to capitalize on sharing advances in emerging technologies, sample and datasets. Regarding other frameworks, ESF is currently streamlining its activities to be in line with the needs of its Member Organizations and during this process there are no plans to launch a Call for Research Networking Programmes. On the other hand, ESA and EUREKA are not appropriate frameworks for this Action's research topic. Societal benefits of this Action will focus on improving health for citizens of Europe and worldwide. Since CRC represents a highly frequent malignancy, seriously affecting quality of life of individuals, collaborative approaches on CRC etiology may permit to use genetic predisposition components for this disease to improve preventive measures in order to diminish CRC incidence and improve treatment efficacy. By doing so, economical benefits such as reducing hospitalization and treatment expenses could be expected. Regarding scientific benefits, collaboration studies will be based on previous networking of the participants in a consortium. This initiative includes several research groups actively working on CRC genetics with high success. Participants have access to more than 50,000 CRC cases and 50,000 controls, which will permit to obtain ample statistical power to reach solid conclusions on genetic susceptibility variants.

B.2 Current state of knowledge

CRC is caused by both genetic and environmental factors with 35% of the variation in CRC susceptibility involving inherited genetic differences. Hereditary CRC forms, mainly familial adenomatous polyposis and Lynch syndrome, account only for a minority of the total CRC burden (5%). According to the common disease-common variant (CDCV) hypothesis, part of the heritability in CRC may be explained by multiple common genetic variants with a low-moderate effect on cancer susceptibility. The CDCV hypothesis has been recently vindicated by genome-wide

association studies (GWAS) and, so far, 20 common, low-penetrance genetic variants have been identified for CRC susceptibility. While the risk of CRC associated with each of these variants is modest, taken together, they could make a significant contribution to disease burden by virtue of their high frequencies in the population. Also, the impact of genetic variation at these CRC susceptibility loci will not be universally generic and that some of the risk variants will impact preferentially on CRC subtypes or influence patient's survival and toxicity responses to CRC treatment. Also, GWAS have not identified all CRC susceptibility variants and there is still missing heritability hidden for this disease. These new CRC variants will probably correspond to additional common variants as the ones already identified, other common variants with a more subtle risk effect, and rare variants with higher risk impact.

There is only one current effort for the identification of inherited susceptibility factors to CRC funded by the EU Framework Programme with involvement of some participants in this Action (CHIBCHA: Genetic study of Common Hereditary Bowel Cancers in Hispania and the Americas) that will conclude at the end of the present year. EU-funded research on CRC is mainly focused on somatic tumor changes (COLTHERES, SYSCOL) or environmental effects (EPIC). On the other hand, international consortiums such as C-CFR, GECCO and MECC are collaborative efforts outside Europe to improve understanding of genetic susceptibility to CRC.

This Action aims at addressing CRC high incidence by searching for inherited susceptibility genetic variants that could be used in profiling individual disease risk and be useful for early screening and treatment monitoring. In this manner, these genetic factors will be used to decrease morbidity and mortality expectations for CRC.

B.3 Reasons for the Action

Being CRC such a common disease, it is necessary to identify individuals with medium-high CRC risk in order to develop adequate preventive measures. The identification of genetic factors involved in CRC susceptibility can help to profile individual disease risk and be useful for early screening and treatment monitoring. Therefore, an expert network on inherited susceptibility to CRC is necessary to accelerate the discovery of such factors.

This Action aims at European economic/societal needs and scientific/technological advance. As previously mentioned, societal benefits of this Action will focus on improving health for citizens of Europe and worldwide by improving preventive measures and treatment efficacy to diminish CRC incidence. By doing so, reducing hospitalization and treatment expenses will represent also economical benefits of this Action. Finally, scientific benefits will be based on previous networking

of the participants in the Action. This initiative includes several research groups actively working on CRC genetics with high success. Participants have access to more than 50,000 CRC cases and 50,000 controls, which will permit to obtain ample statistical power to reach solid conclusions on genetic susceptibility variants and, therefore, maximizing productive outcomes of this Action. Also, the high number of available cases will allow subgroup analyses for genotype-phenotype correlations. There will be also improvement in the statistical modeling of CRC risk to take into account interactions between genetic variants and environmental factors.
In general, optimized communication between partners and effective scientific collaboration between teams powered by this Action will result in new approaches and strategies in CRC research (e.g. implementation and validation of new biomarkers). This consortium will stimulate a regular overview of a complex and rapidly developing area of research, establish the extent of progress, facilitate consensus among participants and set new priorities through meetings and workshops. Technological and scientific transfers will be conducted by means of short term scientific missions (STSM) of young scientists in participating laboratories.

B.4 Complementarity with other research programmes

This Action may benefit partially from experience and goals of on-going Action BM1006 regarding next generation sequencing data analysis.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The main objective of this Action is to comprehensively understand the impact of inherited susceptibility in CRC for profiling individual disease risk and performing early screening and treatment monitoring. By doing so, new molecular biomarkers will be implemented and validated for personalized CRC medicine.

C.2 Objectives

The following specific objectives will be pursued in order to achieve the previous general aim:
1. *Identification of new CRC susceptibility variants*: A polygenic model of inherited susceptibility to CRC implies the co-inheritance of multiple risk variants. So far, 20 common, low-penetrance genetic variants for CRC susceptibility have been identified by GWAS. This Action will permit to

boost sample size and statistical power (participating cohorts sum up more than 50,000 cases and 50,000 controls) and, therefore, it is very likely that additional genetic variants linked to CRC will be identified. Large-scale meta-analyses of existing and newly generated GWAS data will be performed and replication of initial GWAS findings in additional cohorts will be used to robustly confirm those genetic variants that participate in CRC susceptibility.

2. *Functional links for CRC susceptibility variants*: Most GWAS variants are unlikely to alter protein function and fine mapping and functional studies will be used to identify a correlated functional variant. The identification of the functional variation that causes increased CRC risk may lead to the development of new means of preventing the disease. However, the journey from the associated polymorphism to functional variant is not simple and will require additional work. In order to perform an initial search for readily identifiable functional variants, fine mapping in the regions close to each disease-associated single nucleotide polymorphism (SNP) or copy number variant (CNV) should be undertaken, enriching for variants in strong linkage disequilibrium (LD) with that SNP/CNV and with possible functional effects. Basic functional work should also be performed, such as assessing the levels of mRNAs and proteins in each region in patients of known genotypes, as well as more complex studies such as chromatin mapping, gene reporter and allele-specific expression experiments.

3. *Genetic variants involved in CRC survival and treatment toxicity*: CRC genetic susceptibility variants could also act as biomarkers for CRC survival and treatment response. For instance, inherited genetic variants can modulate the pharmacokinetics/pharmacodynamics of drugs used in CRC treatment by substantially affecting individual response and toxicity to chemotherapy. Therefore, GWAS data will be analyzed regarding CRC survival and treatment toxicity in order to identify genetic variants linked to differential prognosis and adverse drug reactions.

4. *Genetic variants enriched in CRC subgroups*: The impact of CRC susceptibility genetic variation will not be universally generic and some of the risk variants will impact preferentially on CRC subtypes, such as early-onset or microsatellite-unstable CRC (MSI+ CRC). If some of the CRC genetic susceptibility variants appear to be associated with some clinical and familial features, it could have potential important implications for screening and surveillance strategies for this disease.

5. *New predisposition genes for CRC in families with unknown genetic basis*: Next generation sequencing will be useful to identify new CRC predisposition genes in selected high-risk and early-onset families with unknown genetic basis from the participating cohorts.

6. *Interactions between CRC susceptibility variants and environment*: CRC risk is undoubtedly determined by complex interactions between genetic and lifestyle/dietary risk factors.

Epidemiological studies have established several dietary risk factors for colorectal neoplasia; these include low vegetable and high red meat consumption and micronutrient deficiency and excessive alcohol intake. CRC genetic susceptibility variants are thus likely to interact with these environmental lifestyle risk factors to modify risk and they should be incorporated into models of predisposition.

7. *High risk CRC profile of inherited variants by statistical modelling*: Besides gene-environment interactions, it is also entirely conceivable that epistatic interactions between CRC genetic susceptibility variants may exist. A high-risk CRC profile using mentioned parameters could be developed using data from all participating cohorts and be very useful as a molecular tool for personalized CRC medicine.

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

This Action will permit 19 research groups to work together with a common objective to comprehensively understand the impact of inherited susceptibility in CRC in order to apply it in early screening and treatment monitoring. The most important means available to do so will be participating cohorts that sum up more than 50,000 CRC cases and 50,000 controls with ample sample size, already available GWAS data in some of them, genotyping data for the known CRC genetic susceptibility variants in most cohorts, and an excellent research track and expertise in CRC genetics. The previous objectives will be achieved by regular meetings. In addition, exchange of early stage scientists through the STSM mechanism will be used to integrate novel data analysis and maximize output from existing datasets. In general, an improvement of communication between partners and organization of effective scientific collaboration between teams will help to perform the proposed approaches and strategies.

C.4 Potential impact of the Action

Societal benefits of this Action will focus on improving health for citizens of Europe and worldwide. Since CRC represents a highly frequent malignancy, seriously affecting quality of life of individuals, collaborative approaches on CRC etiology may permit to use genetic predisposition components for this disease to improve preventive measures and diminish CRC incidence and enhance treatment efficacy. By doing so, economical benefits, such as reducing hospitalization and

treatment expenses, could be expected. Besides, regarding scientific benefits, collaboration studies will be based on previous networking of the participants in a consortium. This initiative includes several research groups actively working on CRC genetics with high success and with access to more than 50,000 CRC cases and 50,000 controls, which will permit to obtain ample statistical power to reach solid conclusions on genetic susceptibility variants. Also, the high number of available cases will allow subgroup analyses for genotype-phenotype correlations. There will be also improvement in the statistical modeling of CRC risk to take into account interactions between genetic variants and environmental factors.

C.5 Target groups/end users

End users of the outcomes of this Action will be the whole scientific community, regulatory bodies and policy makers in health care system (in both preventive strategies and optimized treatment), the general population in terms of reducing risk factors associated with CRC, and CRC patients since some genetic variants related to therapy efficacy may improve their prognosis and survival.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The most important research tasks to be coordinated by this Action are listed below, and described for each specific objective:

1. *Identification of new CRC susceptibility variants*: This objective will be pursued by performing genetic association studies in the form of GWAS and replication for positive hits in additional DNA samples. There are existing GWAS datasets for some participating cohorts, and there will be also newly generated GWAS data. GWAS data from different cohorts will be combined in meta-analyses in order to increase statistical power and be able to identify additional CRC susceptibility variants. When possible, SNP and CNV will be analyzed. Afterwards, replication of initial GWAS findings in additional cohorts will be used to robustly confirm if those genetic variants participate in CRC susceptibility. In fact, this Action will permit to boost sample size and statistical power since participating cohorts sum up more than 50,000 cases and 50,000 controls. Regarding human and technical means, a majority of involved participants have readily available DNA samples from CRC cases and matched controls from their respective cohorts. Those participants not contributing with

samples will be involved in functional studies and statistical analyses. Genotyping facilities and statistical analysis capacities are available to most participants in their institutions. Access of other partners from various European countries will be always enabled and desirable since it will permit to increase sample size and corroborate findings in more CRC cohorts.

2. *Functional links for CRC susceptibility variants*: This objective will be pursued by performing fine mapping of the identified CRC susceptibility variants and functional studies in order to pinpoint the molecular defects associated with CRC susceptibility variants. Different ethnic groups can have different LD block patterns which can be used to refine the location of a disease susceptibility locus prior to fine mapping genotyping and functional analyses. One recent development that greatly facilitates fine-mapping is the use of imputation of untyped SNPs from reference population panels which have been extensively genotyped. HapMap 2 has until recently been a major source of such reference data providing genotypes for ~8 M SNPs in four main ethnicities. Initiatives such as the 1000Genomes project have greatly improved polymorphic annotation of the human genome harvesting ~30 M SNPs, thereby increasing the value of imputation. In order to perform an initial search for readily identifiable functional variants, fine mapping in the regions close to each disease-associated SNP/CNV should be undertaken, enriching for variants in strong LD with that SNP/CNV and with possible functional effects. Basic functional work should also be performed, such as assessing the levels of mRNAs and proteins in each region in patients of known genotypes, as well as more complex studies such as chromatin mapping, gene reporter and allele-specific expression experiments. Regarding human and technical means, most involved participants have capacity to perform fine mapping and basic functional studies. Besides, there is one participant with a high degree of expertise in functional studies that will be in charge of the more complex functional studies previously mentioned.

3. *Genetic variants involved in CRC survival and treatment toxicity*: This objective will be pursued by correlating available genotyping data and newly generated GWAS data (including SNP and CNV if possible), as well as genotyping data of the 20 known CRC susceptibility variants, with CRC survival and treatment toxicity data in the different participating cohorts. Then, genetic variants linked to differential prognosis and adverse drug reactions will be identified by logistic regression. Regarding human and technical means, most participating cohorts have data for prognosis and adverse drug reactions from their CRC patients. Again, access of other partners from various European countries will be always enabled and desirable since it will permit to increase sample size and corroborate findings in more CRC cohorts.

4. *Genetic variants enriched in CRC subgroups*: This objective will be pursued by logistic regression correlating genotyping available data and newly generated GWAS data (including SNP

and CNV if possible), as well as genotyping data of the 20 known CRC susceptibility variants, with CRC subgroup data in the different participating cohorts. Examples of variables analyzed to define CRC subgroups will include gender, age at diagnosis, family history of cancer, previous CRC, synchronous CRC or adenoma, and tumor features such as MSI+ histology, location, TNM stage and degree of differentiation. Regarding human and technical means, most participating cohorts have clinical data available to perform this kind of sub-analyses. While stratified analyses provide a means of teasing out important subtype specific effects, the numbers of cases in many subgroups will inevitably constraint study power. This fact further underscores the value of bringing together independent case–control series for validation analyses through initiatives such this Action. Therefore, access of other partners from various European countries will be always enabled and desirable since it will permit to increase sample size and corroborate findings in more CRC cohorts.
5. New predisposition genes for CRC in families with unknown genetic basis: : This objective will be pursued by next generation whole-genome or exome sequencing in selected CRC families collected in the participating cohorts. Selected families will include those with a high degree of familial aggregation but without alterations in the known genes involved in hereditary CRC. This Action will permit data sharing and replication of interesting findings in additional cohorts in order to corroborate its implication in CRC predisposition. Regarding human and technical means, most participating cohorts have families with strong CRC aggregation without alterations in the known hereditary genes involved available through high-risk CRC clinics. Access to next generation sequencing is limited to some participants but there are several platforms available in Europe. As before, access of other partners from various European countries will be always enabled and desirable since it will permit to increase sample size and corroborate findings in more CRC cohorts.
6. *Interactions between CRC susceptibility variants and environment*: This objective will be pursued by analyzing interactions between the known 20 CRC susceptibility variants, as well as for those newly identified in the course of this Action, with environment (body mass index, physical activity, alcohol/red meat/fiber intakes, smoking habit, nonsteroidal anti-inflammatory drugs). Also, CRC susceptibility variants will be analyzed as risk modifiers for hereditary CRC. Regarding human and technical means, most participating cohorts have available environmental data such as smoking habit and alcohol intake, genotyping data for the known 20 CRC susceptibility variants, as well as families with known hereditary CRC syndromes. As for functional studies, although most involved participants have capacity to perform basic analyses, there are four participants with a high degree of expertise that will be in charge of more complex gene-gene and gene-environment analyses.
7. *High risk CRC profile of inherited variants by statistical modelling*: This objective will be

pursued by analyzing epistatic interactions between CRC genetic susceptibility variants, either already known or newly identified. Regarding human and technical means, although most involved participants have capacity to perform basic analyses, there are four participants with a high degree of expertise that will be in charge of epistasis analyses. A high-risk CRC profile using mentioned parameters could be developed to be very useful as a molecular tool for personalized CRC medicine.

D.2 Scientific work plan methods and means

So far, 19 groups are interested in joining efforts in this Action, including 16 CRC cohorts from 11 different countries. Methods and means used and available for this Action are listed below detailed for every specific objective:

1. *Identification of new CRC susceptibility variants.* Methods: Genetic association studies in the form of GWAS and replication for positive hits, and meta-analyses combining several GWAS in different cohorts. Means: Participating cohorts sum up more than 50,000 CRC cases and 50,000 controls and genotyping platforms.

2. *Functional links for CRC susceptibility variants.* Methods: Fine mapping of the identified CRC susceptibility variants including imputation of untyped SNPs using HapMap and 1000genomes data and additional genotyping in the regions of interest. Functional studies assessing mRNA and protein levels, chromatin mapping, gene reporter and allele-specific expression. Means: Genotyping capacity and technical expertise to perform functional studies.

3. *Genetic variants involved in CRC survival and treatment toxicity*. Methods: Correlation by logistic regression of genotyping data with CRC survival and treatment toxicity data. Means: Available genotyping data as well as prognosis and toxicity records for CRC patients in participating cohorts.

4. *Genetic variants enriched in CRC subgroups*. Methods: Correlation by logistic regression of genotyping data with CRC subgroup data. Means: Available genotyping data as well as clinical, pathologic and molecular data for CRC patients from participating cohorts to perform sub-analyses.

5. *New predisposition genes for CRC in families with unknown genetic basis.* Methods: Next generation sequencing (exome or whole-genome). Means: Available germline CRC samples from families with strong CRC aggregation from the participating cohorts. Next generation sequencing platforms in some participants' institutions.

6. *Interactions between CRC susceptibility variants and environment.* Methods: Interaction analysis

between CRC genetic susceptibility variants and environmental factors. CRC genetic susceptibility variants as modifiers for hereditary CRC. Means: Available genotyping data for CRC genetic susceptibility variants, environmental data and germline CRC samples from families with hereditary CRC from the participating cohorts. Expertise in complex statistical analyses.
7. *High risk profile of inherited variants by statistical modelling.* Methods: Epistasis analysis for known and newly identified CRC genetic susceptibility variants. Means: Available genotyping data for CRC genetic susceptibility variants and expertise in complex statistical analyses to develop a high-risk CRC profile.

These activities will be organized in four Working Groups: Genetic Association Studies (WG1), Functional Genomics (WG2), Next Generation Sequencing (WG3) and Statistical Modelling (WG4).

E. ORGANISATION

E.1 Coordination and organisation

This Action will be steered by its Management Committee (MC), led by a Chair and Vice-Chair and composed according to COST rules. MC will consist of heads of Working Groups (WG), members of Steering Committee for Short Term Scientific Missions (STSMs) and Action's Web site Editorial Board for the full period of Action's mission. MC will ensure fulfilment of the planned activities by the establishment of further temporary steering committees and editorial boards, e.g. for planning international conference and publication of proceedings, workshops, reporting, planning of research activities at national level and collaborations between members inside and partners outside the Action.
This Action aims to organize two scientific workshops and one international conference dedicated to dissemination of knowledge and latest results to the broader scientific community and to promote interaction with non-participating specialists. This Action’s Chair will inform Chairs from other Actions about these scientific events so this information reaches a broader audience. In order to introduce special knowledge related to the topics not directly covered by this Action, outstanding experts will be invited to give plenary lectures at Action's meetings. Additional Partners will be engaged to Action whenever possible. The Chair will disseminate information electronically, and through an official Action's Web site with an open public access to ensure Action's visibility. The Web site will contain Summaries of activities, Minutes of Meetings and future Meeting plans, Major achievements, List of published papers, Contacts for scientists interested to join the Action.

A member-only restricted area for participating members will enable sharing knowledge and planning of future activities. Promising young scientists will be exchanged between participating laboratories to expedite technology transfer and accomplish specific and timely research tasks. The Action's organization schedule will greatly strengthen the existing collaboration of scientists from Europe and the rest of the world. Major Action's events will be organized with both academic and commercial participation to encourage transfer of scientific knowledge into practical applications.

E.2 Working Groups

This Action’s activities will be organized in four Working Groups: Genetic Association Studies (WG1), Functional Genomics (WG2), Next Generation Sequencing (WG3) and Statistical Modelling (WG4). WG1 will comprise all activities related to the identification of new CRC genetic susceptibility variants and correlation of known and newly identified CRC genetic susceptibility variants with CRC survival and treatment response, as well as with CRC subtypes. WG2 will cover research undertaken by participants regarding fine mapping and functional studies for known and newly identified CRC genetic susceptibility variants. WG3 will include all activities related to the identification of new predisposition CRC genes by next generation sequencing. Finally, WG4 will consist of research tasks involved in statistical analyses of gene-gene (epistasis and hereditary CRC modifiers) and gene-environment interactions for CRC genetic susceptibility variants, with a final objective of developing a high-risk profile for CRC to be used as a molecular tool for personalized CRC medicine.

E.3 Liaison and interaction with other research programmes

Meetings and conferences will be among the major sources of interaction between Action's members and the international forum of researchers on CRC. The planned meetings will drive collaboration and coordination of research tasks with non-participating partners at European level. This Action may benefit partially from experience and goals of ongoing Action BM1006 regarding next generation sequencing data analysis. There is only one current effort for the identification of inherited susceptibility factors to CRC funded by the Framework Programme with involvement of some participants in this Action (CHIBCHA: Genetic study of Common Hereditary Bowel Cancers in Hispania and the Americas) that will conclude at the end of the present year. Framework

Programme funded research on CRC is mainly focused on somatic tumor changes (COLTHERES, SYSCOL) or environmental effects (EPIC). On the other hand, international consortiums such as C-CFR, GECCO and MECC are collaborative efforts outside Europe to improve understanding of genetic susceptibility to CRC. This Action plans to contact these international consortiums to develop research collaborations of mutual benefit.

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

This Action will aim at keeping an appropriate gender balance in all its activities and the Management Committee (MC) will place this as a standard item on all its MC agendas. The Action will also be committed to considerably involve early-stage researchers. This item will also be placed as a standard item on all MC agendas.

Although there are more than 50% of female researchers in the participants' laboratories (mainly in early-stage career), gender dimension is still an important issue in the goal to achieve and maintain research excellence in Europe. This Action's participants will do their best to increase their low proportion of women among leaders in research groups. The possibility to work from home and offer part-time jobs will be enforced according to specific needs of each of women willing to continue in their scientific career after maternity leave. Working conditions will be monitored and managed in order to make them more gender-sensitive and balance training and STSM opportunities among genders to increase women scientific competence. To integrate the gender dimension into network activities, women vice-leaders or promising candidates will be invited to take part at MC Meetings and participate at Action activity planning and realization at any possible level. Appropriate gender balance will be aimed when recruiting collaborating scientists and new collaborators will have to adhere to gender balance policies. At each MC Meeting the status of implementation of gender balance policy and the respective change from the last setting ratios for participation will be evaluated and available feedback from researchers will be resolved. Setting ratios for participation reflecting the gender balance of Consortium will be included into Midterm and Final Report. On the other hand, several female colleagues acting as PhD students or young postdoctoral fellows will gain the experience during this Action to become MC chairs or WP leaders in future international projects.

As highlighted by previous grant holders, COST is the right instrument to facilitate the close interaction between emerging scientists and more experienced and established researchers. Each MC member will have one assistant at early-stage scientific career (usually at age less than 35 or

maximum 40), who will actively participate in STSMs planning and promote broader involvement of young scientists including pre- and postgraduate students in all Action's activities. Each country research groups (headed by MC members) will organize student conferences at national level and try to attract students also from groups non-participating in the Action. Building a network of ESRs is one of the goals of the proposed Action since such network will ensure the continuation of Action's activities.

F. TIMETABLE

This Action will have a total estimated duration of 4 years. Research activities will be scheduled according to the previously described objectives in Sections C and D. Identification of new CRC susceptibility variants will identified at the beginning, whereas functional links for known and newly identified CRC susceptibility variants will be pursued later on. Genotype-phenotype correlations (objectives 3 and 4) will be performed at the beginning for those known CRC susceptibility variants and in Year 3 for those newly identified. Identification of new genes involved in CRC predisposition will be carried out also at the beginning of this Action, whereas objectives 6 and 7 regarding complex statistical analysis will start in Year 2 and continued until the end of the Action.

Objectives	Year 1	Year 2	Year 3	Year 4
1	**********	**********	**********	
2		**********	**********	**********
3	**********		**********	
4	**********		**********	
5	**********	**********	**********	
6		**********	**********	**********
7		**********	**********	**********

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: AT,CZ,DE,ES,FI,IT,NL,PT,SE,UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 40 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 for the dissemination of this Action's results will be:

1. The scientific community in Europe and worldwide;
2. Clinicians and other healthcare workers in Gastroenterology, Surgery and Oncology departments, and high-risk CRC clinics;
3. European and national regulatory bodies and policy makers in health care systems (both preventive strategies and optimized treatment);
4. General public in terms of reducing risk factors associated with CRC as well as decreasing mortality and morbidity related to CRC;
5. CRC patients as the identified CRC susceptibility variants in relation to prognosis and therapy outcome may improve their survival;
6. Industry interested in the exploitation of gained knowledge for applications including design of new drugs against identified targets, preventive treatments, and invention of predictive testing devices.

H.2 What?

The dissemination methods used for this Action will include:

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 Action's

activities (meetings, workshops), proceedings of meetings, links to publications of participants, links to related institutions and organizations, 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 CRC.
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 research projects conducted by this Action. At a later stage, the findings generated by this Action will be disseminated to the scientific community through;
Scientific publications will be published 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 the international conference will be published as special issues in international high impact journals such as European Journal of Cancer, Annals of Oncology, Cancer Letters or European Journal of Human Genetics.
To promote the timely translation of the CRC research results of this Action into policies on national, European and international level Stakeholder Meetings will be organized.
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 this Action, they will be preferably organized as satellites to major scientific conferences in the field, such as those mentioned above.

H.3 How?

The official Action's web site will play the pivotal role in the "electronic publishing" and dissemination of information gained by planned activities. This Action will disseminate as widely as possibly its activities and findings, capitalizing 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 abovementioned activities and their outcome as well as revise the dissemination plan according to the Domain Committee recommendations. The dissemination plan will be evaluated during the Midterm Report and updated accordingly.